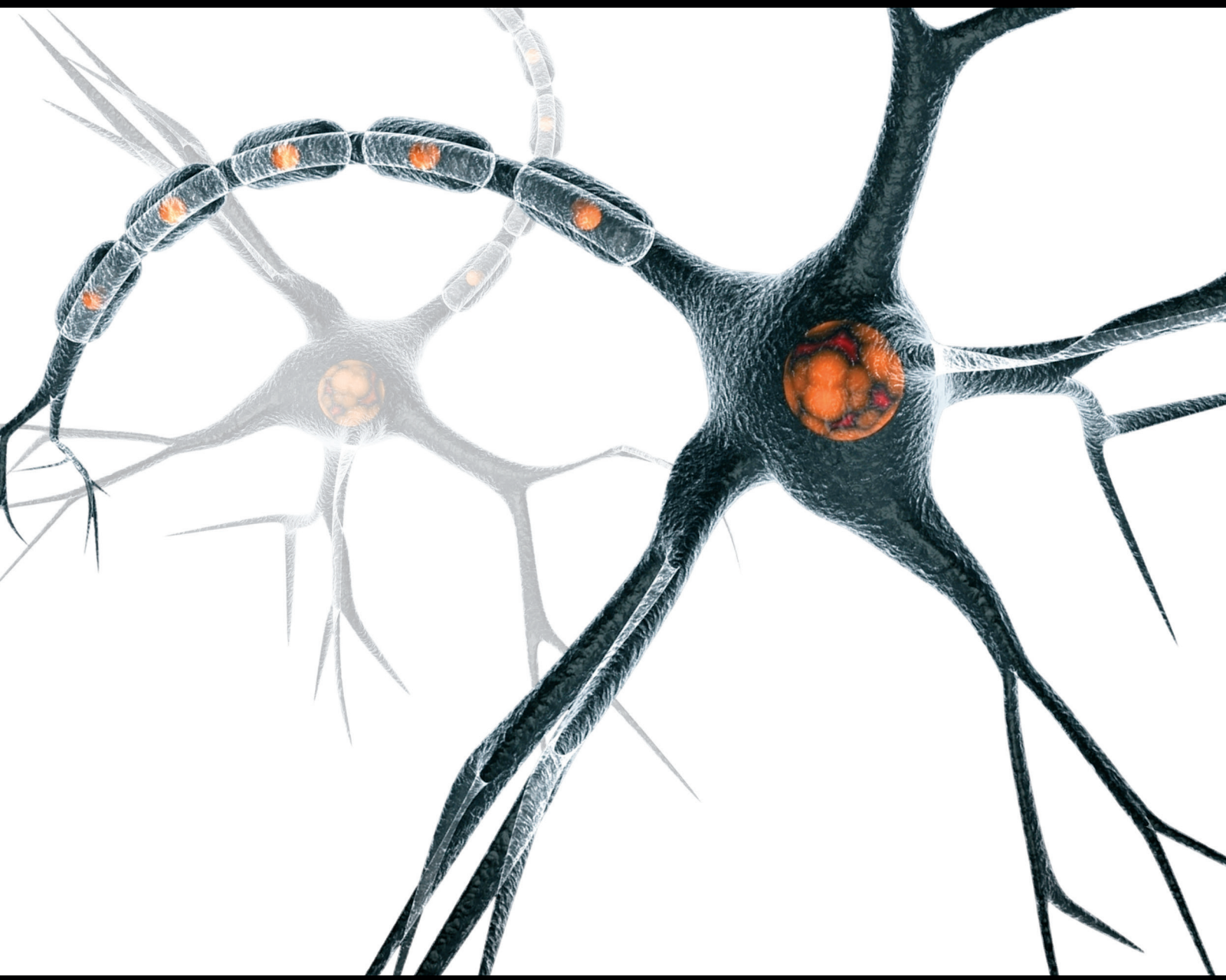
Neural Plasticity

Boosting Action Observation and Motor Imagery to Promote Plasticity and Learning

Lead Guest Editor: Ambra Bisio
Guest Editors: Michela Bassolino, Thierry Pozzo, and Nicole Wenderoth



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Editorial Board

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Editorial

Boosting Action Observation and Motor Imagery to Promote Plasticity and Learning

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In a continuum from fundamental to applied research, many significant scientific contributions in interdisciplinary research fields such as cognitive neuroscience, sport science, and neurorehabilitation provided convincing evidence that action observation (AO, the process of observing actions performed by other people) and motor imagery (MI, the mental execution of action without an overt motor output) might enhance the efficacy of motor training and/or motor recovery by stimulating the activity of the sensorimotor system [1, 2]. The scientific rationale behind this idea is that AO and MI activate neural substrates partially overlapped with those activated by movement execution [3–5]. The existence of a shared neural representation would support the hypothesis that AO and MI may promote neural plastic changes and behavioral improvements in a way similar to movement execution. Moreover, a growing body of evidence in healthy adults proposed that the combination of AO and MI with each other [6] or with central and peripheral noninvasive stimulations might have a greater impact on brain plasticity and motor learning than when these techniques are applied alone [7–10].

In line with this emerging hypothesis, this special issue was published. Authors from 11 countries across Europe, Asia, America, and Australia submitted scientific papers in the format of research article (13), clinical study (2), and review article (2) proposing interesting new insights or reviewing the literature on this topic in different research fields such as neurophysiology, human neuroscience, rehabilitation, and sport neuroscience. The result is a collection of 17 articles showing an increasingly widespread interest in studying the neural mechanisms underlying AO and MI and in applying them in combination with movement execution or other stimulation methodologies.

Four neurophysiological studies examined the combination of MI and AO with peripheral and central stimulations and motor practice to access whether and how these combined techniques evoked changes to the central nervous system activity and improvements in behavioral tasks. In particular, E. Traverse at al. investigated how MI associated with somatosensory electrical stimulation (SS) modulated corticospinal and spinal excitability with respect to MI and SS applied alone. The study by E. Saruco et al. addressed the timing-dependent effects of MI combined with anodal transcranial direct current stimulation (a-tDCS) on improving the performance during a postural task. A critical view on the efficacy of AO associated with a-tDCS in providing advantages to motor learning was raised by the results presented by D. Apšvalka et al. who

investigated whether a-tDCS applied over the primary motor cortex during observational practice facilitated the acquisition and retention of a keypress sequence learning task compared to a sham treatment. Doubts on the efficacy of observational practice, when compared to physical practice, were expressed in the neurophysiological and behavioral investigation by N. Alhajri et al., which evaluated the degree of mu suppression in those conditions.

AO and MI also represent valuable tools to investigate how brain activity changes as a function of age, pathological conditions, or motor expertise. A. Mouthon et al. examined age-related differences in cortical and subcortical activities during AO and MI of postural tasks in an fMRI study. Another fMRI investigation (L. P. Kirsch et al.) evaluated how learning a complex motor skill through physical and observational practices shapes neural and behavioural responses among a dance-naïve sample of young and elderly adults. Current theories on the mechanisms underpinning mirror neuron system (MNS) activation during AO and mirror visual feedback (MVF) in stroke are reported in the review article by J. J. Q. Zhang et al. Related to this topic is the research article from F. Bähr et al. in healthy participants, which clarified that although video therapy and MVF applied separately improved the motor performance, video therapy + MVF had no additional boosting effect. Changes in reciprocal inhibition of the forearm during kinesthetic MI and after an MI-based brain-machine interface training were assessed by M. Kawakami et al. in stroke patients. The functional connectivity networks formed on the sensorimotor cortex were measured by means of EEG recordings in subjects with incomplete spinal cord injury and healthy controls by A. Athanasiou et al. during a task combining AO and visual MI simultaneously. The functional difference between visual MI perspectives, namely, internal/kinesthetic vs. external/visual, was investigated using a mental chronometry paradigm by S. Montuori et al. in healthy participants with different levels of motor expertise in pilates with the aim of offering new insights into the application of mental training techniques in sport. Finally, a review paper from Kuehn and Pleger extends the effect of AO on the tactile domain, by summarizing studies assessing the role of visual cues related to the body or to the observation of touch in boosting tactile processing and promoting somatosensory plasticity.

Five original studies offer new evidence on the efficacy of combining conventional rehabilitation techniques with AO therapy (AOT) and MI practice to promote functional recovery in neurological and orthopedic patients. The efficacy of AOT applied during the rehabilitation of upper limb motor functions in children with cerebral palsy was assessed in the study by G. Buccino et al. through a behavioral paradigm based on clinical scales and an fMRI investigation. E. Pelosin et al. tested the effects of an AOT program delivered in a group-based setting compared with standard physical therapy in improving freezing of gait episodes and mobility in subjects with Parkinson's disease (PD). Improvements in mental imagery ability, disease severity, motor and cognitive functions were the ambitious aims of the Dynamic Neuro-Cognitive Imagery (DNI) training administered to PD patients by A. Abraham et al. A proof of concept by E. Durand et al. evaluated the efficacy of personalized observation, execution, and mental imagery (POEM) therapy, a new approach designed to integrate sensorimotor and language-based strategies to treat verb anomia. Although AO and MI are cognitive stimulation methodologies mostly applied during neurorehabilitation, their efficacy was also shown in the treatment of orthopedic patients. U. Marusic et al. administered an AO + MI intervention combined with conventional rehabilitation techniques to verify its effectiveness in older adults after total hip arthroplasty.

In conclusion, this special issue is aimed at providing a fresh state of the art about new means to evoke neural plasticity and behavioral improvements in healthy adults and sportsmen and suggests innovative therapeutic approaches in addition to pharmacological and conventional treatments during rehabilitation. This collection of papers, together with the existing literature, prompts the use of AO and MI in combination with other stimulation techniques and/or motor practice as a valuable research tool for investigating brain physiology in healthy and pathological conditions and as a fruitful intervention methodology to cope with behavioral and cognitive deficits. Although further studies are necessary to elucidate the brain mechanisms underlying these combined stimulation techniques and to address the criticisms also discussed in this special issue in order to improve and rationalize such a tool, the potentiality of these methods is promising for both clinical and sport performance applications. We hope that this special issue will encourage scientists from different domains to deeply investigate how to boost AO and MI effectiveness with the final aim of discovering new tools for rehabilitation and for performance enhancements in sports.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

[1] A. Pascual-Leone, D. Nguyet, L. G. Cohen, J. P. Brasil-Neto, A. Cammarota, and M. Hallett, "Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills," *Journal of Neurophysiology*, vol. 74, no. 3, pp. 1037–1045, 1995.

[2] M. Bassolino, M. Campanella, M. Bove, T. Pozzo, and L. Fadiga, "Training the motor cortex by observing the actions

of others during immobilization," *Cerebral Cortex*, vol. 24, no. 12, pp. 3268–3276, 2014.

[3] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[4] M. Jeannerod, "Neural simulation of action: a unifying mechanism for motor cognition," *NeuroImage*, vol. 14, no. 1, pp. S103–S109, 2001.

[5] F. Filimon, J. D. Nelson, D. J. Hagler, and M. I. Sereno, "Human cortical representations for reaching: mirror neurons for execution, observation, and imagery," *NeuroImage*, vol. 37, no. 4, pp. 1315–1328, 2007.

[6] D. L. Eaves, M. Riach, P. S. Holmes, and D. J. Wright, "Motor imagery during action observation: a brief review of evidence, theory and future research opportunities," *Frontiers in Neuroscience*, vol. 10, p. 514, 2016.

[7] A. Bisio, L. Avanzino, M. Biggio, P. Ruggeri, and M. Bove, "Motor training and the combination of action observation and peripheral nerve stimulation reciprocally interfere with the plastic changes induced in primary motor cortex excitability," *Neuroscience*, vol. 348, pp. 33–40, 2017.

[8] G. Bonassi, M. Biggio, A. Bisio, P. Ruggeri, M. Bove, and L. Avanzino, "Provision of somatosensory inputs during motor imagery enhances learning-induced plasticity in human motor cortex," *Scientific Reports*, vol. 7, no. 1, p. 9300, 2017.

[9] E. Saruco, F. di Rienzo, S. Nunez-Nagy et al., "Anodal tDCS over the primary motor cortex improves motor imagery benefits on postural control: a pilot study," *Scientific Reports*, vol. 7, no. 1, p. 480, 2017.

[10] N. Wenderoth, "Changing the brain with multimodal mirrors: combining visual and somatosensory stimulation to enhance motor plasticity," *Clinical Neurophysiology*, vol. 126, no. 6, pp. 1065-1066, 2015.

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Research Article

The Neural and Behavioral Correlates of Anomia Recovery following Personalized Observation, Execution, and Mental Imagery Therapy: A Proof of Concept

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The impact of sensorimotor strategies on aphasia recovery has rarely been explored. This paper reports on the efficacy of personalized observation, execution, and mental imagery (POEM) therapy, a new approach designed to integrate sensorimotor and language-based strategies to treat verb anomia, a frequent aphasia sign. Two participants with verb anomia were followed up in a pre-/posttherapy fMRI study. POEM was administered in a massed stimulation schedule, with personalized stimuli, resulting in significant improvement in both participants, with both trained and untrained items. Given that the latter finding is rarely reported in the literature, the evidence suggests that POEM favors the implementation of a word retrieval strategy that can be integrated and generalized. Changes in fMRI patterns following POEM reflect a reduction in the number of recruited areas supporting naming and the recruitment of brain areas that belong to the language and mirror neuron systems. The data provide evidence on the efficacy of POEM for verb anomia, while pointing to the added value of combined language and sensorimotor strategies for recovery from verb anomia, contributing to the consolidation of a word retrieval strategy that can be better generalized to untrained words. Future studies with a larger sample of participants are required to further explore this avenue.

1. Introduction

Aphasia is an acquired language impairment following brain damage, such as stroke, whose consequences can be devastating [1]. Anomia is the most frequent and pervasive symptom for people with aphasia, regardless of the aphasia type. Anomia is described as difficulty in retrieving words in structured tasks, such as picture naming, sentence completion, or spontaneous speech. Anomia can affect different types of words, including nouns and verbs. Research has long focused on noun retrieval, while therapies targeting verb anomia remain rare [2]. This is somewhat surprising, considering the central role of verbs in sentence and speech production [3].

In recovery from aphasia, the attempt to compensate for anomia may be related to the concept of neuroplasticity. Neuroplasticity refers to a number of brain mechanisms involved in learning and relearning and is reflected in changes in brain activation patterns highlighted by functional magnetic resonance imaging (fMRI). Two main forms of neuroplasticity have been studied in the context of aphasia recovery: functional reactivation, which occurs when previously damaged and inactive areas recover their function after a latency period, and functional reorganization, which reflects compensation for the permanent damage of specific brain areas by the recruitment of other areas not previously involved in the given function [4]. Different types of neuroplasticity may be involved in recovery from anomia; adaptive neuroplasticity results in functional recovery, whereas maladaptive neuroplasticity results in persistence of errors [4, 5]. There is a long-standing debate in the anomia recovery literature regarding functional reorganization: Is better recovery supported by perilesional left hemisphere (LH) language processing areas or right hemisphere (RH)

homologues of those areas? However, the extent to which an RH shift reflects adaptive or maladaptive neuroplasticity remains controversial (Anglade et al., 2014). Moreover, the impact that different therapy procedures may have on the recruitment of canonical or noncanonical language processing circuits remains to be explored.

With regard to verb anomia, therapy approaches have been designed with reference to models of word processing that view the phonological and semantic processing of words as key elements for word retrieval (see [2], for a review). Thus, phonological approaches use sound cues and rhymes to elicit words, whereas semantic approaches use semantic cues and reinforce the semantic features of a given word to facilitate word naming. The efficacy of both approaches has been proven, in particular with treated items [2]. Conversely, poor generalization of treatment effects to untrained verbs has been consistently reported [6–12]. Furthermore, none of these studies have explored the neural substrates sustaining recovery from verb anomia. Regarding the lack of generalization of therapy effects to untrained verbs, it should be noted that none of the publications cited took into consideration the dynamic component of verb processing. The meaning of an action verb includes a dynamic semantic feature that an object does not require. This assumption—grounded in embodied cognition theory—implies that word meaning depends on modal experiences. Thus, semantic processing of a given word—noun or verb—will depend upon the sensory and motor modalities by which objects and actions corresponding to those words are learned and how this learning impacts the functional brain networks supporting word processing ([13, 14]; Pulvermüller et al., 1996). In other words, the learning modality and features of a given word will determine the conceptual and brain-related substrates supporting word retrieval; with verbs, particularly action verbs, these should include sensorimotor features and brain processing areas [15].

An interesting example of how word encoding influences the efficacy of a given strategy for word retrieval comes from the work by Marangolo et al. showing that action observation on its own can represent a useful tool for verb retrieval [16, 17]. Action observation therapy (AOT) principles were first developed for stroke patients who suffered from a motor deficit affecting the upper limbs. Several studies have consistently shown that AOT is an effective way to enhance motor function [18–21]. Ertelt et al. [18] first showed that patients in the chronic stage after stroke experienced significantly improved motor function following a four-week video therapy program compared with a control therapy; additionally, neural activations associated with the AOT showed a significant rise in activity in areas sustaining the action observation/action execution matching system [18]. This system includes the mirror neuron system, which will be discussed below.

In the language rehabilitation domain, Marangolo et al. [17] administered AOT to stroke patients who suffered from aphasia in order to improve verb retrieval. They compared action observation with action observation and execution and found that the mere observation of the performed action was sufficient to activate the corresponding sensorimotor representation in the semantic system, which served as input at the lexical level facilitating verb retrieval. However, their results were not replicated by another recent work [22] and the effect was restricted to trained items. Moreover, the neural substrate underlying recovery with AOT has not yet been investigated.

Several studies have examined the efficacy of other sensorimotor strategies to facilitate verb retrieval. For example, Raymer et al. (2006) examined the effect of gesture execution in aphasia treatment, using pantomimes paired with verbal training for noun and verb retrieval in a group of aphasic patients. Their results showed improved naming of trained nouns and verbs but no generalization of treatment effects to untrained words. Similarly, Rose and Sussmilch [23] obtained significant results following therapy combining verb naming and gesture production; again, the results were restricted to trained items. In sum, observation of action and gesture execution, both associated with verb naming, yielded positive results with trained verbs but not with untrained ones. None of those studies included fMRI segregation analysis of areas sustaining recovery, and thus the behavioral changes observed cannot be linked to any specific neural substrate. Thus, while functional neuroimaging data on verb processing have mostly been related to healthy populations, very little is known about therapy-induced neuroplasticity in the recovery from verb anomia.

In healthy adults, action verb naming has been shown to be supported by left frontal cortical areas, including the left prefrontal cortex (Shapiro et al., 2001), the left superior parietal lobule, the left superior temporal gyrus (Shapiro et al., 2006), the left superior frontal gyrus (Shapiro et al., 2005), and the primary motor cortex in the posterior portion of the precentral gyrus (Porro et al., 1996, [13], and Pulvermüller et al., 2005). As discussed by Durand and Ansaldo [15], these areas have also been associated with the so-called mirror neuron system (MNS), which is thought to support AOT in motor neurorehabilitation after stroke. Mirror neurons are a particular class of visuomotor neurons, originally discovered in area F5 of the monkey premotor cortex, that discharge both when a monkey does a particular action and when it observes another monkey or a human doing a similar action [24]. The MNS is a mechanism that unifies perception and action, transforming sensory representations of the behavior of others into motor representations of the same behavior in the observer's brain [25]. From this perspective, some authors have suggested that language evolved from a gestural system, first as pantomime and gradually as conventional gestures, eventually developing into a symbolic code [24, 26, 27]. This sensorimotor system is considered to be the structure underlying vocabulary and grammar development [26, 28]. In this view, mirror neurons are considered to be embodied cognitive agents, as they coordinate multimodal information resulting from an individual's interaction with the environment. According to such theories, the MNS may play a central role in the development of language in humans [24, 26, 27] and in semantic processing, especially action semantic processing.

Apart from the MNS, several links can be made between vision and action. The cortical visual system is known to be

segregated into two anatomically and functionally distinct pathways: a ventral occipitotemporal pathway that subserves object perception and a dorsal occipitoparietal pathway that subserves object localization and visually guided action [29–31]. Goodale and Goodale and Milner [30, 32] proposed a model in which the perceptual detection of possible actions in the environment involves the dorsal stream, stretching from the primary visual cortex to the posterior parietal lobe and reaching the premotor areas and a distributed network of areas in the caudal frontal cortex. More than just a visual detection system, the dorsal stream allows action selection with continuous matching between the visual and motor areas [33]. A recent study has shown that, along the dorsal pathway, the anterior intraparietal area and the ventral premotor cortex extract sensorimotor information from perceptual stimuli, making it possible to detect action possibilities from the information detected through the retinotopic map [33].

Recent research shows that sensorimotor processes play a crucial role in language processing. Thus, both behavioral studies [34] and neurofunctional studies [35–44] suggest that the understanding of action words recruits motor areas. Along the same lines, Tremblay and Small [44] showed that functional specialization of specific premotor areas is involved in both action observation and execution. Moreover, Tomasino and Rumiati (2013) showed that the involvement of sensorimotor areas depends on the strategy used to perform the task. Specifically, if the task requires a person to imagine actions, sensorimotor areas will be involved. Visual mental imagery allows one to obtain an internal representation that functions as a weak form of perception [45]. Mental imagery is known to be an efficient therapy tool for rehabilitation of motor impairments. In language rehabilitation, mental imagery is a relatively new tool, though some studies on aphasia recovery report the activation of visual mental imagery processing areas, such as the inferior occipital gyrus [46].

Taking into account the promising but limited results obtained with anomia therapy approaches based on action observation, gesture, or mental imagery used separately, we designed a new therapy approach combining three sensorimotor strategies previously used to treat verb anomia, namely, action observation, gesture execution, and mental imagery, and combined the three of them in a massed practice format. Thus, personalized observation, execution, and mental imagery therapy (POEM therapy) was designed based on principles of experience-dependent neuroplasticity, namely, stimulus specificity and salience, and a time/frequency ratio corresponding to massed stimulation (for a review of this issue, see [5]). Several studies have shown the benefits of massed practice, defined as practice of a given number of trials in a short time [47–49].

In sum, POEM therapy was developed based on evidence, while incorporating principles of experience-dependent neuroplasticity and targeted, repetitive, and intensive practice of action naming, with the purpose of contributing to strategy development and integration [5]. Moreover, to identify the neural substrates associated with the outcomes of POEM therapy, we used fMRI to assess functional brain activity before and after intervention with POEM therapy and thus assess treatment-induced neuroplasticity.

The purpose of this study is to examine the effects of POEM therapy on the recovery from verb anomia in the context of chronic aphasia and to identify the neural changes associated with behavioral improvement. Two participants with chronic nonfluent aphasia were examined before and after POEM therapy, and behavioral and event-related fMRI measures were taken. Participants received three sessions of POEM therapy per week over five weeks, in line with a massed therapy approach [47, 48, 50]. Activation maps obtained in the context of oral verb naming were obtained before and after POEM therapy. It was expected that

(1) POEM therapy would result in significant recovery of verb naming;

(2) a series of motor and premotor areas would sustain the observed recovery.

2. Material and Methods

2.1. Participants. Aphasia severity and typology were determined by an experienced speech-language pathologist (SLP: ED). Inclusion criteria were (1) a single LH stroke, (2) a diagnosis of moderate-to-severe aphasia according to the Montreal-Toulouse Battery (Nespoulous et al., 1986), (3) the presence of anomia according to a standardized naming task [51], (4) having French as their mother tongue, and (5) being right-handed prior to the stroke (Edinburgh Inventory; Oldfield, 1971). Exclusion criteria were (1) the presence of a neurological or psychiatric diagnosis other than stroke, (2) incompatibility with fMRI testing, or (3) diagnosis of mild cognitive impairment or dementia prior to stroke [52]. Participants gave written informed consent according to the Declaration of Helsinki. This study was approved by the Ethics Committee of the Regroupement de Neuroimagerie Québec. Table 1 contains sociodemographic information on the two participants, and Figure 1 shows their structural magnetic resonance imaging (MRI) results.

2.1.1. Participant 1. P1 is a 65-year-old right-handed woman, who was 7 years postonset from a left temporal stroke, which resulted in nonfluent aphasia and right hemiparesia. She benefited from individual language therapy for a short time just after the stroke; since then, she has participated in activities organized by the association for persons with aphasia. At the beginning of the study, she was not receiving any language therapy. Aphasia testing conducted at that point showed moderate transcortical motor aphasia with moderate apraxia of speech.

2.1.2. Participant 2. P2 is a 72-year-old right-handed woman, who was 34 years postonset from a left temporal stroke, which resulted in nonfluent aphasia and right upper limb hemiplegia. She had received individual language therapy intermittently over the previous 20 years, particularly during the first years after the stroke. She often participates in activities organized by the association for persons with aphasia. At the beginning of the study, she was not receiving any

language therapy. Aphasia testing conducted at that point showed severe transcortical motor aphasia with mild apraxia of speech.

2.2. Experimental Procedure. The experimental protocol is similar to previous studies conducted in our lab (Marcotte and Ansaldo, 2010, 2012, and 2013). A baseline language assessment was conducted prior to therapy, followed by an initial fMRI session (T1), which identified the neural substrate of spontaneous correct naming. Afterward, patients received therapy from a trained SLP (ED). A second fMRI session (T2) was performed after five weeks of therapy. This session allowed us to identify the brain areas that subserved therapy-induced neuroplasticity. During both fMRI sessions, patients performed an overt naming task. (See Table 2 for the MRI results.)

2.2.1. Language Assessment. Before therapy, the participants were examined with subtests from Montreal-Toulouse 86 Beta version (Nespoulous et al., 1986) to assess global comprehension, repetition, and fluency; the kissing and dancing test (KDT) for verb comprehension [53]; the dénomination de verbes lexicaux (DVL38) for verb naming [51]; the test de dénomination de Québec (TDQ) for noun naming [54]; and three subtests of the Apraxia Battery for Adults—Second Edition [55]—to measure the presence and severity of verbal, limb, and oral apraxia. These tests allow a complete description of the aphasia profile.

2.2.2. Baseline and Items for fMRI Session and Therapy. Stimuli used for the baseline, the fMRI naming task, and the therapy sessions were 5-second action videos (Durand et al., in prep.). Before therapy, the participant underwent three baseline naming assessments using 134 action videos. Baselines were separated by at least four days; the participant had to show stable oral naming performance. In order to provide more individualized therapy, a set of stimuli was created for the participants on the basis of individual performance on the baseline as follows: correctly named (spontaneous, $n = 20$) and incorrectly named ($n = 60$). Of the incorrectly named items, only 20 were trained and the remaining 40 items allowed us to measure the generalization of therapy effects to untrained items. All sets of items (spontaneous, trained, and untrained) were matched for word frequency, number of phonemes, and syllabic complexity. Statistical analysis of the lists showed nonsignificant differences regarding these variables.

Before the first fMRI session, each participant took part in a practice session in a mock scanner. They could therefore become accustomed to the scanner noise and environment.

For the pretherapy fMRI sessions, a set of items was developed including correctly named (spontaneous, $n = 20$) and incorrectly named ($n = 60$) items and scrambled videos that were optimized to fit the same parameters (motion, colors) as the videos for the control conditions ($n = 40$). For the posttherapy fMRI session, the same set was presented, but this time, the incorrectly named items ($n = 60$) were divided into trained items ($n = 20$) and untrained items ($n = 40$) to measure generalization.

Table 1: Sociodemographic, clinical, and cognitive data for the 2 participants.

Patient ID	P1	P2
Sociodemographic data		
Age (years)	65	72
Gender	F	F
Education (years)	18	11
Clinical data		
Handedness	R	R
Etiology	Ischemia	Ischemia
Months postonset	84	408
Aphasia type	Transcortical motor	Transcortical motor
Lesion volume (cm^3)	38	132
Level of verb anomia	68%	55%
Cognitive data (CASP)		
Language (max. 6)	5	6
Visuoconstructive functions (max. 6)	6	5
Executive functions (max. 6)	6	6
Memory (max. 6)	6	6
Praxis (max. 6)	6	5
Orientation (max. 6)	4	6
Total CASP (max. 36)	33	34

CASP: Cognitive Assessment scale for Stroke Patients (Benaim et al., 2015).

During the fMRI scanning, participants were instructed to name the randomly presented videos and to say "baba" in response to scrambled videos. After therapy, the same set of items was presented. Oral responses were audio-recorded with Audacity software.

2.2.3. fMRI Sessions. Participants lay in a supine position on the MRI scanner bed with their head stabilized by foam. Stimuli were pseudorandomly displayed in an optimized order projected by means of E-Prime software (Psychology Software Tools) from a computer onto a screen at the head of the bore and were visible in a mirror attached to the head coil. Each video and picture was presented for 5000 ms, with an interstimulus interval (ISI) ranging from 1104 to 10,830 ms. As shown in Figure 2, participants were instructed to name each action and object, as clearly and accurately as possible, and to say "baba" each time they saw a distorted picture, while avoiding head movements. An MRI-compatible microphone was placed close to the participant's mouth, and Audacity software (http://www.audacityteam.org) was used to record oral responses.

2.2.4. Functional Neuroimaging Parameters. Images were acquired using a 3T MRI Siemens Trio scanner, which was updated (Prisma Fit) during our data collection, with a standard 32-channel head coil. The image sequence was a $T2^*$-weighted pulse sequence (TR = 2200 ms; TE = 30 ms; matrix = 64×64 voxels; FOV = 210 mm; flip angle = 90°; slice thickness = 3 mm; and acquisition = 36 slides in the axial

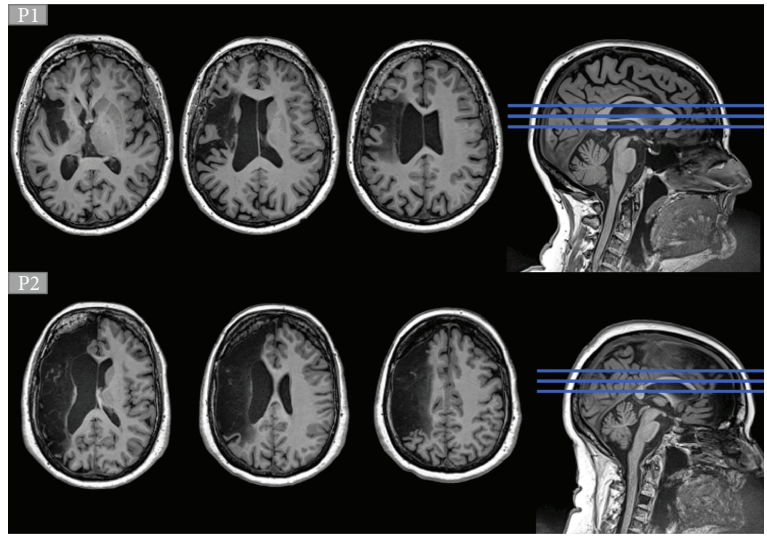

Figure 1: Lesion location on anatomical MRI for P1 (top three slices) and for P2 (bottom three slices).

Table 2: Language assessment and verb naming scores during the pre- and posttherapy MRI sessions for both participants.

Patient ID	P1		P2	
Language assessment	Pre	Post	Pre	Post
Comprehension (max. 47)	46	45	32	N/A
Repetition (max. 33)	30	30	N/A	N/A
Fluency	11	5	15	16
TDQ (max. 60)	40	47	52	57
KDT (max. 52)	51	49	48	N/A
DVL38 (max. 114)	77	81	63	65
Verb naming scores during fMRI session	Pre	Post	Pre	Post
Score for trained items (/20)	9	16	10	19
Score for untrained items (/40)	24	30	15	13

Pre: pre-POEM therapy; Post: post-POEM therapy.

plane with a distance factor of 25% in order to scan the whole brain, including the cerebellum). A high-resolution structural image was obtained before the two functional runs using a 3D T1-weighted imaging sequence using an MP-RAGE (TFE) sequence (TR = 2300 ms; TE = 2.98 ms; 192 slices; matrix = 256 × 256 mm; voxel size = 1 × 1 × 1 mm; and FOV = 256 mm).

2.2.5. Language Therapy with POEM. A trained SLP (ED) provided the POEM therapy, which lasted for one hour and was provided three times per week, over five weeks. During each session, participants were trained to name 20 actions presented in 5-second videos. If the participant could not name the action within 5 to 10 s, she was asked to make the gesture associated with this action, helped by the SLP. If she could not name the action, the participant was asked to imagine the action in a personal context. For instance, with the action *to water*, the following sequence can be produced after the action observation: the SLP says "Show me what the person is doing with your hands," and the participant can imitate someone who is watering. If the action is still not named, the SLP says "Imagine this action in your garden." After these prompts, the word was given to the participant, who was asked to repeat it once.

2.3. Behavioral and fMRI Data Analysis. Responses to the fMRI naming task were recorded and coded offline by an experienced SLP (ED), in order to build the design matrices. Preprocessing and statistical analyses were performed using SPM12 software (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London), running on MATLAB_R2016b (MathWorks Inc., MA, USA). fMRI images were preprocessed with the usual spatial realignment and slice timing. Motion was assessed to ensure that the naming task did not involve head motion exceeding 3 mm. Because precise, valid normalization is critical to understanding the neural substrates of treatment-induced recovery, we used the "Clinical toolbox" extension [56]. This toolbox allows optimal segmentation and registration of brains with distorted anatomy due to lesions. Lesion masks (PB) hand-traced on T1-weighted images were used to minimize the impact of the lesion on the normalization estimates, by substituting healthy tissue for homologous regions of the intact hemisphere [57]. This yields transformation matrices for normalization into the standard stereotaxic space (MNI space) with $3 \times 3 \times 3\,\text{mm}^3$ voxel size. A spatially smoothed 8 mm Gaussian filter was chosen for the smoothing step. Preprocessed data were analyzed using the general linear model implemented in SPM12. Statistical parametric maps were obtained for each subject and each measurement period (first and second fMRI sessions), by applying linear contrasts to the parameter estimates for the conditions of interest (successful naming with trained/untrained items). Neuroimaging data analyses were performed only on correct responses. Individual maps were calculated for each condition for the whole brain with cluster size superior to 10 voxels and $p < 0.001$ uncorrected.

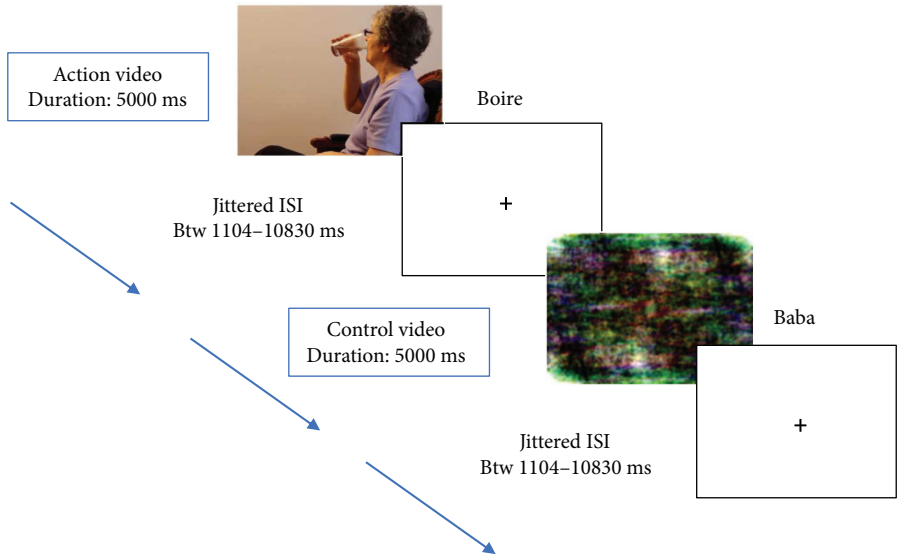

Figure 2: Naming task during fMRI acquisition.

Furthermore, a Lehéricy index (LI) was calculated for each participant to estimate the relative contribution of the LH and RH to verb naming in each condition, pre- and posttherapy. We applied Lehéricy's algorithm, defined as follows: $(L - R)/(L + R)$, where L represents the number of activated voxels in the LH and R represents the number of activated voxels in the RH. LIs were calculated using voxels in clusters ($k \geq 10$) that exceeded the threshold ($p < 0.001$ uncorrected). LIs can range from −1.0 to +1.0. By convention, values between −0.2 and +0.2 represent bilateral language distribution, values between −0.2 and –1.0 represent RH dominance, and values between +0.2 and +1.0 represent LH dominance. Values between ±0.5 and ±1.0 are considered to reflect strong hemisphere dominance [58].

3. Results

3.1. Participant 1. By the end of the therapy period, P1 was able to name all of the 20 trained items. However, her performance in the scanner was less accurate than that at the last therapy session, as she named 16 trained items in the posttherapy fMRI session, which occurred one day after the end of therapy. In addition, P1 named 30 of the 40 untrained items that she was unable to name before therapy. Moreover, P1 showed improved verb naming on the DVL38 and noun naming on the TDQ.

As for her fMRI results, spontaneous correct naming before therapy significantly activated the left primary motor cortex, left angular gyrus, and right fusiform gyrus, with predominant LH activation according to the LI. (See Table 3 for fMRI results and Table 4 for LIs.)

Regarding trained items after the therapy, the activation map revealed significant activation in the left cerebellum, left and right middle temporal gyri, and right fusiform gyrus. Moreover, the LI indicated an increase in predominant LH activation (0.17).

Finally, with untrained items, the posttherapy activation map showed significant activation of regions similar to those activated for the trained items, namely, the left middle temporal gyrus and right fusiform gyrus, with the addition of the right inferior frontal gyrus. The LI in this case showed a shift to predominant RH recruitment.

3.2. Participant 2. Following therapy, P2 was able to name all of the 20 trained items and correctly named 19 trained items in the posttherapy fMRI session. P2 also named 13 of the 40 untrained items she had been unable to name before therapy. Again, her performance outside the scanner was better for untrained items. Finally, like P1, P2 showed improved verb naming ability on the DVL38 and noun naming ability on the TDQ.

The activation map for correct naming before therapy showed the recruitment of a large set of areas, including bilateral activation of the angular gyrus, superior parietal lobule, premotor cortex, left middle and inferior occipital gyri, and right cerebellum. The LI (0.6) corresponded to a predominant LH activation. (See Table 3 for fMRI results and Table 4 for LIs.)

With trained items, posttherapy activation maps were much smaller, as fewer areas were recruited, namely, the right premotor cortex and left cerebellum, and the LI showed predominant RH activation (−0.58). Unfortunately, it was not possible to obtain an activation map for untrained items, due to the lack of a suprathreshold cluster number.

4. Discussion

This study examined the behavioral and neural correlates of personalized observation, execution, and mental imagery (POEM) therapy, a new approach combining sensorimotor and language-based strategies to treat verb anomia, which was delivered in a massed stimulation format. Two participants with nonfluent chronic aphasia were examined

Table 3: Significantly activated areas associated with the production of correct verbs for the two participants.

Patient ID	Condition	Pretherapy														Posttherapy													
		Left hemisphere SPM results						Right hemisphere SPM results								Left hemisphere SPM results						Right hemisphere SPM results							
		Region	BA	X	Y	Z	*T*-score	Cluster size	Region	BA	X	Y	Z	*T*-score	Cluster size	Condition	Region	BA	X	Y	Z	*T*-score	Cluster size	Region	BA	X	Y	Z	*T*-score	Cluster size
P1	Spontaneously named > baba	Primary motor	4	−39	−25	65	4.82	20	Fusiform	37	60	−46	5	4.79	28	Spontaneously named > baba								Middle temporal gyrus	21	60	−43	2	4.2	19
		Angular gyrus	39	−60	−49	35	3.74	13																						
P1	Incorrectly named > baba	Angular gyrus	39	−60	−43	26	3.49	10	Fusiform	37	60	−46	5	4.2	15		Cerebellum		−24	−88	−28	4.6	31	Fusiform	37	60	−49	5	4.42	32
			39	−60	−52	32	3.37									Trained > baba	Middle temporal gyrus	21	−60	−22	−4	4.02	14	Middle temporal gyrus	21	48	−40	5	3.46	
																	Middle temporal gyrus	21	−54	−31	−1	3.52								
																Untrained > baba	Middle temporal gyrus	21	−60	−25	−4	4.68	21	Fusiform	37	60	−46	5	5.04	82
																	Middle temporal gyrus	21	−54	−31	−1	3.81		Inferior frontal gyrus	44	39	11	17	4.32	54
P2	Spontaneously named > baba	Angular gyrus	39	−27	−67	32	5.2	1117	Superior parietal lobule	7	33	−55	53	4.35	117		Premotor cortex	6	−15	−19	50	4.5	59	Premotor cortex	6	51	−4	35	5.56	114
		Superior parietal lobule	7	−27	−67	44	5.08		Angular gyrus	39	30	−67	26	3.64			Middle occipital gyrus	18	−24	−94	2	3.49	20	Cerebellum		15	−73	−31	3.56	12
		Superior parietal lobule	7	−21	−61	35	4.84		Angular gyrus	39	33	−64	35	3.47		Spontaneously named > baba	Middle occipital gyrus	18	−12	−85	−10	3.47	14							
		Inferior occipital gyrus	19	−33	−73	−4	4.76	167	Cerebellum		−18	−76	−19	3.95	115		Cerebellum		−33	−73	−28		16							
		Middle occipital gyrus	18	−24	−97	−1	4.23				−24	−70	−25	3.91					−27	−64	−25								
		Premotor cortex	6	−15	14	47	4.22	100			−33	−70	−28	3.67															
			6	−12	8	62	4.09		Cerebellum		12	−39	−49	3.97	69														
			6	−21	11	56	3.92		Premotor cortex	6	54	−4	35	5.03	56														
		Fusiform	37	−51	−40	−10	4.09	46	Prefrontal cortex-SMA	8	42	5	35	3.74	11														
		Fusiform		−48	−52	−19	3.19																						
		Middle occipital gyrus	18	−3	−70	2	3.75	33																					
		Striate cortex	17	−18	−79	14	3.78	17																					
P2	Incorrectly named > baba	Superior parietal lobule	7	−21	−61	35	5.59	1273	Cerebellum		18	−25	−34	5.58	471	Trained > baba	Cerebellum		15	−73	−31	3.75	10	Premotor cortex	6	51	−4	35	4.25	38
		Primary motor	4	−3	−28	74	4.96		Cerebellum		9	−37	−49	4.75																
		Middle occipital gyrus	18	−27	−85	5	4.34		Angular gyrus	39	36	−58	44	3.91	76	Untrained > baba	No suprathreshold cluster							No suprathreshold cluster						
		Premotor cortex	6	−3	8	65	4.58	230	Superior parietal lobule	7	30	−61	35	3.6																
			6	−15	14	47	4.13		Primary motor	4	57	−1	32	4.37	39															
									Middle frontal gyrus	9	54	26	20	3.91	22															
									Inferior frontal gyrus	45	54	29	11	3.69																
									Anterior middle frontal gyrus	46	48	35	17	3.25																

BA: Brodmann area; baba: condition control.

Table 4: Lateralization indexes related to successful verb naming in the different conditions pre- and posttherapy for P1 and P2.

Lehéricy index	P1	P2
Spontaneous pretherapy	0.08	0.6
Spontaneous posttherapy	−1	−0.07
Incorrect pretherapy	−0.2	0.42
Incorrect—trained posttherapy	0.17	−0.58
Incorrect—untrained posttherapy	−0.73	N/A

with a verb naming task during event-related fMRI scanning, before and after therapy. Both participants benefited from POEM, with improvements observed with both trained and untrained items. Concurrently with the behavioral improvement, changes in the neural substrates sustaining verb naming were observed in both participants, with distinctive activation patterns observed posttherapy, including areas related to the nature of POEM therapy.

As hypothesized, the outcomes revealed the positive effects of POEM therapy on verb naming for both participants. The results are in line with previous studies showing that sensorimotor strategies are efficient therapy tools for recovery from verb anomia secondary to aphasia [16, 17, 22, 23]. However, none of those studies found positive therapy effects on untrained items. Two possible interpretations of these results were considered: on the one hand, they could be due to the origins of verb anomia; on the other hand, they could be due to the types of strategies used. In their study using semantic plus gesture treatments for verb anomia, Rose and Sussmilch [23] reported significant improvement for two participants with lexical-phonological-based anomia, but there is no improvement for the participant with semantic-based anomia. Similarly, Marangolo et al. [17] obtained positive results with AOT on verb retrieval for participants with lexical-phonological-based verb anomia, but there is no improvement for those who presented semantic-based verb anomia. The authors of those studies suggested that the severity of the semantic impairment underlying the anomia was responsible for the lack of improvement after the therapy. In our study, the semantic processing assessment showed that each participant had a preserved semantic system before the therapy. Because sensorimotor strategies are related to the semantic component of action, the improvement in verb retrieval would have been facilitated by preserved semantic abilities.

Furthermore, improvement was also observed on the untrained list after POEM therapy. Although this result was limited for P2 in the context of fMRI, the improvement was noted behaviorally and the same result has been found consistently with a group of 10 participants who have received POEM therapy (Durand et al., in prep). However, a generalization to untrained items was not found in several earlier studies using sensorimotor strategies. The sensorimotor strategies applied by Marangolo et al. [17], Raymer et al. (2007), and Rose and Sussmilch [23] used only one type of sensorimotor cue—gesture or observation in association with verb naming—whereas with POEM therapy, several sensorimotor cues were provided—observation of the action, gesture, and mental imagery—which may have facilitated word retrieval. According to cognitive models of word naming, this combination of semantic inputs could increase activation at the semantic level and facilitate the flow to the lexical and articulation levels and verb naming [59, 60]. Moreover, in line with the embodied theory, the various sensorimotor cues in POEM therapy tap into the specific encoding features of verbs [14, 26, 36, 42, 44], thus enhancing the therapy's specificity, another factor that has been shown to contribute to therapy efficacy [2].

The personalized approach potentially contributes to POEM's efficacy and generalization effects. Thus, verbs targeted with POEM were selected according to each participant's naming performance before therapy. Personalization of therapy items is considered to increase motivation, and thus attention focus, and has been shown to contribute to therapy efficacy [61].

Finally, as shown by previous works [47–49], massed stimulation with the POEM protocol may also explain the differences observed between our study and the other studies considered. The structured and massed practice on a limited number of items may have contributed to the implementation of a naming strategy that could be generalized to untreated items.

The improvement observed for our two participants occurred concomitantly with changes in neural recruitment. As hypothesized, the recovery following POEM therapy involves the recruitment of an alternative circuit, including the activation of motor and premotor areas. Although the behavioral improvement looks the same for both participants, two different patterns appeared after the POEM therapy.

In the case of P1, the pretherapy fMRI session showed bilateral distribution according to the LI. More specifically, considering the activation maps for spontaneously named items to be trained or untrained, the recruitment includes the left primary motor area, left angular gyrus, and right fusiform gyrus. The left primary motor area and left angular gyrus are canonical areas, part of the dorsal stream pathway of language [62], that reveal the perilesional recruitment associated with aphasia recovery. These two areas are also known to be involved in verb naming [13, 63]. The angular gyrus, which is an associative area between somatosensory information and visual information, participates in the processing of sequence actions, which may be related to the processing of the action videos (Crozier et al., 1999). The recruitment of the right fusiform gyrus can also be related to the processing of visual stimuli. The fusiform gyrus is involved in lexical-semantic association, that is, associating words with visual stimuli [64]. To summarize, for P1, the pretherapy fMRI session revealed the recruitment of canonical areas for verb naming, including perilesional areas, in line with a functional reactivation.

After the POEM therapy, the activation map for trained items reveals that distribution is still bilateral (LI = 0.17), including the right fusiform gyrus and the bilateral middle temporal gyri and left cerebellum. The bilateral middle temporal gyri participate in semantic processing, word generation, and observation of motion [65]. Classically, the

cerebellum is known to regulate motor movement and be involved in motor speech planning. But recent fMRI studies have revealed the contribution of the cerebellum to other kinds of language processing [66, 67], namely, verb generation [68]. To sum up, post-POEM therapy, the activation pattern is consistent with the sensorimotor nature of POEM therapy and therefore is likely to have been therapy-induced.

More interestingly, in P1, the activation patterns for trained and untrained items posttherapy included common areas, with the activation of the left middle temporal gyrus, right fusiform gyrus, and right inferior frontal gyrus. The similarity of neural recruitment for trained and untrained items after POEM therapy suggests that the same kind of processing was used to name the verbs. Furthermore, these similar activations occur concomitantly with the generalization observed in behavioral results. The behavioral and neural results are evidence of the potential application of the same strategies to retrieve verbs.

In the case of P2, the pretherapy fMRI session showed dominant LH activation according to the LI. Considering the large lesion on the left hemisphere, it is not surprising that the activation for spontaneously named items included posterior visual processing areas such as the striate cortex and middle and inferior occipital gyri. But canonical areas for verb naming were also recruited, namely, the angular gyrus and premotor cortex bilaterally. These areas are known to be part of the action naming network in the LH [13, 14, 44]. The bilateral activations on the activation map pretherapy revealed adaptive neuroplasticity with a functional reorganization, which included the homologous areas for verb naming.

After P2's POEM therapy, there was a dramatic decrease in the number of areas recruited for verb naming. The posttherapy activation is supported exclusively by the right premotor area and the left cerebellum. As discussed above, these two areas are involved in action observation and verb naming [44, 66, 67]. This significant reduction in the number of brain areas supporting correct naming suggests that POEM therapy could lead to a more economical use of brain resources. Moreover, considering the LI (−0.58), there was a shift to the RH. This shift is related to adaptive neuroplasticity and is not surprising considering P2's large lesion. This result is in line with the suggested complementary role of the RH in the context of large lesions proposed by Anglade et al. (2013) who argued that, when there is a large lesion with near-complete destruction of the primary language processing areas, significant RH activation is involved.

Our preliminary results showed that neural changes appeared together with behavioral improvements in verb naming after POEM therapy was applied. Although neurorehabilitation studies in the physical domain had provided convincing evidence that action observation and motor imagery might enhance the efficacy of motor training and/or motor recovery by stimulating the activity of the sensorimotor system [69–72], no studies had explored this combination in the case of language rehabilitation. However, the link between action observation, motor imagery, and the sensorimotor system through the MNS system may apply to language too. As discussed by Durand and Ansaldo [15], the MNS is considered to have provided a natural platform for the development of language in humans. Several studies in the field of embodied cognition have provided evidence that the sensorimotor system can be considered an embodied cognitive agent, as it coordinates multimodal information resulting from an individual's interaction with the environment and constitutes a physiological substrate for empirical data linking language and motor processing [24, 26, 27].

Several fMRI studies have shown links between language and motor processing areas within the MNS. Specifically, language comprehension and production tasks engage somatotopic activations, that is, the recruitment of specific motor areas, depending on the body part involved in the action associated with the language target [35, 43]. These findings suggest that the MNS plays an important role in the reintegration of sensorimotor representations during the conceptual processing of actions evoked by linguistic stimuli. Thus, the cooccurrence of these activations weaves connections between motor and language processing areas. These connections represent an interesting framework devoted to the enhancement of skill recovery in language rehabilitation. They were exploited through the application of POEM therapy, leading to preliminary results with two participants.

This work concerns two case studies, and thus, it represents a proof of concept for further investigation of the effects of POEM. Thus, larger experimental samples are required to test for the external validity of these findings. This being said, the two single-case studies reported here concern two different cases, in terms of lesion size, location, and volume, thus providing evidence for the efficacy of POEM in more than one type of aphasia patients. Hence, while group study strength lies on statistical power, single-case studies are informative in terms of the variables that can influence recovery. In particular, group studies average activations, while single-case studies show different patterns of neurofunctional changes, in particular perilesional activations, which are known to better correlate with functional recovery [73]. The present study shows how similar behavioral improvement across the two participants is observed in the context of different lesion volumes and neurofunctional patterns.

Another potential caveat of the present study concerns sociodemographic differences between the two participants, in particular, time poststroke, lesion volume, and education level. Specifically, P2 was 408 months poststroke, while P1 was 84 months poststroke. Time elapsed after stroke has been shown to play an important role in treatment-related changes, but this concerns particularly the acute or subacute phase of recovery, as opposed to the chronic state, which is generally considered to go beyond 6–12 months after stroke [74, 75]. Consequently, we do not think that differences in neurofunctional patterns observed in P1 and P2 can be accounted for by time elapsed after stroke but reflect the influence of lesion size and volume, while these two factors do not seem to modulate POEM therapy efficacy, as documented by equivalent improvement across the two participants.

In all, the results of this study provide evidence for the efficacy of POEM and its neural correlates, in two cases of

chronic verb anomia, resulting from lesions varying in size, location, and volume, and in participants with different educational backgrounds. Future studies will examine the effects of POEM on larger samples (Durand et al., in prep.) and gather both the anatomical and functional correlates of language and motor networks sustaining its efficacy. It will possibly increase our understanding of the mechanisms underlying the recovery from verb anomia, so that more efficient and synergistic rehabilitative interventions based on the links between motricity and language can be designed.

Disclosure

The results of this study will be presented as a scientific poster at the Tenth Annual Meeting of the Society for the Neurobiology of Language (Québec, Canada, August 16–18, 2018).

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

[1] J. M. C. Lam and W. P. Wodchis, "The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents," *Medical Care*, vol. 48, no. 4, pp. 380–387, 2010.

[2] J. Webster and A. Whitworth, "Treating verbs in aphasia: exploring the impact of therapy at the single word and sentence levels," *International Journal of Language and Communication Disorders*, vol. 47, no. 6, pp. 619–636, 2012.

[3] P. Conroy, K. Sage, and M. A. Lambon Ralph, "Towards theory-driven therapies for aphasic verb impairments: a review of current theory and practice," *Aphasiology*, vol. 20, no. 12, pp. 1159–1185, 2006.

[4] J. Grafman, "Conceptualizing functional neuroplasticity," *Journal of Communication Disorders*, vol. 33, no. 4, pp. 345–356, 2000.

[5] J. A. Kleim and T. A. Jones, "Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage," *Journal of Speech, Language and Hearing Research*, vol. 51, pp. S225–S239, 2008.

[6] R. S. Berndt, C. C. Mitchum, A. N. Haendiges, and J. Sandson, "Verb retrieval in aphasia. 1. Characterizing single word impairments," *Brain and Language*, vol. 56, no. 1, pp. 68–106, 1997.

[7] P. Conroy, K. Sage, and M. A. Lambon Ralph, "The effects of decreasing and increasing cue therapy on improving naming speed and accuracy for verbs and nouns in aphasia," *Aphasiology*, vol. 23, no. 6, pp. 707–730, 2009.

[8] P. Conroy, K. Sage, and M. L. Ralph, "Improved vocabulary production after naming therapy in aphasia: can gains in picture naming generalise to connected speech?," *International Journal of Language and Communication Disorders*, vol. 44, no. 6, pp. 1036–1062, 2009.

[9] J. Marshall, T. Pring, and S. Chiat, "Verb retrieval and sentence production in aphasia," *Brain and Language*, vol. 63, no. 2, pp. 159–183, 1998.

[10] A. M. Raymer, M. Ciampitti, B. Holliway et al., "Semantic-phonologic treatment for noun and verb retrieval impairments in aphasia," *Neuropsychological Rehabilitation*, vol. 17, no. 2, pp. 244–270, 2007.

[11] A. M. Raymer and L. Rothi, "Clinical diagnosis and treatment of naming disorders," in *The Handbook of Adult Language Disorders: Integrating Cognitive Neuropsychology, Neurology and Rehabilitation*, A. E. Hillis, Ed., pp. 163–182, Psychology Press, New York and East Sussex, 2002.

[12] J. L. Wambaugh and M. Ferguson, "Application of semantic feature analysis to retrieval of action names in aphasia," *Journal of Rehabilitation Research and Development*, vol. 44, no. 3, pp. 381–394, 2007.

[13] F. Pulvermüller, "Brain mechanisms linking language and action," *Nature Reviews Neuroscience*, vol. 6, no. 7, pp. 576–582, 2005.

[14] F. Pulvermüller, "Meaning and the brain: the neurosemantics of referential, interactive, and combinatorial knowledge," *Journal of Neurolinguistics*, vol. 25, no. 5, pp. 423–459, 2012.

[15] E. Durand and A. I. Ansaldo, "Recovery from anomia following semantic feature analysis: therapy-induced neuroplasticity relies upon a circuit involving motor and language processing areas," *The Mental Lexicon*, vol. 8, no. 2, pp. 195–215, 2013.

[16] S. Bonifazi, F. Tomaiuolo, G. Altoè, M. Ceravolo, L. Provinciali, and P. Marangolo, "Action observation as a useful approach for enhancing recovery of verb production: new evidence from aphasia," *European Journal of Physical and Rehabilitation Medicine*, vol. 49, 2013.

[17] P. Marangolo, S. Bonifazi, F. Tomaiuolo et al., "Improving language without words: first evidence from aphasia," *Neuropsychologia*, vol. 48, no. 13, pp. 3824–3833, 2010.

[18] D. Ertelt, S. Small, A. Solodkin et al., "Action observation has a positive impact on rehabilitation of motor deficits after stroke," *NeuroImage*, vol. 36, pp. T164–T173, 2007.

[19] M. Franceschini, M. Agosti, A. Cantagallo, P. Sale, M. Mancuso, and G. Buccino, "Mirror neurons: action observation treatment as a tool in stroke rehabilitation," *European Journal of Physical and Rehabilitation Medicine*, vol. 46, no. 4, pp. 517–523, 2010.

[20] M. Franceschini, M. G. Ceravolo, M. Agosti et al., "Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial," *Neurorehabilitation and Neural Repair*, vol. 26, no. 5, pp. 456–462, 2012.

[21] M.-H. Zhu, J. Wang, X. D. Gu et al., "Effect of action observation therapy on daily activities and motor recovery in stroke patients," *International Journal of Nursing Sciences*, vol. 2, no. 3, pp. 279–282, 2015.

[22] S. Routhier, N. Bier, and J. Macoir, "The contrast between cueing and/or observation in therapy for verb retrieval in

post-stroke aphasia," *Journal of Communication Disorders*, vol. 54, pp. 43–55, 2015.

[23] M. Rose and G. Sussmilch, "The effects of semantic and gesture treatments on verb retrieval and verb use in aphasia," *Aphasiology*, vol. 22, no. 7-8, pp. 691–706, 2008.

[24] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[25] G. Rizzolatti and C. Sinigaglia, "The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations," *Nature Reviews Neuroscience*, vol. 11, no. 4, pp. 264–274, 2010.

[26] M. C. Corballis, "Mirror neurons and the evolution of language," *Brain and Language*, vol. 112, no. 1, pp. 25–35, 2010.

[27] M. Gentilucci and G. C. Campione, "From action to speech," in *Language and Action in Cognitive Neuroscience*, Y. Coello and A. Bartolo, Eds., pp. 59–79, Psychology press Taylor & Francis Group, London and New York, 2012.

[28] V. Gallese and G. Lakoff, "The brain's concepts: the role of the sensory-motor system in conceptual knowledge," *Cognitive Neuropsychology*, vol. 22, no. 3-4, pp. 455–479, 2005.

[29] E. Freud, D. C. Plaut, and M. Behrmann, "'What' is happening in the dorsal visual pathway," *Trends in Cognitive Sciences*, vol. 20, no. 10, pp. 773–784, 2016.

[30] M. A. Goodale, "Transforming vision into action," *Vision Research*, vol. 51, no. 13, pp. 1567–1587, 2011.

[31] R. D. McIntosh and T. Schenk, "Two visual streams for perception and action: current trends," *Neuropsychologia*, vol. 47, no. 6, pp. 1391–1396, 2009.

[32] M. A. Goodale and A. D. Milner, "Separate visual pathways for perception and action," *Trends in Neurosciences*, vol. 15, no. 1, pp. 20–25, 1992.

[33] S. Zipoli Caiani and G. Ferretti, "Semantic and pragmatic integration in vision for action," *Consciousness and Cognition*, vol. 48, pp. 40–54, 2017.

[34] P. Aravena, Y. Delevoye-Turrell, V. Deprez et al., "Grip force reveals the context sensitivity of language-induced motor activity during "action words" processing: evidence from sentential negation," *PLoS One*, vol. 7, no. 12, article e50287, 2012.

[35] L. Aziz-Zadeh, S. M. Wilson, G. Rizzolatti, and M. Iacoboni, "Congruent embodied representations for visually presented actions and linguistic phrases describing actions," *Current Biology*, vol. 16, no. 18, pp. 1818–1823, 2006.

[36] M. Bedny, A. Caramazza, A. Pascual-Leone, and R. Saxe, "Typical neural representations of action verbs develop without vision," *Cerebral Cortex*, vol. 22, no. 2, pp. 286–293, 2012.

[37] J. R. Binder, R. H. Desai, W. W. Graves, and L. L. Conant, "Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies," *Cerebral Cortex*, vol. 19, no. 12, pp. 2767–2796, 2009.

[38] V. Boulenger, O. Hauk, and F. Pulvermüller, "Grasping ideas with the motor system: semantic somatotopy in idiom comprehension," *Cerebral Cortex*, vol. 19, no. 8, pp. 1905–1914, 2009.

[39] G. Buccino, F. Lui, N. Canessa et al., "Neural circuits involved in the recognition of actions performed by nonconspecifics: an fMRI study," *Journal of Cognitive Neuroscience*, vol. 16, no. 1, pp. 114–126, 2004.

[40] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[41] L. Fernandino, L. L. Conant, J. R. Binder et al., "Parkinson's disease disrupts both automatic and controlled processing of action verbs," *Brain and Language*, vol. 127, no. 1, pp. 65–74, 2013.

[42] D. Jirak, M. M. Menz, G. Buccino, A. M. Borghi, and F. Binkofski, "Grasping language – a short story on embodiment," *Consciousness and Cognition*, vol. 19, no. 3, pp. 711–720, 2010.

[43] M. Tettamanti, G. Buccino, M. C. Saccuman et al., "Listening to action-related sentences activates fronto-parietal motor circuits," *Journal of Cognitive Neuroscience*, vol. 17, no. 2, pp. 273–281, 2005.

[44] P. Tremblay and S. L. Small, "From language comprehension to action understanding and back again," *Cerebral Cortex*, vol. 21, no. 5, pp. 1166–1177, 2011.

[45] J. Pearson, T. Naselaris, E. A. Holmes, and S. M. Kosslyn, "Mental imagery: functional mechanisms and clinical applications," *Trends in Cognitive Sciences*, vol. 19, no. 10, pp. 590–602, 2015.

[46] E. Gleichgerrcht, J. Fridriksson, C. Rorden, T. Nesland, R. Desai, and L. Bonilha, "Separate neural systems support representations for actions and objects during narrative speech in post-stroke aphasia," *NeuroImage: Clinical*, vol. 10, pp. 140–145, 2016.

[47] E. Maas, D. A. Robin, S. N. Austermann Hula et al., "Principles of motor learning in treatment of motor speech disorders," *American Journal of Speech-Language Pathology*, vol. 17, no. 3, pp. 277–298, 2008.

[48] E. L. Middleton, M. F. Schwartz, K. A. Rawson, H. Traut, and J. Verkuilen, "Towards a theory of learning for naming rehabilitation: retrieval practice and spacing effects," *Journal of Speech, Language, and Hearing Research*, vol. 59, no. 5, pp. 1111–1122, 2016.

[49] F. Pulvermüller and M. L. Berthier, "Aphasia therapy on a neuroscience basis," *Aphasiology*, vol. 22, no. 6, pp. 563–599, 2008.

[50] F. Pulvermüller and L. Fadiga, "Chapter 26 - brain language mechanisms built on action and perception," in *Neurobiology of Language*, G. Hickok and S. L. Small, Eds., Academic Press, San Diego, 2016.

[51] C. Hammelrath, *DVL 38: test de dénomination des verbes lexicaux en images*, Ortho éd, 1999.

[52] J. L. Barnay, G. Wauquiez, H. Y. Bonnin-Koang et al., "Feasibility of the Cognitive Assessment scale for Stroke Patients (CASP) vs. MMSE and MoCA in aphasic left hemispheric stroke patients," *Annals of Physical and Rehabilitation Medicine*, vol. 57, no. 6-7, pp. 422–435, 2014.

[53] T. H. Bak and J. R. Hodges, *Kissing and Dancing Test Sydney (Australia) Neuroscience Research Australia*, Neuroscience Research Australia NeuRA, 2003.

[54] J. Macoir, C. Beaudoin, J. Bluteau, O. Potvin, and M. A. Wilson, "TDQ-60–a color picture-naming test for adults and elderly people: validation and normalization data," *Aging, Neuropsychology, and Cognition*, vol. 24, pp. 1–14, 2017.

[55] B. L. Dabul, *Apraxia Battery for Adults*, Pro-ed, 2nd edition, 2000.

[56] C. Rorden, L. Bonilha, J. Fridriksson, B. Bender, and H.-O. Karnath, "Age-specific CT and MRI templates for

spatial normalization," *NeuroImage*, vol. 61, no. 4, pp. 957–965, 2012.

[57] P. Nachev, E. Coulthard, H. R. Jäger, C. Kennard, and M. Husain, "Enantiomorphic normalization of focally lesioned brains," *NeuroImage*, vol. 39, no. 3, pp. 1215–1226, 2008.

[58] M. Catani, D. K. Jones, and D. H. Ffytche, "Perisylvian language networks of the human brain," *Annals of Neurology*, vol. 57, no. 1, pp. 8–16, 2005.

[59] M. Goldrick and B. Rapp, "A restricted interaction account (RIA) of spoken word production: the best of both worlds," *Aphasiology*, vol. 16, no. 1-2, pp. 20–55, 2002.

[60] W. J. M. Levelt, "Spoken word production: a theory of lexical access," *Proceedings of the National Academy of Sciences*, vol. 98, no. 23, pp. 13464–13471, 2001.

[61] K. Marcotte, D. Adrover-Roig, B. Damien et al., "Therapy-induced neuroplasticity in chronic aphasia," *Neuropsychologia*, vol. 50, no. 8, pp. 1776–1786, 2012.

[62] G. Hickok and D. Poeppel, "Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language," *Cognition*, vol. 92, no. 1-2, pp. 67–99, 2004.

[63] K. Herholz, A. Thiel, K. Wienhard et al., "Individual functional anatomy of verb generation," *NeuroImage*, vol. 3, no. 3, pp. 185–194, 1996.

[64] S. Abrahams, L. H. Goldstein, A. Simmons et al., "Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses," *Human Brain Mapping*, vol. 20, no. 1, pp. 29–40, 2003.

[65] G. Rizzolatti, L. Fadiga, M. Matelli et al., "Localization of grasp representations in humans by PET: 1. Observation versus execution," *Experimental Brain Research*, vol. 111, no. 2, pp. 246–252, 1996.

[66] H. J. De Smet, P. Paquier, J. Verhoeven, and P. Mariën, "The cerebellum: its role in language and related cognitive and affective functions," *Brain and Language*, vol. 127, no. 3, pp. 334–342, 2013.

[67] P. Mariën, H. Ackermann, M. Adamaszek et al., "Consensus paper: language and the cerebellum: an ongoing enigma," *The Cerebellum*, vol. 13, no. 3, pp. 386–410, 2014.

[68] M. Frings, A. Dimitrova, C. F. Schorn et al., "Cerebellar involvement in verb generation: an fMRI study," *Neuroscience Letters*, vol. 409, no. 1, pp. 19–23, 2006.

[69] M. Bassolino, M. Campanella, M. Bove, T. Pozzo, and L. Fadiga, "Training the motor cortex by observing the actions of others during immobilization," *Cerebral Cortex*, vol. 24, no. 12, pp. 3268–3276, 2014.

[70] M. Bassolino, G. Sandini, and T. Pozzo, "Activating the motor system through action observation: is this an efficient approach in adults and children?," *Developmental Medicine and Child Neurology*, vol. 57, pp. 42–45, 2015.

[71] A. Bisio, L. Avanzino, N. Gueugneau, T. Pozzo, P. Ruggeri, and M. Bove, "Observing and perceiving: a combined approach to induce plasticity in human motor cortex," *Clinical Neurophysiology*, vol. 126, no. 6, pp. 1212–1220, 2015.

[72] R. Gentili, C. Papaxanthis, and T. Pozzo, "Improvement and generalization of arm motor performance through motor imagery practice," *Neuroscience*, vol. 137, no. 3, pp. 761–772, 2006.

[73] M. Meinzer, P. M. Beeson, S. Cappa et al., "Neuroimaging in aphasia treatment research: consensus and practical guidelines for data analysis," *NeuroImage*, vol. 73, pp. 215–224, 2013.

[74] M. Meinzer and C. Breitenstein, "Functional imaging studies of treatment-induced recovery in chronic aphasia," *Aphasiology*, vol. 22, no. 12, pp. 1251–1268, 2008.

[75] D. Saur, R. Lange, A. Baumgaertner et al., "Dynamics of language reorganization after stroke," *Brain*, vol. 129, no. 6, pp. 1371–1384, 2006.

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Research Article

Dance Training Shapes Action Perception and Its Neural Implementation within the Young and Older Adult Brain

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How we perceive others in action is shaped by our prior experience. Many factors influence brain responses when observing others in action, including training in a particular physical skill, such as sport or dance, and also general development and aging processes. Here, we investigate how learning a complex motor skill shapes neural and behavioural responses among a dance-naïve sample of 20 young and 19 older adults. Across four days, participants physically rehearsed one set of dance sequences, observed a second set, and a third set remained untrained. Functional MRI was obtained prior to and immediately following training. Participants' behavioural performance on motor and visual tasks improved across the training period, with younger adults showing steeper performance gains than older adults. At the brain level, both age groups demonstrated decreased sensorimotor cortical engagement after physical training, with younger adults showing more pronounced decreases in inferior parietal activity compared to older adults. Neural decoding results demonstrate that among both age groups, visual and motor regions contain experience-specific representations of new motor learning. By combining behavioural measures of performance with univariate and multivariate measures of brain activity, we can start to build a more complete picture of age-related changes in experience-dependent plasticity.

1. Introduction

Throughout the lifespan, when learning a new skill such as riding a bicycle or dancing the tango, we benefit from not only physically practicing the new skill but also from watching others who can already perform that skill. Our ability to learn by physical practice as well as by observation is a key ingredient for acquiring new motor skills and is thus essential for us to survive and thrive within a social world. For over a century, it has been suggested that actions learned by physical or observational practice are represented within common cognitive and neural structures [1]. However, behavioural and brain-based investigations to date have not satisfactorily examined the extent to which this is actually the case. Moreover, how the aging process impacts our ability to learn via physical practice and observation remain underexplored. Such a lack of knowledge means that critical questions for understanding how best to facilitate new learning in educational and therapeutic contexts are ripe for exploration.

Prior work demonstrates the existence of an action observation network (AON), comprising sensorimotor brain regions including premotor, parietal, and occipitotemporal cortices [2–4]. These brain regions have been shown to be engaged when watching others in action and respond more robustly when observing actions that have been physically practiced [5–9] or visually experienced [10–14], compared with similar actions with which participants have had no prior experience.

Since the original work establishing the functionality of the action observation network, a rich literature examining

how laboratory-based complex action training interventions shape the relationship between action and perception has emerged [5, 15–22]. As mentioned above, what many of these studies demonstrate is that the more familiar an action is, the stronger the response is within core AON regions [5, 6, 18, 23, 24]. On the other hand, an increasing number of studies report findings demonstrating that AON activity does not *necessarily* follow this linear trend of increasing engagement with increasing familiarity [17, 25–28]. These studies demonstrate equivalent or greater AON activity when participants observe *less* familiar actions (compared to more familiar actions), which is often interpreted as increases in neural efficiency [29–32].

Such marked differences in how the response amplitude of sensorimotor cortices changes after learning have been well documented in the motor control literature more broadly (see [33–35] for reviews). This has led to the suggestion that human neuroimaging investigations of sensorimotor learning are limited by the blunted sensitivity of traditional magnitude-based blood oxygen level-dependent (BOLD) approaches [36, 37]. An increasing number of studies are moving beyond univariate approaches of examining sensorimotor learning in the human brain, by attempting to evaluate *representations* of learning, as evidenced by more subtle modulations of the voxel-by-voxel activity patterns within the same area of cortex (e.g., [38, 39]). The ability to more closely evaluate learning representations is made possible using multivoxel pattern analyses (MVPA), an analytic approach we use in the present study to not only address how complex action learning shapes engagement of sensorimotor cortices but also how the same complex action training paradigm shapes brain responses within both young and older adults. Through combining training interventions with the increased analytical sophistication of MVPA, the present study explores how physical and observational learning impacts behaviour and the corresponding neural representations of actions.

With advancing age, sensorimotor and cognitive resources needed for learning a new motor skill decline and the efficacy of the matching process between observed and executed actions appear to be compromised [40]. However, this is modulated by the type of action observed. Evidence from studies investigating age-related changes in biological motion perception, motor imagery, and action observation suggests that forming an internal action representation may remain relatively preserved with advancing age for simple movement sequences, whereas it appears to become more imprecise in conditions with higher task complexity or when flexible adaptations to changes in the environment are required [41–43]. Such changes in behavioral performance are typically accompanied by a loss of neural selectivity in relevant regions of the aging brain [44, 45]. Overactivations, particularly in sensory cortices, are frequently reported leading to the assumption that older adults might be less adept at embodying new actions compared to younger adults [46, 47]. Thus, their ability to form an action representation based on physical and observational training might be limited, particularly compared to younger adults.

However, it remains unknown how learning complex whole-body actions, such as those that might be required in a fitness or social dance class, shapes behavioural and brain responses in young compared to older adults. In the present study, we aimed to explore this question by manipulating the type of sensorimotor experience that young and older adults received with dance sequences to determine how experience shapes responses at behavioural and brain levels. We attempt to address three main questions: (i) How do different types of training influence complex action performance among young compared to older adults? (ii) How do different types of training shape brain responses at a global level during action observation among young compared to older adults? (iii) How does physical training shape brain responses at the level of action representations? To address the first two questions, we implemented similar behavioural and univariate functional magnetic neuroimaging (fMRI) procedures reported in previous training studies [3, 18, 48] and studies that have compared the impact of complex action experience among young and older adults [43, 49]. To address the third aim, we used multivariate decoding procedures [50] to determine whether distributed voxel activity could be used to discriminate between patterns associated with viewing physically trained and untrained movements in the brains of young compared to older adult participants.

2. Methods

2.1. Participants. Twenty-three physically and neurologically healthy young adults were recruited from the Bangor University student population, and nineteen physically and neurologically healthy older adults were recruited from the local community. Older adults were screened for any past medical history, and we excluded any participants who reported any prior neurological diseases or use of medication that might alter their performance during the task or fMRI scanning. In addition, they were asked to complete the MMSE [51] to assess any cognitive impairment (M = 28.9, range = 26.5–30.0, maximum score: 30) and an fMRI safety screening questionnaire. The older adult participants were also invited to perform one dance sequence from the Dance Central Kinect Game before the study began, to ensure they felt comfortable with the technical equipment and were able to take part in all the procedures that would be required in the full study. Only those older adults who enjoyed this experience and were eager to take part after this prestudy trial were selected to take part. All participants (young and older adults) were dance naïve, meaning they had limited or no experience performing or observing dance, and none reported prior experience playing dance video games. All participants were right-handed or ambidextrous (ranging from moderately right-handed to strong right-handed; young adults M = 60.78, SD = 22.20; older adults M = 86.58, SD = 20.91, range 33–100), as assessed by the Edinburgh Handedness Inventory [52]. Two younger adult participants were excluded from the final sample due to excessive head motion artefacts whilst undergoing fMRI scanning, and one younger adult dropped out of the study half way through the training phase and thus was excluded due to having an

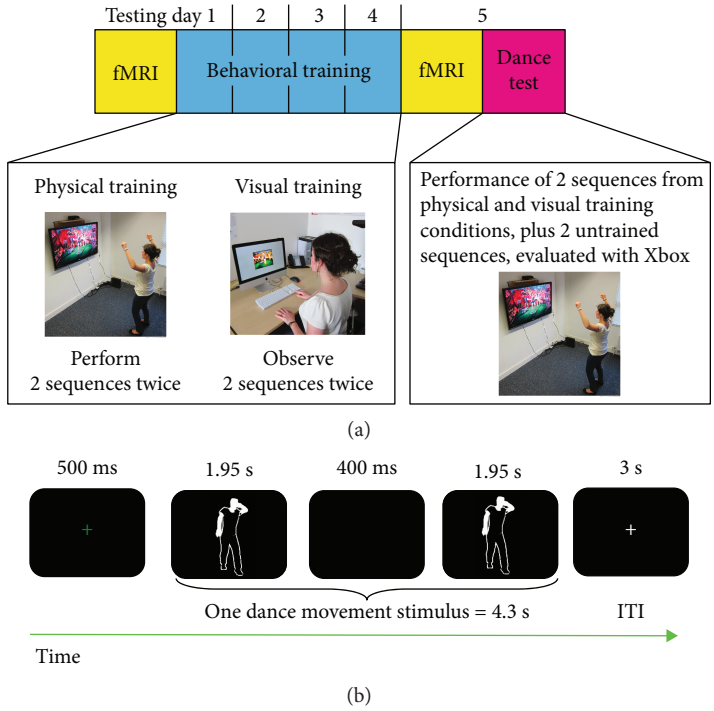

Figure 1: (a) Overview of experimental procedures. Participants of both age group underwent the exact same procedure. First they underwent a scanning session on day 1 and then started the behavioural training on that same day and the following 3 days. During each training day (days 1–4), participants physically trained with 2 long sequences and visually trained with other long sequences. Two other long sequences remained untrained. On day 5, participants underwent the same scanning session as on day 1. After scanning on day 5, participants had to physically perform all the long sequences (physically, visually trained, and untrained). (b) Schematic of an example fMRI trial. Each typical fMRI trial consisted of a 500 ms fixation cross, one dance movement stimulus lasting for 4.3 s, and an intertrial interval (ITI) of 3 s.

incomplete dataset. The final sample comprised 20 younger participants (12 females) with a mean age of 19.5 years (SD = 1.54 years, range 18–23 years) and 19 older participants (11 females) with a mean age of 63.6 years (SD = 4.4 years, range 55–69 years). All participants provided a written informed consent prior to taking part in any study procedures and were reimbursed for their involvement with either cash or course credit. The Bangor University School of Psychology Research Ethics Committee approved all components of this study (protocol number 2014-13123-A12806).

2.2. Stimuli and Apparatus. Six dance sequences from the dance game "Dance Central 2" (Harmonix Music Systems, 2011) for the Xbox 360 Kinect™ console were chosen that featured gender-neutral dance movements. The six chosen dance sequences were specifically selected so as to contain no overlapping dance moves between songs (i.e., each move was uniquely associated to one song/dance sequence). Each dance sequence was set to a popular song (e.g., *Like a G6* by Far East Movement or *What is love* by Haddaway) and varied in length from 2:20 to 2:29 minutes (average length = 2.22 s; SD = 10 s) and in tempo between 105 and 129 bpm (average tempo = 118.83 bpm; SD = 11.21). To focus participants' attention on the avatar whose moves they were learning, the same background setting was selected for all dance videos, which had a minimal amount of extraneous movement. The difficulty of the dance sequences (complexity and amplitude of dance movements) was set to a minimum level to ensure participants across both age groups could perform them to some degree from the very first training day but would still have ample room for improvement. The six dance sequences were paired to create three groups whose composition was matched for number and complexity of specific dance movements, as well as tempo. Each pair of sequences was assigned to one of the three training conditions: physical training, visual training, and no experience/untrained (Figure 1). A total of three different training groups were assembled, meaning that each pair of dance sequences was trained in all three training conditions across participants.

Animated silhouettes from the game depicting individual movements from the preselected dance sequences were captured and used as stimuli during both pre- and post-training fMRI sessions. The use of silhouettes, instead of original game footage, was specifically chosen to reduce visual cues associated with the original training context and to focus attention on the movements alone [48]. In this way, brain activity recorded when observing these pared-down dance movements should be more attributable to sensorimotor experience. 18 short animated silhouettes dance segments without music were extracted using iMovie '11 (Apple Inc.) and edited using Adobe Premiere Pro (Version 7.1 for Microsoft Windows 7), three sequences from each full dance sequence. The resultant 18 stimuli were matched for length to all be 1.95 seconds. Each stimulus was edited so that it featured one complete, coherent dance move involving

whole-body motion and significant spatial displacement of the limbs (cf. [53]). All stimuli were novel to the participants during the pre-training fMRI scan.

2.3. Behavioural Training Procedure and Analysis. Both age groups underwent identical training and testing procedures. Participants were randomly assigned to one of three training groups in which they experienced the same pairs of sequences assigned to the two training conditions (place between the pre- and post-training fMRI scanning sessions) (Figure 1). For each training session, participants completed physical and visual training on the set of sequences to which they had been randomly assigned. Participants physically practiced the same two sequences twice (once with a female and once with a male avatar) and observed two different sequences twice. The order in which participants completed the training conditions was counterbalanced within and between participants across training days. Each training session lasted approximately 30 minutes.

2.3.1. Physical Training. For sequences of which participants physically practiced, they stood approximately 2 meters away from a 52″ Sharp flat screen television mounted on the wall in front of them. Participants' task was to mirror the dance movements of the avatar in the *Dance Central 2* Xbox 360 game as closely as possible and concentrate on improving their performance during subsequent sessions. The Kinect motion capture system compared participants' movements to the avatar's movements and assigned a score based on accuracy of mirroring the avatar. The Kinect's scoring system is based on how closely participants match the temporal and spatial features of the avatar's movements, including the avatar's movement amplitude. As the Kinect is a closed system consumer product, further details about how scores are assigned are not available. Similar procedures using this system were successfully applied in previous studies measuring the neural effects of dance training in young adults (see also [18, 48, 54, 55]). The game provides on-screen feedback about performance accuracy in the form of a final score after each sequence. However, to make the physical training condition as comparable as possible to the visual training condition (where no performance feedback was given), we covered the side margin of the TV screen (where the score is displayed after performance) so that participants were not aware of their dance scores after performing each sequence. These participant dance scores were recorded by the researcher and used as an objective measure of dance performance ability for the behavioural analyses.

The four overall dance scores participants received each day for the dance sequences in the physical training condition were averaged so that each participant had a single score representing dance performance for each training day. A mixed ANOVA with training day assigned as a within-subjects factor with four levels (training days 1–4), and age group as between-subject factor (young adults, older adults) was conducted on these scores in order to determine how performance across consecutive days of training compared between age groups. Additionally, we performed a repeated measure ANOVA for each age group separately to confirm the training manipulation worked and that physical performance increased across the daily training sessions.

2.3.2. Visual Training. For the sequences for which participants acquired visual experience, they sat comfortably in front of a computer running Psychophysics Toolbox 3 in MATLAB R2010a (MathWorks Inc.), which presented the full dance videos. Each video was shown twice, once for each avatar (male, female), in a random order. The dimensions of the dance videos were 640×480 mm, which reflected perceptually similar scaling to the physical training condition. As well as visual information, participants listened to the soundtrack that accompanied each sequence via the computer speakers. Participants were instructed to pay close attention to the dance sequences and were told that they would have to perform the sequences at the end of the week, so they should try to learn the movements as best as they could. To test that they were paying close attention, at the end of each music video, ten short dance segments (five from the videos they had just watched) were displayed, without music, each followed by the question "Did you see this movement in the video you just watched?". Participants had to respond "yes" or "no" using the keyboard arrow keys. All test videos were presented silently (as the task would have been too easy if the accompanying soundtracks were also presented).

An accuracy score for each participant for each of the four days of training was calculated based on their performance on this task. Similar analyses done for the physical dance scores were performed on the visual accuracy scores.

2.3.3. Post-Training Performance Assessment. On the final day of the study (day 5), participants returned to the laboratory to perform the four full dance sequences used in training (two physically trained sequences and two visually trained sequences) as well as the two untrained sequences (segments that they had observed during both fMRI sessions only). The test followed the same paradigm as the physical training phase of the study: participants physically performed the dance sequences from all six songs, mirroring the avatar's dance movements as closely as possible whilst the Kinect system captured and scored their movements. The six sequences were randomised and balanced for the gender of the avatar. Objective performance scores were obtained in the same way as for the physical training condition.

Raw scores from both exemplars from each training category were averaged within training conditions to produce an average score per participant for each of the three test conditions. We first performed a mixed-design ANOVA using an age group as a between-groups factor to compare dance performance between young and older adults on day 5. To further investigate performance in each age group independently, we next performed repeated-measures ANOVAs on these scores to investigate the impact of different kinds of experience on physical performance. Pairwise comparisons (Bonferroni corrected for multiple comparisons, with adjusted alpha levels of 0.025) were subsequently evaluated to investigate differences between conditions in more detail.

Degrees of freedom reflect the Greenhouse-Geisser correction where sphericity has been violated.

2.3.4. Training Modality Categorization Task. On day 5, immediately following the post-training fMRI scan and before the post-training performance assessment, participants performed a short control task, similar to the one in Sumanapala et al. [48]. In this task, participants watched again each dancing silhouette stimulus they observed during scanning (18 in total; 6 per training category). After each stimulus, participants were asked to categorize the movement as being either "physically trained," "visually trained," or "untrained", using the 1, 2, and 3 keys on a computer keyboard. Answers were untimed. Accuracy scores for each training condition were computed for each age group.

2.4. Neuroimaging Procedure. Each participant completed one fMRI session prior to the training procedures and an identical session immediately following the four days of training (Figure 1(a)). Participants completed 6 runs within each scanning session, lasting an average of 9 min and containing 60 trials each. In each run, participants watched three times 18 stimuli featuring short dance segments taken from the three training conditions (physically trained, visually trained, and untrained; 6 stimuli per training condition). Unlike the video footage used during training, the videos used during scanning featured the silhouette of an avatar performing each dance movement, which lasted 1.95 seconds. Each individual dance movement was presented twice in a row with a 400 ms black screen between each presentation (see Figure 1(b)). Each stimulus was preceded by a green fixation cross presented for 500 milliseconds, to announce the next trial. Each dance stimulus was followed by a fixation cross presented for a fixed duration of 3 seconds. After this, the next trial started. Finally, six additional video stimuli (featuring dance movements that were not part of the full set of 18 videos taken from the training conditions—these dance movements were never encountered outside of scanning) were included for attentional control questions. After each of these six test trials, participants were asked a question that required a yes or no response (button responses were counterbalanced across participants, with an index finger press corresponding to a yes response and a middle finger press corresponding to a no response for half of the participants and the inverse response schedule for the other half of participants). Participants had 4 seconds to provide a response via a four-button fibre optic response box placed on their lap on which they rested the index finger and middle fingers of both hands over the buttons. The question that appeared was randomly selected to be one of the following four: "Did the dancer place at least one arm above his head?," "Did the dancer reproduced the same movement on the left and on the right?," "Did the dancer take a step forward?," or "Did the dancer move his legs?." These questions appeared in a random order and were designed to ensure participants paid full attention to the dancer's movement in each stimulus. Each test trial was followed by a 12-second fixation cross that served as implicit baseline. Participants were familiarized outside the scanner prior to the pre-training scan with all features of the experiment and what they would be asked to do whilst in the scanner.

Stimulus presentation and response recording was done via a Mac desktop computer running MATLAB R2013a (MathWorks, Natick, MA) and Psychophysics Toolbox 3 [56–58]. The video stimuli were presented on a 24″ LCD BOLDscreen (Cambridge Research Systems), which was visible to participants via a mirror mounted on the head coil. The experiment was carried out in a 3 T Philips MRI scanner using a SENSE phased-array 32-channel head coil. For functional imaging, a single-shot echo planar imaging (EPI) sequence was used (T2∗-weighted, gradient echo sequence; echo time TE = 30 ms; flip angle, 90°). The scanning parameters were set as follows: repetition time TR = 2500 ms; 38 transverse slices; voxel dimensions, 2.3×2.3 mm with voxel slice thickness = 3 mm; slice gap = 0.1 mm; field of view, $224 \times 224 \times 118$ mm; matrix size, 96×95 mm $\times$ 38 slices; and anterior-posterior phase encoding. Parameters for T1-weighted anatomical scans were $240 \times 224 \times 175$ mm; voxel dimensions, $1 \times 1 \times 1$ mm; TR = 12 ms; TE = 3.5 ms; and flip angle = 8°. All the scans were collected in an ascending order. For each run of each scanning session, the first two brain volumes were discarded to reduce saturation effects. 224 volumes per functional run were collected for each participant.

2.5. fMRI Data Analysis

2.5.1. Univariate Analyses. Neuroimaging data from each scanning session (before and after training) were preprocessed together to facilitate the construction of first-level design matrices including data from both scanning sessions. When there are several sessions, data can be either preprocessed separately or together. We decided to combine neuroimaging data from both scan sessions at the first level of analyses, for several reasons: (i) this leads to both days sharing the same implicit baseline, subsequently reducing the likelihood of results emerging simply due to differences between the two scanning sessions that are not result of the training manipulation, per se; (ii) the smoothness estimation on the data should be better with more data points, thereby reducing the threshold for multiple comparison correction using random field theory; and (iii) this preprocessing method was necessary for the subsequent RSA analyses.

Using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK), data were realigned and unwarped, coregistered to the individual participants' T1 scans, and normalized to the Montreal Neurological Institute (MNI) template. Slice timing correction was performed after realignment, and all images were finally spatially smoothed using an 8 mm FWHM Gaussian kernel. A design matrix was fitted for each participant with a high-pass filter cut-off of 128 s, with each type of dance video (physical training, visual training, and untrained conditions), as well as attentional control videos and button presses associated, modelled together as a boxcar function convolved with the hemodynamic response function with temporal and dispersion derivatives. Additionally, participant-specific movement parameters were modelled as separate regressors of no interest.

The univariate analyses were designed to achieve three aims:

(i) To test both direct matching and neural efficiency accounts of experience-dependent plasticity, we first examined both increases and decreases in training-related brain activity among young and older adults separately. The most rigorous test of these effects involves evaluating scanning session by training experience interactions (i.e., to assess physical training experience, e.g., this would involve contrasting physical training > untrained on the post-training scan session compared to the pre-training scan session and the inverse (e.g., [18, 27, 59])). However, when evaluating these analyses in both directions, for physical and visual training experience separately, and among young and older adults independently, no brain regions survived a $p < 0.05_{\text{FWEcorrected}}$ threshold. This is not necessarily a cause for concern, as the type of manipulation and stimuli we have used in the present study could reasonably be expected to have subtle effects that do not meet the most stringent imaging threshold criteria (see, e.g., [3, 16]).

In order to probe more subtle influences of our training manipulation and visual task in the scanner, we also evaluate direct contrasts comparing each training condition to itself in the pre- and post-training scans. We therefore examined brain regions that showed either increases or decreases in BOLD responses after compared to before training, for physical and visual training separately. These analyses were performed at the whole brain level while focusing on activations that survived a FWE-corrected threshold of $p < 0.001$ at the cluster level. This was achieved by contrasting pre- and post-training brain activity separately for dancing silhouettes that were associated with physical training or visual training at the 1st level for each participant and then conducting one-sample t-tests at the group level. The identical procedures were repeated for the young and older adults' data.

(ii) The second set of univariate analyses directly compared neural responses between young and older adults from the physical training condition. We focused on this training condition in particular as this was the most intensive type of training where we would reasonably expect the most robust effects to emerge [16, 18, 39]. This was achieved by using a two-sample t-test at the group level, which compared the 1st-level contrasts evaluating physical training before and after training, among young adults compared to older adults. To avoid any contamination of brain findings due to differences in physical performance scores/abilities between young and older adults, physical performance gains (calculated as the difference between physical performance scores on day 5 – day 1) were included as a covariate.

(iii) Finally, similarities between young and older adults when observing sequences that have been physically trained were examined through a customised conjunction analysis based on that reported in [18]. This analysis examined brain regions that showed increases or decreases after four days of physical training when both young adults and older adults observed these sequences after physical training compared to pre-training.

2.5.2. Multivariate Analyses. After evaluating magnitude-based univariate analyses, we next performed multivariate analyses to ascertain with finer detail on how sensorimotor training experience shapes neural representations during action observation among young and older adults. Specifically, this approach enabled us to explore how young and older brains distinguish between different types of training experience. Using The Decoding Toolbox scripts [50], we performed whole-brain searchlight decoding to assess the degree of outcome adaptation in local fMRI patterns surrounding each voxel (radius 8 mm) for each participant using the unsmoothed, realigned, and normalized imaging data.

This procedure involves extracting voxel pattern information from individual subject beta values generated during first-level preprocessing within SPM. Pattern information is specifically extracted from these beta values using support vector machine (SVM) algorithms that maximise mathematically defined representational distances within a shared coordinate space between different classes of data [50, 60]. To achieve this distinction, a data set is usually split into "training sets" and "test sets" before being introduced to SVM pattern recognition algorithms for classification. The algorithms are trained to identify patterns of data associated with specific classes within a training set before being tested on their ability to identify class membership on an unknown "test" set. Within neuroimaging, training sets and test sets can be shuffled in a leave-one-out cross-validation procedure [61], which limits the likelihood that spurious noise within specific subsets of data may lead to biases in pattern classification accuracy.

Following this, we implemented GLM analyses similar to the ones described for the univariate analyses. This involved modelling each training condition separately (physical, visual, and untrained) as well as attentional control videos and button presses. Also included in this model were participant-specific movement parameters, modelled as separate regressors of no interest. Physical and untrained events served as inputs for the classifiers and were labelled according to the model. Data were then split into different training and testing subsets depending on the model, using in turn each separate run as training and test runs [62]. Classification accuracy values (corresponding to observed prediction accuracy minus chance prediction for each voxel, with chance being 50%) for each analysis were entered into second-level t-tests for group-level analysis on a voxel-by-voxel basis. We decided to take "to be physically trained" and "to remain

untrained" sequences as input for the classifiers, as previous literature [17, 39] documents that the most robust differences emerge after physical training, a finding corroborated by the univariate analyses from this study as well.

The multivariate analyses were designed to achieve two distinct aims:

(i) The first set of analyses is aimed at identifying brain regions that can distinguish between physical and untrained movement sequences after training compared to before training, among young and older adults separately. Naturally, we would predict this between-category classification accuracy to be better overall after training compared to before training, when all stimuli were equally unfamiliar. This was achieved by running the searchlight decoding scripts on the 1st-level data from pre-training and post-training scans separately, taking as the two classifiers the "physically trained" movement sequences and the "untrained" movement sequences, and then running paired-sample t-tests at the group level, separately for young and older adults.

(ii) The aim of the second set of analyses was to compare classification accuracies between the two age groups. We were particularly interested in accuracy to distinguish between physically trained and untrained sequences after physical training (which entails examination of the post-training scan data only). To achieve this, we first ran a separate whole-brain decoding analysis to determine which brain regions distinguish between physically trained and untrained sequences after training, separately for each age group. The results of this analysis for both age groups are presented in Supplementary Table 1. Then, contrasts from post-training classification for young and older adults were entered into a two-sample t-test. Finally, we explored which regions in young and older adults could similarly distinguish between physically trained and untrained movements after training by running a conjunction analysis, similarly to the one done for the univariate analysis above (and in [18]).

3. Results

3.1. Behavioural Results

3.1.1. Physical and Visual Training. For each participant, physical performance was assessed each day by averaging performance scores across both dance sequences assigned to the physical training condition (Figure 2(a)). When evaluating young and older adults' physical performance across days of training, a main effect of training day was observed ($F_{(2.086,75.088)} = 79.476$, $p < 0.001$, $\eta_p^2 = 0.688$) as well as an interaction between age group and performance across days, with younger adults performing better than older adults ($F_{(2.086,75.088)} = 14.320$, $p < 0.001$, $\eta_p^2 = 0.285$). In both age groups, a main effect of training day was observed whereby physical performance significantly improved across the four days of training (young adults: $F_{(2.026,36.47)} = 50.218$, $p < 0.001$, $\eta_p^2 = 0.736$; older adults: $F_{(3,54)} = 33.417$, $p < 0.001$, $\eta_p^2 = 0.748$). Pairwise comparisons indicate that significant differences were observed between all possible pairs of days (young adults: day 1 versus day 2: $t_{(18)} = -5.430$, $p < 0.001$; day 2 versus day 3: $t_{(18)} = -3.960$, $p = 0.001$; and day 3 versus day 4: $t_{(18)} = -3.375$, $p = 0.003$; older adults: day 1 versus day 2: $t_{(18)} = -5.225$, $p < 0.001$; day 2 versus day 3: $t_{(18)} = -2.981$, $p = 0.008$; and day 3 versus day 4: $t_{(19)} = -3.375$, $p = 0.003$).

Participants' performance on the visual training task was assessed through a movement recognition task after observing two different sequences (Figure 2(b)). A main effect of visual training was found across groups ($F_{(2.311,83.201)} = 17.224$, $p < 0.001$, $\eta_p^2 = 0.324$); however, no interaction emerged between training scores and age group, yielding no differences in the visual training manipulation among young and older adults ($F_{(2.311,83.201)} = 1.376$, $p = 0.258$, $\eta_p^2 = 0.037$). Average response accuracy appeared to improve across the four days of training for both age groups (young adults: $F_{(1.799,32.376)} = 5.846$, $p = 0.008$, $\eta_p^2 = 0.245$; older adults: $F_{(3,54)} = 11.856$, $p < 0.001$, $\eta_p^2 = 0.397$), indicating that participants were consistently able to recognize movements that had appeared in the visually trained videos. This effect was driven by a significant improvement from day 1 to day 2 (young adults: $t_{(18)} = -2.851$, $p = 0.011$; older adults: $t_{(18)} = -4.237$, $p < 0.001$) and no further significant improvements between any other pairs of consecutive days (all p values > 0.05: young adults: day 2 versus day 3: $t_{(18)} = -0.498$, $p = 0.624$; day 3 versus day 4: $t_{(19)} = -1.299$, $p = 0.210$; older adults: day 2 versus day 3: $t_{(18)} = 0$, $p = 1$; day 3 versus day 4: $t_{(18)} = -0.137$, $p = 0.893$). This suggests that the performance level of participants in both age groups reached ceiling after the second day of training.

3.1.2. Physical Performance on Day 5. On the final day of testing, after the second fMRI session was completed, participants were asked to perform all six dance sequences (two from each training category: physically trained, visually trained, and untrained conditions) in order to generate an objective measure of their ability to perform each of the dance movements they observed during both fMRI sessions and assess the impact of differentiated sensorimotor experience on motor performance (Figure 2(c)).

A main effect of training type was observed across groups ($F_{(1.684,62.307)} = 46.048$, $p < 0.001$, $\eta_p^2 = 0.554$) as well as an interaction between age group and training condition ($F_{(1.684,62.307)} = 8.139$, $p = 0.001$, $\eta_p^2 = 0.180$), and a main effect of age confirming that young adults performed better overall than older adults ($F_{(1,37)} = 15.013$, $p < 0.001$, $\eta_p^2 = 0.289$). A one-way ANOVA ran within each age group separately revealed a main effect of training type on dance performance in both groups (young adults: $F_{(2,38)} = 40.802$, $p < 0.001$, $\eta_p^2 = 0.682$; older adults: $F_{(2,36)} = 9.284$, $p = 0.001$,

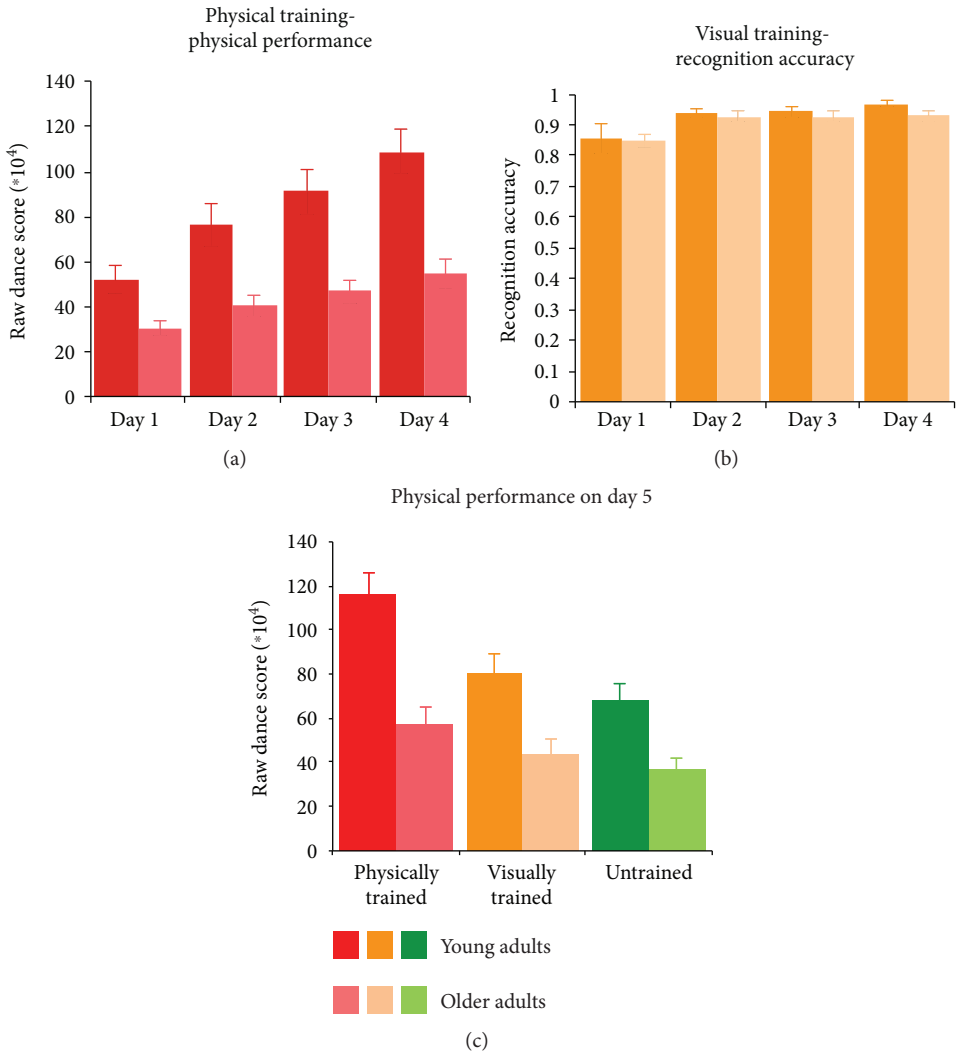

Figure 2: Training performances for both age groups. (a) Physical performance across the 4 consecutive days of physical training, for both younger (bright red) and older adults (pale red). (b) Recognition accuracy after each day of visual training, for both younger (bright orange) and older adults (pale orange). (c) Average physical performance on day 5, for each training condition (physical, visual, and untrained sequences), for both younger (darker bars) and older adults (lighter bars).

$\eta_p^2 = 0.340$). Pairwise comparisons indicate that physically trained sequences were performed significantly better than visually trained or untrained sequences, among both young and older adults (young adults: physically versus visually trained: $t_{(19)} = 7.556$, $p < 0.001$; physically trained versus untrained: $t_{(19)} = 7.251$, $p < 0.001$; older adults: physically versus visually trained: $t_{(18)} = 3.275$, $p = 0.008$; physically trained versus untrained: $t_{(18)} = 3.551$, $p = 0.004$). Differences in performance between observed and untrained sequences did not reach significance, with the Bonferroni-corrected alpha level of 0.025 (young adults: $t_{(19)} = 2.331$, $p = 0.031$; older adults: $t_{(18)} = 1.613$, $p = 0.124$).

3.1.3. Training Modality Categorization Task Performance. As a follow-up task, immediately following the post-training scan on day 5 of the study, participants were asked to watch each silhouette stimulus again (6 per training condition) and to categorize each stimulus as either being physically trained, visually trained, or untrained (see Supplementary Figure 1). Overall, young adults were better than older adults in identifying the training category to which each stimulus belonged ($F_{(1,36)} = 65.560$, $p < 0.001$). Moreover, we observed a main effect of the training type ($F_{(2,56.315)} = 25.501$, $p < 0.001$) and a nonsignificant trend towards an interaction between training category and age group ($F_{(2,56.315)} = 3.093$, $p = 0.065$). This marginal interaction suggests that older adults are overall not performing poorly at recognizing the training category for those videos that have been physically or visually trained (all above chance level). However, they do perform particularly poorly at categorizing the untrained videos (categorizing them as trained in 79% of cases). It is to note that this task was not designed to definitively determine how well participants can match specific movements with a prior training condition (as was the aim in [48]), as participants only performed a total of 18 trials in this follow-up test (one trial for each stimulus). However, this exploratory follow-up task was designed to give us an

indication of how well young and older adults can explicitly categorize the training condition associated with the different moves they observed in the scanner.

3.2. Effect of Sensorimotor Training among Young and Older Adults at the Whole Brain Level. Our first neuroimaging objective was to examine the effects of physical and visual training on whole brain activity. We did this first within each age group separately and then comparing young with older adults. As a reminder, we always evaluated contrasts to explore both increases and decreases in BOLD responses after training (comparing post and pre-training scans in both directions).

All of the following analyses were run with both days modelled in the same design matrix at the 1st level (and pre-processed together). All contrasts were evaluated at $p_{\text{unc}} < 0.001$, $k = 10$ voxels, and here, we focus on those results that survive correction of $p_{\text{FWEcorr}} < 0.05$ at the cluster level.

3.2.1. Brain Regions Involved in Physical and Visual Learning in Younger Adults

(1) Effects of Physical Training: Younger Adults. Among young adults, the observation of body movements after physical training compared to before (post-training > pre-training) did not yield any significant increases in neural activity. However, this same contrast did reveal several brain regions that demonstrated a decreased response after training, including areas associated with sensorimotor processing, such as the left paracentral lobule and postcentral gyrus and right precentral gyrus and inferior temporal gyrus. In addition, the amygdala and middle occipital gyrus also demonstrated decreased response amplitude when observing those movements that had been physically trained (Table 1(a)).

(2) Effects of Visual Training: Younger Adults. Among younger adults, the observation of body movements encountered after visual training compared to before did not lead to any significant increases in activation. In comparison, several brain regions in the right hemisphere showed a marked decrease in response amplitude after four days of visual training, including the fusiform gyrus, postcentral gyrus, and middle temporal gyrus (Table 1(b)).

3.2.2. Brain Regions Involved in Physical and Visual Learning in Older Adults

(1) Physical Training: Older Adults. Among older adults, the observation of body movements after physical training compared to before physical training resulted in increased activation in the right precuneus, and activity decreases within the right superior and inferior parietal lobules (SPL and IPL) and the right thalamus (Table 2(a)).

(2) Visual Training: Older Adults. In older adults, the observation of body movements after visual training compared to before four days of visual training resulted in an increase of activation of the right precuneus, similarly than after physical training but with no significant decrease of activity in any region (Table 2(b)).

3.2.3. Differences and Similarities between Age Groups, by Training Experience

(1) Differences between Young and Older Adults. In order to evaluate regions in which activation varied as a function of the age group, young and older adults were compared to each other while the factor performance gain was included as covariate of no interest. These contrasts were evaluated as two-sample t-tests. Compared to older adults, young adults showed decreased recruitment of the left inferior parietal lobule after training compared to before physical training (Figure 3). No other contrasts yielded any significant difference between young and older adults when comparing pre- and post-training scans (including the positive effect of performance). It is to note that running the same contrasts with performance on day 5 as the covariate of no interest (instead of performance gain) lead to a nearly identical pattern of activation, with the only significant activation emerging within the left inferior parietal lobule ($x = -50$, $y = -28$, $z = 48$, $p_{\text{FWE-corr}} = 0.001$, $t = 4.8$) when comparing young adults to older adults.

(2) Common Regions Influenced by Training among Young and Older Adults. When analysed separately, training effects among young and older adults mainly resulted in decreased activity after physical training compared to before. For this reason, we focused on this contrast to see which regions were similarly showing a decrease of activity in both age groups after physical training compared to before. This conjunction analysis (using $t > 3.5$ as the threshold) yielded overlapping activation across 87 voxels, in three main regions, namely, the left fusiform gyrus, the right inferior temporal gyrus, and the right inferior parietal lobule (Figure 4).

3.3. Effects of Training on Neural Representations of Actions

3.3.1. Regions That Discriminate Better between Dance Movements after Compared to before Training in Each Age Group. This first set of decoding analyses is aimed at identifying which brain regions were better able to distinguish between physically trained and untrained movement sequences after compared to before training, among young and older adults separately.

All results reported are $p_{\text{FWEcorr}} < 0.05$ at the cluster level, with a threshold at $p_{\text{unc}} < 0.005$, $k = 20$ voxels.

(1) Younger Adults. When comparing regions that could better distinguish between physically trained and untrained sequences after training compared to before training, the left angular gyrus (IPC) and right middle frontal gyrus (close to IFS) were the two only regions that could discriminate accurately (i.e., above chance) after training between physically trained and untrained sequences (Figure 5(a) and Table 3(a)).

(2) Older Adults. When comparing regions that could distinguish between physically trained and untrained sequences after training better than before training, left SMA and primary somatosensory cortex were the only regions that came

Table 1: Regions associated with an increase and decrease of activity post-training compared to pre-training among younger adults, depending on the type of training.

(a) Physical training

Region	BA	MNI coordinates			t value	Cluster size	$p\text{FWE}_{\text{corr}}$ value
		x	y	z			
(i) Increase post-training compared to pre-training							
No cluster survived the threshold							
(ii) Decrease post-training compared to pre-training							
L paracentral lobule	**5**	**−10**	**−34**	**58**	**7.17**	**233**	**<0.001**
L postcentral gyrus	1	−28	−36	56	4.50		
L superior parietal lobule	3b	−20	−42	58	4.13		
R precentral gyrus	**4**	**34**	**−28**	**58**	**6.02**	**706**	**<0.001**
R postcentral gyrus	1	38	−38	56	5.07		
R postcentral gyrus	1	26	−32	58	5.06		
R inferior temporal gyrus	**37**	**50**	**−50**	**−16**	**5.89**	**380**	**<0.001**
R inferior temporal gyrus	37	40	−52	−14	5.51		
R inferior temporal gyrus		36	−60	−4	3.85		
R hippocampus		**26**	**−4**	**−24**	**5.65**	**168**	**0.003**
R hippocampus		34	−4	−22	5.05		
R middle temporal gyrus	21	46	−4	−20	4.55		
L postcentral gyrus	1	**−40**	**−30**	**56**	**5.00**	**94**	**0.048**
L postcentral gyrus	1	−44	−22	56	4.26		
R middle occipital gyrus	**19**	**46**	**−76**	**18**	**4.63**	**153**	**0.005**
R middle occipital gyrus	19	40	−84	14	4.59		
R middle occipital gyrus	19	52	−64	14	4.55		

(b) Visual training

Region	BA	MNI coordinates			t value	Cluster size	$p\text{FWE}_{\text{corr}}$ value
		x	y	z			
(i) Increase post-training compared to pre-training							
No cluster survived the threshold							
(ii) Decrease post-training compared to pre-training							
L inferior temporal gyrus	20	−40	−32	−18	6.30	83	0.081
L inferior temporal gyrus	37	−42	−40	−18	4.68		
L fusiform gyrus	37	−38	−56	−18	4.14		
R amygdala		30	−2	−24	5.68	80	0.092
R parahippocampal gyrus	36	24	−26	−24	4.44		
R parahippocampal gyrus	36	20	−12	−24	4.36		
R fusiform gyrus	**37**	**42**	**−42**	**−16**	**5.58**	**394**	**<0.001**
R inferior temporal gyrus	37	40	−52	−14	4.86		
R inferior temporal gyrus	37	50	−50	−16	4.46		
R postcentral gyrus	**1**	**30**	**−32**	**58**	**5.40**	**498**	**<0.001**
R postcentral gyrus	1	28	−40	66	4.86		
R postcentral gyrus	1	36	−34	66	4.69		
R middle temporal gyrus	**19**	**52**	**−66**	**12**	**5.36**	**180**	**0.002**
R middle occipital gyrus	19	46	−80	12	4.88		
R middle occipital gyrus	39	40	−58	12	3.91		

BA: Brodmann's area; R: right; L: left. Analysis performed at $p < 0.001$, uncorrected, $k = 10$ voxels, and regions in bold font are FWE cluster corrected at the $p < 0.05$ level. Up to three local maxima are listed when a cluster has multiple peaks more than 8 mm apart.

Table 2: Regions associated with increases and decreases of activity post-training compared to pre-training in older adults, depending on the type of training.

(a) Physical training

Region	BA	MNI coordinates			t value	Cluster size	pFWEcorr value
		x	y	z			
(i) Increase post-training compared to pre-training							
R precuneus	**7**	**4**	**−68**	**30**	**6.68**	**510**	**<0.001**
R precuneus	31	10	−66	24	5.45		
L cuneus	18	−6	−66	22	4.98		
(ii) Decrease post-training compared to pre-training							
R thalamus		**8**	**−26**	**6**	**5.88**	**314**	**<0.001**
L thalamus		−2	−24	6	5.66		
L thalamus		−12	−32	2	5.26		
R superior parietal lobule	**39**	**32**	**−56**	**48**	**5.55**	**187**	**0.002**
R superior occipital gyrus	7	22	−62	48	4.72		
R superior parietal lobule	7	26	−50	46	4.31		
R inferior temporal gyrus	37	50	−50	14	5.22	69	0.147
R inferior temporal gyrus		44	−54	−6	4.53		
R fusiform gyrus		34	−54	−12	3.97		
R inferior parietal lobule	**1**	**60**	**−20**	**36**	**4.92**	**182**	**0.002**
R supramarginal gyrus	40	60	−30	38	4.83		
R supramarginal gyrus	40	54	−28	48	4.05		

(b) Visual training

Region	BA	MNI coordinates			t value	Cluster size	pFWEcorr value
		x	y	z			
(i) Increase post-training compared to pre-training							
R precuneus	**31**	**10**	**−66**	**24**	**5.67**	**220**	**<0.001**
R precuneus	31	18	−62	22	4.34		
L precuneus	31	−2	−66	28	4.33		
(ii) Decrease post-training compared to pre-training							
No cluster survived the threshold (all pFWEcorr > 0.1)							

BA: Brodmann's area; R: right, L: left. $p < 0.001$, uncorrected; $k = 10$ voxels. Regions in bold font are FWE cluster corrected at the $p < 0.05$ level. Up to three local maxima are listed when a cluster has multiple peaks more than 8 mm apart.

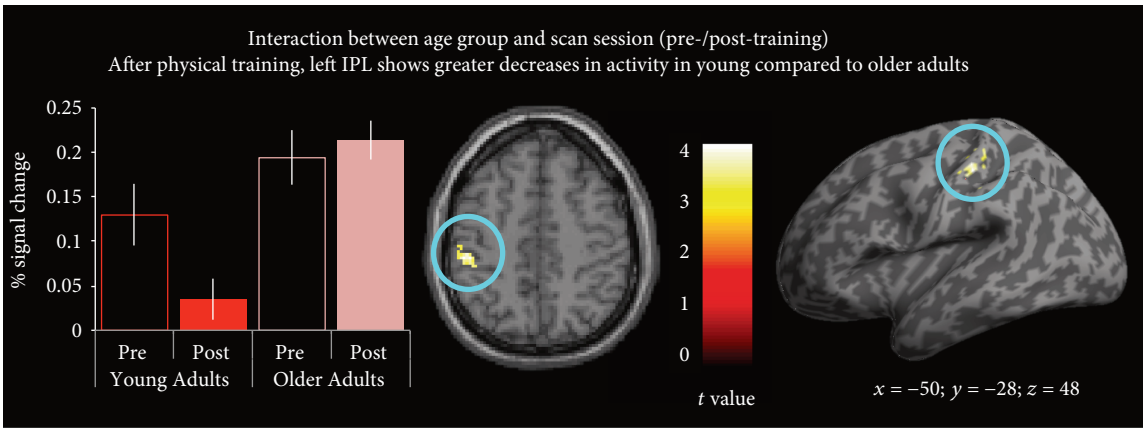

Figure 3: Training experience by age group interaction. The left inferior parietal lobule (IPL) demonstrates more marked decreases in engagement after physical training among the young adult participant sample compared to the older adults ($p_{\text{FWE-corr}} = 0.01$, $t = 4.3$).

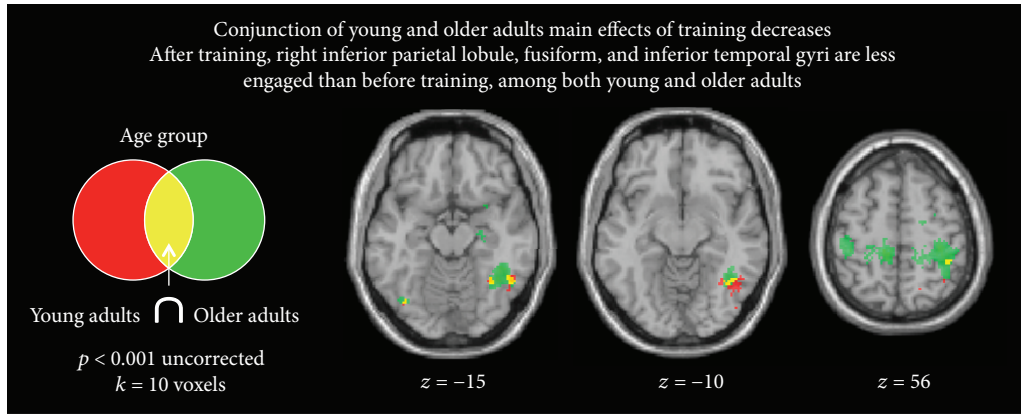

Figure 4: Common regions among young and older adults demonstrating a decreased response after physical training.

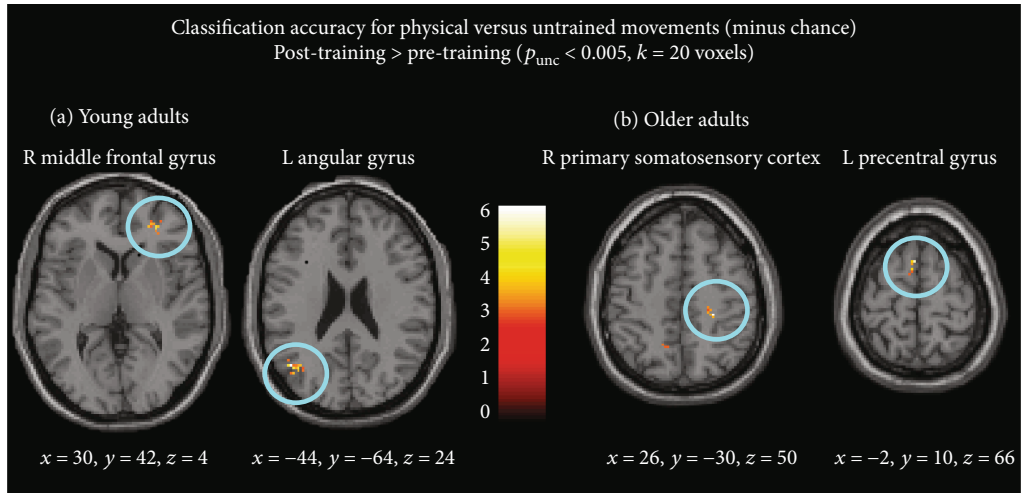

Figure 5: Regions that can accurately discriminate better between physically trained and untrained movements after training compared to before training. (a) In young adults. (b) In older adults. Coordinates of the centre of the cluster are given for all cluster-corrected regions (x, y, and z in MNI coordinates).

close to the FWEcorr threshold criteria ($p_{\text{FWEcorr}} = 0.05$ and $p_{\text{FWEcorr}} = 0.07$, resp.; Figure 5(b) and Table 3(b)).

3.3.2. Effect of Age on Discrimination Accuracy after Physical Training. In the following analyses, only accuracy maps from post-training scans were taken into account, to explore which regions can accurately discriminate between physically trained sequences and untrained sequences after training, comparing younger and older adults. When evaluating this contrast on the post-training data, the right superior parietal lobule and the right cerebellum discriminate between physically trained and untrained sequences more accurately in young adults compared to older adults (Figure 6(a) and Table 4(a)). In contrast, the inverse contrast, evaluating brain regions that discriminate between physically trained and untrained sequences better in older adults compared to young adults, yielded the right angular gyrus and left middle occipital gyrus (Figure 6(b) and Table 4(b)).

Finally, we conducted an exploratory conjunction analysis on the accuracy maps (using $t > 3.5$ as the threshold), to determine whether there were any common brain regions among young and older adults that could distinguish between physically trained and untrained sequences after training (for full results of these maps on day 5 for young and older adults separately, please see Supplementary Materials). This conjunction analysis yielded overlap across 794 voxels, including multiple subregions within the occipital cortex, as well as sensorimotor areas, including the left paracentral gyrus (Figure 7).

4. Discussion

In the present study, we manipulated the type of sensorimotor experience that young and older adults received with dance sequences to determine how experience shapes responses at behavioural and brain levels, during early and later adulthood. We set out to address three main questions: (i) How do different types of training influence complex action performance among young compared to older adults? (ii) How do different types of training shape brain responses at a global level during action observation among young compared to older adults? (iii) How does physical training shape brain responses at the level of action representations?

Table 3: Regions that can accurately discriminate better between physically trained and untrained movements after training compared to before training. (a) Young adults. (b) Older adults.

Region	BA	MNI coordinates			t value	Cluster size	pFWEcorr value
		x	y	z			
(a) Physically trained versus untrained in younger adults							
L angular gyrus	**39**	**−44**	**−64**	**24**	**6.05**	**69**	**<0.001**
L angular gyrus	39	−34	−66	26	4.00		
L middle occipital gyrus	19	−38	−68	18	3.94		
R middle frontal gyrus	**10**	**30**	**42**	**4**	**4.68**	**40**	**0.048**
R middle frontal gyrus	10	28	48	−2	4.21		
R middle frontal gyrus		28	40	12	3.35		
(b) Physically trained versus untrained in older adults							
R postcentral gyrus	3	26	−30	50	6.12	46	0.053
R middle cingulate cortex		16	−28	46	4.38		
L precentral gyrus	6	−2	10	66	5.68	43	0.078
L precentral gyrus	6	−8	2	60	3.75		

BA: Brodmann's area; R: right, L: left. $p < 0.001$, uncorrected; $k = 10$ voxels. Regions in bold font are FWE cluster corrected at the $p < 0.05$ level. Up to three local maxima are listed when a cluster has multiple peaks more than 8 mm apart.

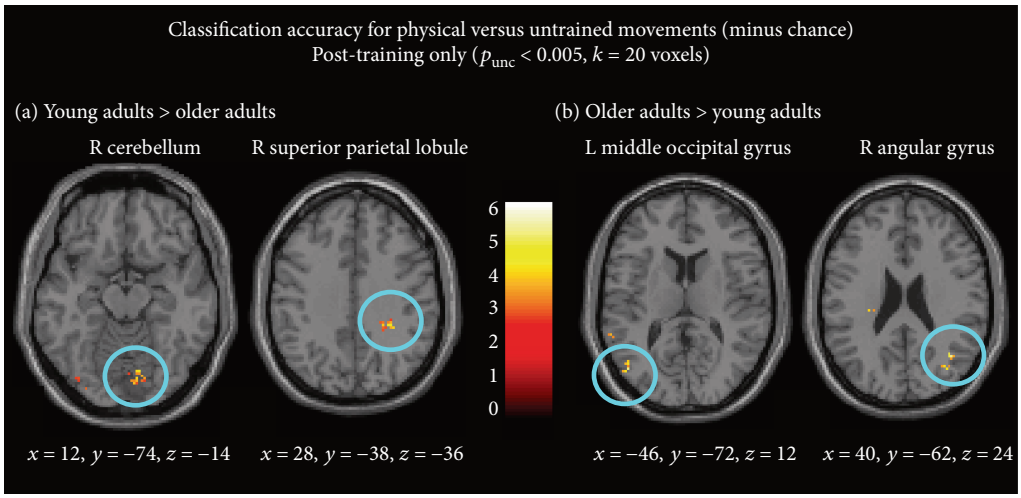

Figure 6: Direct comparison of classification accuracy for physical versus untrained sequences, minus chance, comparing young and older adults. (a) Brain regions that are better able to discriminate between physical and untrained movements in young adults compared to older adults. (b) Brain regions better able to discriminate between physical and untrained movements in older adults compared to young adults. Coordinates are reported in MNI space (x, y, and z).

Overall, participants' behavioural performance on motor and visual tasks improved across the training period, with younger adults showing greater performance gains than older adults. At the brain level, both age groups demonstrated overall *decreases* in sensorimotor cortical engagement after physical training, with younger adults showing more pronounced decreases in the inferior parietal lobule (IPL) activity compared to older adults. However, it is of note that the older adult population also showed an *increase* in precuneus activity after training. Neural decoding results show that among both young and older adults, visual and motor cortices contain experience-specific representations of new motor learning. In the following, we consider each of these findings, including how they relate to prior work and how they might form a foundation for future research.

4.1. Behavioural Differences between Younger and Older Adults. Both young and older adults' performance on both behavioural tasks (physical and visual learning tasks) improved across the four days of training. However, young adults outperformed older adults overall in terms of physical performance, and as Figure 2(a) shows, this performance discrepancy was present from the first day of training. This pattern of findings is likely explained by overall better physical condition and motor learning abilities among younger adults, whose movements are also more fluid than those made by individuals in advanced age [46, 63, 64]. However, the young adults did not outperform older adults in terms of recognition accuracy on the visual training task. This might be driven by the fact that participants in both age groups found the recognition task very easy, and the plots

Table 4: Physical versus untrained classification accuracy minus chance comparing young and older adults. (a) Young adults > older adults. (b) Older adults > young adults.

Region	BA	MNI coordinates			t value	Cluster size	pFWEcorr value
		x	y	z			
(a) Young adults > older adults							
R superior parietal lobule		**28**	**−38**	**36**	**4.62**	**46**	**0.039**
R cerebellum		**12**	**−74**	**−14**	**4.43**	**81**	**<0.001**
R calcarine gyrus	18	14	−70	−6	4.35		
R lingual gyrus	17	8	−82	−12	3.86		
(b) Older adults > young adults							
R angular gyrus	**39**	**40**	**−62**	**24**	**4.28**	**46**	**0.039**
R middle occipital gyrus		34	−70	26	4.07		
L middle occipital gyrus	**19**	**−46**	**−72**	**12**	**4.24**	**47**	**0.034**
L middle temporal gyrus	39	−50	−62	18	4.15		
L middle temporal gyrus	39	−40	−60	20	3.62		

BA: Brodmann's area; R: right, L: left. $p < 0.001$, uncorrected; $k = 10$ voxels. Regions in bold font are FWE cluster corrected at the $p < 0.05$ level. Up to three local maxima are listed when a cluster has multiple peaks more than 8 mm apart.

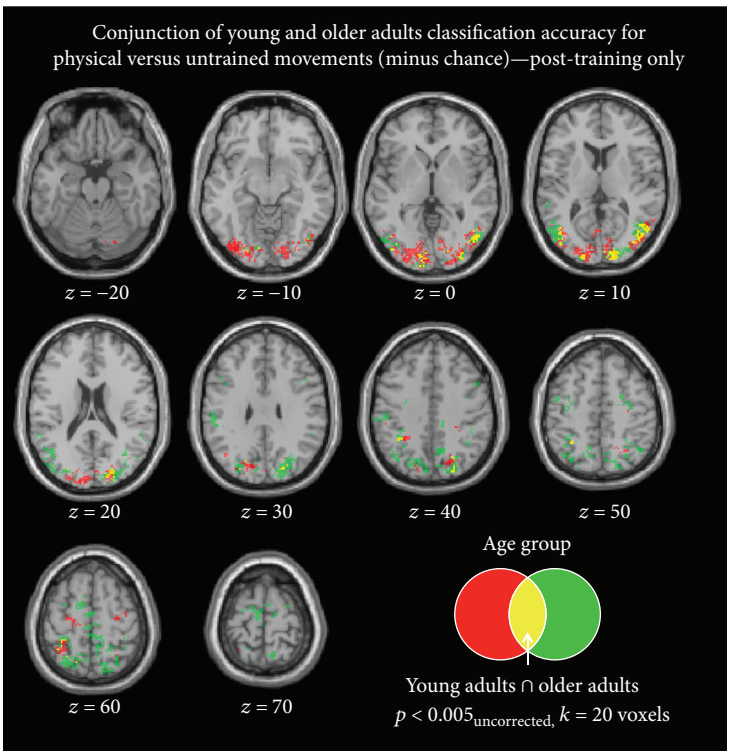

Figure 7: Conjunction analysis: common regions among young and older adults for accurately discriminating between physical and untrained sequences, on day 5.

of behavioural performance on this task (Figure 2(b)) document that participants from both age groups were more or less performing at ceiling from day 2 onwards.

When considering physical performance score discrepancies between young and older adults, it is also worth noting that the Kinect motion tracking system and the Xbox scoring system take into account the fluidity or smoothness of a performer's movements and participants have the potential to score many extra "bonus points" when they reproduce a move being performed by the avatar on screen in a particularly smooth manner. This aspect of the video game design might have penalized older adults' physical performance scores, as research demonstrates that gross bodily movements become less fluid/smooth with advancing age [46]. However, such differences between young and older adults' general kinematics should not affect the overall improvements across days within each age group, but here again, we also see more marked improvements among younger

adults. To better understand the underlying neural basis for these differences between the two age groups, we investigated our main hypotheses by means of fMRI.

4.2. Effect of Training at a Global Brain Level during Action Observation. Taken together, the univariate analyses show a similar pattern of results among both young and older adults, characterised by activity decreases post-training. Specifically, evidence emerges that the right ITG and IPL, brain regions associated with the AON, show decreased response amplitude after physical training among both groups of participants. The left fusiform gyrus demonstrates a similar response profile in both groups. It thus appears that, regardless of age, physical training results in less recruitment of these sensorimotor and higher-order visual association cortices that are robustly recruited when observing unfamiliar or novel actions [26, 27, 65]. In a recent meta-analysis, Hardwick and colleagues [34] report similar decreases in activity among these same brain regions following motor learning, even though many of the studies included in this meta-analysis report increases in activity after training. This line of results helps to further illuminate how physical training influences brain regions recruited during observation of complex whole-body movements, with no other cue than a pared-down silhouetted representation of the movement.

The only increase of activity found after training in the present study emerged from the older adults group in the right precuneus, after both physical and visual training. This finding suggests that in advanced age, the precuneus is sensitive to the type of visuomotor training examined in the present study. More generally, the precuneus has been implicated in higher-order cognitive processes such as episodic memory, motor imagery, and spatial aspects of motor behaviour control [66–68] and has also been shown to respond more robustly during motor tasks in advanced age [69]. However, as this region did not emerge from the direct contrast comparing older and younger adults, it is not possible to conclude that its increased engagement when observing movements that have been associated with visuomotor or visual experience is due to age, per se. Further investigation, perhaps taking a longitudinal approach, would be beneficial for clarifying the relationship between precuneus activity, aging, and visuomotor learning.

The fact that we fail to find robust increases of activity within brain regions classically associated with the AON after physical training, as we report previously with similar training paradigm [3, 18], might seem surprising at first, until a number of factors are taken into consideration. First, the pattern of results we report here is broadly consistent with the fine movement motor learning literature [39, 59], which reliably documents decreases in whole brain activity after training as a signature of neural efficiency [17, 37, 70, 71]. For example, Higuchi and colleagues [71] report that for both observation and execution of guitar chords, reliable neural efficiency effects emerged across training days. The field would benefit from studies using complex, multisensory training paradigms looking more systematically at both increases and decreases of activity. A recent study by Gardner and colleagues has attempted to explore the issue of post-training increases and decreases in neural response amplitude by using guitar training to probe the subjective nature of the prediction error signal [17]. These authors report results consistent with a predictive coding account of AON engagement during action observation and execution that also takes into account effects of changes in neural efficiency, providing a promising theoretical grounding for taking this work further.

It is also important to consider how the training and testing approach used in the present study differs from prior work that reports increased response amplitude with increased experience (e.g., [5, 6, 19, 22, 49]). First, many prior studies look at effects of years, if not decades, of training experience on perception [5, 6, 22], while those examining the effects of aging often study how physical skills that older adults learned when they were still young are perceived [43, 49]. Such a short-term training intervention, like the one used in the present study, might thus be suboptimal for generating robust age-related differences in brain activity. In addition, the movements observed during brain scanning were far simpler in the present study than those used in many previous studies [6, 18, 19, 22, 53]. As such, the kind of learning examined in the present study might be quite different from what our group and others have previously found [18, 49]. In further contrast to previous studies, the pared-down action silhouettes used here revealed no further information about each action beyond its kinematics [48]. This means that any training effect found at the brain level should be linked to pure motor learning and visual movement processing, which might further contribute to subtle findings compared to previous work in this vein. Moreover, in contrast to recent work by our group [18], it is important to note that the task participants performed in the scanner was also markedly different and very likely contributed to the different pattern of results we report here. In Kirsch and Cross's earlier study [18], each trial was followed by one of two questions: "How much did you *like* the movement you just watched?" and "How well could you *reproduce* the movement you just watched?" It should be evident that these two questions required much deeper kinematic, visual, and aesthetic processing than what was required in the present study (participants watch closely each movement and respond to occasional probe questions about very simple kinematic features of the previously viewed movement). For this reason, it is imperative to consider the different tasks and stimuli when evaluating discrepant results reported by previous studies that have used similar training paradigms, such as Kirsch and Cross [18], and the present study. These different patterns of findings also provide a useful consideration for future studies, namely, future work can examine the extent to which decreases in sensorimotor engagement following training are due to strengthened purely 'kinematic' representations or to observers' not being prompted to think about their physical abilities to reproduce observed moves during action observation.

Even though the right IPL was found to be less activated after training among both age groups (Figure 4), the left IPL was the only region to demonstrate more marked decreases

in engagement after physical training among young compared to older adults (Figure 3). The parameter estimate plot on this figure suggests that this finding is being driven by decrease in IPL engagement among young adults, while this region's response profile remains relatively unchanged among older adults. This could be indicative of processing efficiency gains among young adults that are simply not present among older adults. It is to note that no regions showed a greater decrease or increase after training in older adults compared to younger adults, when we control for physical gain performance. The IPL is one of the core regions of the AON, and its activity has been shown to be modulated by training [6, 16, 18].

In terms of visual training effects, we observed decreased engagement of sensorimotor and visual processing regions among young adults, similar to physical training. This is in line with previous literature showing common regions sensitive to observational and physical training [1–3, 14, 18]. However, among older adults, no regions showed decreased activity after visual training. This raises the possibility that visual training effects among older adults are either subtler or perhaps altogether different, perhaps due to declines in attentional and visual processing decline with advancing age [34]. A challenge for future research will be to examine in more depth age-related differences in observational training effects, possibly using a different task that can better capture performance and improvement via observation (which our task clearly failed to capture, as all participants were performing at ceiling by day 2).

Moreover, taking into account the results from the training modality categorization task participants completed after the post-training scan session, one could argue that the differences seen between young and older adults' brain activity is due to older adults not being able to accurately identify the training modality of the observed movements. Our results show that older adults performed more poorly than young adults on this task overall and that they were more likely to categorize untrained moves as trained. This finding of a carry-over effect is consistent with previous studies showing that older adults frequently show this tendency to misclassify new material as being familiar, which has been interpreted as showing that internal representations of events become more rigid with age [72]. However, as this categorization task did not include multiple trials for each stimulus (thus reducing its power) and our main aim was to examine differences before and after training within one training category (physical practice), we are reluctant to place too much stock in age differences on this task in our particular study. One final reason to be cautious with how we interpret young and older adults' performance on the categorization task is because even if older adults do not explicitly recognize the training category to which each stimulus belongs as well as younger adults, our main interest was in the neural implementation of the training, where we do see differences.

4.3. Examining the Impact of Physical Training on a Representational Level. The present study was designed to enable investigation of how physical training shapes brain responses not just at the level of magnitude differences but also at the level of more fine-grained action representations. The aim of our first set of pattern analyses was to identify brain regions that can distinguish between physical and untrained movement sequences after training compared to pre-training, among young and older adults separately. We predicted this between-category classification accuracy to be better overall after training compared to before training, when all stimuli were equally unfamiliar. Among younger adults, we found that the left angular gyrus and MFG could discriminate better after training between physically trained and untrained sequences, whereas among older adults, the left supplementary motor area and sensorimotor cortex could discriminate better after training between physically trained and untrained sequences.

The second set of analyses compared classification accuracies between the age groups, in particular their accuracy at distinguishing between physically trained and untrained sequence after physical training. These analyses yielded clear age-related differences, with better discrimination within the right superior parietal lobule and cerebellum in young compared to that in older adults. In contrast, older adults showed better discrimination in visual processing areas and multisensory integration areas such as the right angular gyrus and left MOG, compared to young adults.

This broad pattern of results is consistent with literature documenting that older adults rely more on sensory cortices during action observation than younger adults, even if the observed actions are familiar to them [47]. Computational models of cognitive aging posit that neural representations become less distinctive in old age [73]. Recent work by Carp and colleagues [74] reported that neural distinctiveness was reduced in older adults throughout the motor network. Neuroimaging studies of visual perception support this view, indicating that distributed patterns of brain activation evoked by different visual stimuli are less distinctive among older adults compared to young adults [75, 76]. In the present study, our findings do not speak to reductions in neural distinctiveness in advanced age per se, but instead we find different regions involved in distinguishing between different categories of stimuli (physically trained versus untrained) in young compared to older adults. As such, our findings suggest that the kind of training manipulation we used here has a specific effect that goes beyond the natural dedifferentiation that occurs with aging and instead leads to distinct networks mediating training-induced neural representations among young compared to older adults. While this part of the study was exploratory in nature, it provides useful point of departure for continued investigation of the changing nature of the representation of new sensorimotor learning across the lifespan. Moreover, one might speculate that older adults process the stimuli differently than younger adults or are at a different stage of learning when being scanned (as the behavioural data might suggest). These factors could also explain some of the differences seen with young adults. Older adults might still be in the consolidation phase on day 5, whereas in young adults, the top-down modulation of sensory regions has possibly already taken place [45, 47, 77]. Future studies could add scanning sessions at more time points (or include longer training manipulations with

scanning sessions interspersed regularly throughout them), in order to explore whether older adults achieve the same performance as young adults, which is also reflected as (more) similar patterns of brain activation.

Finally, we explored which brain regions among young and older adults similarly distinguish between physically trained and untrained movements post-training. This conjunction analysis yielded common regions in occipital and motor cortices, demonstrating finer motor representations on day 5 for both age groups. This suggests that physical training plays an important role in the coding of fine movements in higher-order visual and motor areas, lending further support to the neural efficiency theory and findings in the motor domain [39].

4.4. Limitations and Future Directions. As with any study and with exploratory studies in particular, this work has several important limitations and has raised a number of possibilities for future research that warrant consideration. Since the present study was the first to tackle questions of complex action learning at brain and behavioural levels among young and older adults, we chose to investigate age group differences when both groups attempt to learn initially novel actions for the same amount of time. In this way, performance at the end of training was consequently not matched between the age groups. Thus, we cannot clearly disentangle whether our between-age group results are related to the way participants learn and represent dance sequences or due to the fact that young and older adults are at different stages of the learning process. An alternative design could have continued training the older adults until they performed at the same level as the younger adults and then compared brain activity. Future studies might explore this possibility and implement paradigms in which performance is better matched at the end of training. However, with respect to physically trained sequences in particular, general changes in motor control might prevent older adults from reaching the same performance level as younger adults irrespective of the amount of training provided [63].

Moreover, the technology used for our training intervention might have had an impact on participants' dance experience and the extent to which they perceive the task as "real" dancing. Similarly, age differences could possibly impact participants' willingness to dance in front of a large TV with avatars. However, devices such as the Kinect system have become more and more common in many households in recent years. Consequently, more on more people, including older generations, are becoming accustomed to interacting with them (and indeed, several of our older participants mentioned at the conclusion of the study that they had seen their grandchildren playing games with the Xbox Kinect in the past and had never participated as they thought the technology was not for them, but their minds had been changed since taking part in our study). In addition, we asked older adults to try the Kinect dance set up in a separate session before actual testing, and only those older adults who felt comfortable to do the training took part in the main experiment. Finally, as all participants also reported having enjoyed the experience, we believe that our results are not biased due to differences in the perception of the training set-up between young and older adults.

5. Conclusions

To our knowledge, this is the first study to combine a complex, whole-body training paradigm with univariate and multivariate analyses to investigate the impact of sensorimotor learning on action representations among young and older adults. While this study was exploratory in nature, our results should contribute to building a more complete picture of age-related changes in experience-dependent plasticity. Ultimately, we hope that insights gained from this approach will inform visuomotor learning and rehabilitation interventions for those in early and advanced adulthood.

Conflicts of Interest

The authors declare no competing financial interests.

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Supplementary Materials

Supplementary Table 1: regions that can accurately discriminate better between physically trained and untrained movements on day 5. (a) Younger adults. (b) Older adults. Supplementary Figure 1: recognition accuracy average scores in young and older adults. After the post-training scan on day 5, participants watched each dance movie stimulus again (6 training conditions) and were asked to categorize them as either being physically trained, visually trained, or untrained. *(Supplementary Materials)*

References

[1] W. Prinz, "A common coding approach to perception and action," in *Relationships between Perception and Action: Current Approaches*, O. Neumann and W. Prinz, Eds., pp. 167–201, Spring-Verlag, Berlin, 1990.

[2] S. H. Frey and V. E. Gerry, "Modulation of neural activity during observational learning of actions and their sequential orders," *The Journal of Neuroscience*, vol. 26, no. 51, pp. 13194–13201, 2006.

[3] E. S. Cross, D. J. M. Kraemer, A. F. C. Hamilton, W. M. Kelley, and S. T. Grafton, "Sensitivity of the action observation network to physical and observational learning," *Cerebral Cortex*, vol. 19, no. 2, pp. 315–326, 2009.

[4] S. Vogt and R. Thomaschke, "From visuo-motor interactions to imitation learning: behavioural and brain imaging

studies," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 497–517, 2007.

[5] B. Calvo-Merino, D. E. Glaser, J. Grèzes, R. E. Passingham, and P. Haggard, "Action observation and acquired motor skills: an FMRI study with expert dancers," *Cerebral Cortex*, vol. 15, no. 8, pp. 1243–1249, 2005.

[6] E. S. Cross, A. F. C. Hamilton, and S. T. Grafton, "Building a motor simulation de novo: observation of dance by dancers," *NeuroImage*, vol. 31, no. 3, pp. 1257–1267, 2006.

[7] H. Lee and U. Noppeney, "Long-term music training tunes how the brain temporally binds signals from multiple senses," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 51, pp. E1441–E1450, 2011.

[8] S. L. Liew, T. Sheng, and L. Aziz-Zadeh, "Experience with an amputee modulates one's own sensorimotor response during action observation," *NeuroImage*, vol. 69, pp. 138–145, 2013.

[9] N. N. Rüther, E. C. Brown, A. Klepp, and C. Bellebaum, "Observed manipulation of novel tools leads to mu rhythm suppression over sensory-motor cortices," *Behavioural Brain Research*, vol. 261, pp. 328–335, 2014.

[10] E. S. Cross, A. F. C. Hamilton, D. J. M. Kraemer, W. M. Kelley, and S. T. Grafton, "Dissociable substrates for body motion and physical experience in the human action observation network," *The European Journal of Neuroscience*, vol. 30, no. 7, pp. 1383–1392, 2009.

[11] J. Jastorff, Z. Kourtzi, and M. A. Giese, "Visual learning shapes the processing of complex movement stimuli in the human brain," *The Journal of Neuroscience*, vol. 29, no. 44, pp. 14026–14038, 2009.

[12] C. Jola, A. Abedian-Amiri, A. Kuppuswamy, F. E. Pollick, and M. H. Grosbras, "Motor simulation without motor expertise: enhanced corticospinal excitability in visually experienced dance spectators," *PLoS One*, vol. 7, no. 3, article e33343, 2012.

[13] A. A. G. Mattar and P. L. Gribble, "Motor learning by observing," *Neuron*, vol. 46, no. 1, pp. 153–160, 2005.

[14] S. Torriero, M. Oliveri, G. Koch, C. Caltagirone, and L. Petrosini, "The what and how of observational learning," *Journal of Cognitive Neuroscience*, vol. 19, no. 10, pp. 1656–1663, 2007.

[15] E. S. Cross, N. R. Cohen, A. F. C. Hamilton, R. Ramsey, G. Wolford, and S. T. Grafton, "Physical experience leads to enhanced object perception in parietal cortex: insights from knot tying," *Neuropsychologia*, vol. 50, no. 14, pp. 3207–3217, 2012.

[16] E. S. Cross, A. F. C. Hamilton, N. R. Cohen, and S. T. Grafton, "Learning to tie the knot: the acquisition of functional object representations by physical and observational experience," *PLoS One*, vol. 12, no. 10, article e0185044, 2017.

[17] T. Gardner, A. Aglinskas, and E. S. Cross, "Using guitar learning to probe the Action Observation Network's response to visuomotor familiarity," *NeuroImage*, vol. 156, pp. 174–189, 2017.

[18] L. P. Kirsch and E. S. Cross, "Additive routes to action learning: layering experience shapes engagement of the action observation network," *Cerebral Cortex*, vol. 25, no. 12, pp. 4799–4811, 2015.

[19] B. Calvo-Merino, J. Grèzes, D. E. Glaser, R. E. Passingham, and P. Haggard, "Seeing or doing? Influence of visual and motor familiarity in action observation," *Current Biology*, vol. 16, no. 19, pp. 1905–1910, 2006.

[20] J. F. Christensen, A. Gomila, S. B. Gaigg, N. Sivarajah, and B. Calvo-Merino, "Dance expertise modulates behavioral and psychophysiological responses to affective body movement," *Journal of Experimental Psychology. Human Perception and Performance*, vol. 42, no. 8, pp. 1139–1147, 2016.

[21] L. P. Kirsch, K. A. Drommelschmidt, and E. S. Cross, "The impact of sensorimotor experience on affective evaluation of dance," *Frontiers in Human Neuroscience*, vol. 7, p. 521, 2013.

[22] G. Orgs, J. H. Dombrowski, M. Heil, and P. Jansen-Osmann, "Expertise in dance modulates alpha/beta event-related desynchronization during action observation," *The European Journal of Neuroscience*, vol. 27, no. 12, pp. 3380–3384, 2008.

[23] G. Buccino, F. Lui, N. Canessa et al., "Neural circuits involved in the recognition of actions performed by nonconspecifics: an fMRI study," *Journal of Cognitive Neuroscience*, vol. 16, no. 1, pp. 114–126, 2004.

[24] S. Shimada, "Deactivation in the sensorimotor area during observation of a human agent performing robotic actions," *Brain and Cognition*, vol. 72, no. 3, pp. 394–399, 2010.

[25] V. Gazzola, H. van der Worp, T. Mulder, B. Wicker, G. Rizzolatti, and C. Keysers, "Aplasics born without hands mirror the goal of hand actions with their feet," *Current Biology*, vol. 17, no. 14, pp. 1235–1240, 2007.

[26] S.-L. Liew, T. Sheng, J. L. Margetis, and L. Aziz-Zadeh, "Both novelty and expertise increase action observation network activity," *Frontiers in Human Neuroscience*, vol. 7, p. 541, 2013.

[27] E. S. Cross, R. Liepelt, A. F. d. C. Hamilton et al., "Robotic movement preferentially engages the action observation network," *Human Brain Mapping*, vol. 33, no. 9, pp. 2238–2254, 2012.

[28] C. M. Tipper, G. Signorini, and S. T. Grafton, "Body language in the brain: constructing meaning from expressive movement," *Frontiers in Human Neuroscience*, vol. 9, p. 450, 2015.

[29] C. Babiloni, C. del Percio, P. M. Rossini et al., "Judgment of actions in experts: a high-resolution EEG study in elite athletes," *NeuroImage*, vol. 45, no. 2, pp. 512–521, 2009.

[30] C. Babiloni, N. Marzano, F. Infarinato et al., ""Neural efficiency" of experts' brain during judgment of actions: a high-resolution EEG study in elite and amateur karate athletes," *Behavioural Brain Research*, vol. 207, no. 2, pp. 466–475, 2010.

[31] C. del Percio, C. Babiloni, N. Marzano et al., ""Neural efficiency" of athletes' brain for upright standing: a high-resolution EEG study," *Brain Research Bulletin*, vol. 79, no. 3-4, pp. 193–200, 2009.

[32] V. B. Penhune and J. Doyon, "Cerebellum and M1 interaction during early learning of timed motor sequences," *NeuroImage*, vol. 26, no. 3, pp. 801–812, 2005.

[33] E. Dayan and L. G. Cohen, "Neuroplasticity subserving motor skill learning," *Neuron*, vol. 72, no. 3, pp. 443–454, 2011.

[34] R. M. Hardwick, C. Rottschy, R. C. Miall, and S. B. Eickhoff, "A quantitative meta-analysis and review of motor learning in the human brain," *NeuroImage*, vol. 67, pp. 283–297, 2013.

[35] V. B. Penhune and C. J. Steele, "Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning," *Behavioural Brain Research*, vol. 226, no. 2, pp. 579–591, 2012.

[36] N. N. Oosterhof, A. J. Wiggett, and E. S. Cross, "Testing key predictions of the associative account of mirror neurons in humans using multivariate pattern analysis," *Behavioral and Brain Sciences*, vol. 37, no. 2, pp. 213–215, 2014.

[37] C. J. Steele and V. B. Penhune, "Specific increases within global decreases: a functional magnetic resonance imaging investigation of five days of motor sequence learning," *The Journal of Neuroscience*, vol. 30, no. 24, pp. 8332–8341, 2010.

[38] N. N. Oosterhof, S. P. Tipper, and P. E. Downing, "Viewpoint (in)dependence of action representations: an MVPA study," *Journal of Cognitive Neuroscience*, vol. 24, no. 4, pp. 975–989, 2012.

[39] T. Wiestler and J. Diedrichsen, "Skill learning strengthens cortical representations of motor sequences," *eLife*, vol. 2, article e00801, 2013.

[40] J. A. Bernard and R. D. Seidler, "Moving forward: age effects on the cerebellum underlie cognitive and motor declines," *Neuroscience & Biobehavioral Reviews*, vol. 42, pp. 193–207, 2014.

[41] A. Saimpont, F. Malouin, B. Tousignant, and P. L. Jackson, "The influence of body configuration on motor imagery of walking in younger and older adults," *Neuroscience*, vol. 222, pp. 49–57, 2012.

[42] J. F. Norman, S. M. Payton, J. R. Long, and L. M. Hawkes, "Aging and the perception of biological motion," *Psychology and Aging*, vol. 19, no. 1, pp. 219–225, 2004.

[43] N. Diersch, E. S. Cross, W. Stadler, S. Schütz-Bosbach, and M. Rieger, "Representing others' actions: the role of expertise in the aging mind," *Psychological Research*, vol. 76, no. 4, pp. 525–541, 2012.

[44] L. Zapparoli, P. Invernizzi, M. Gandola et al., "Mental images across the adult lifespan: a behavioural and fMRI investigation of motor execution and motor imagery," *Experimental Brain Research*, vol. 224, no. 4, pp. 519–540, 2013.

[45] N. Diersch, A. L. Jones, and E. S. Cross, "The timing and precision of action prediction in the aging brain," *Human Brain Mapping*, vol. 37, no. 1, pp. 54–66, 2016.

[46] M. C. Costello and E. K. Bloesch, "Are older adults less embodied? A review of age effects through the lens of embodied cognition," *Frontiers in Psychology*, vol. 8, p. 267, 2017.

[47] E. Kuehn, M. B. Perez-Lopez, N. Diersch, J. Döhler, T. Wolbers, and M. Riemer, "Embodiment in the aging mind," *Neuroscience & Biobehavioral Reviews*, vol. 86, pp. 207–225, 2018.

[48] D. K. Sumanapala, L. A. Fish, A. L. Jones, and E. S. Cross, "Have I grooved to this before? Discriminating practised and observed actions in a novel context," *Acta Psychologica*, vol. 175, pp. 42–49, 2017.

[49] N. Diersch, K. Mueller, E. S. Cross, W. Stadler, M. Rieger, and S. Schütz-Bosbach, "Action prediction in younger versus older adults: neural correlates of motor familiarity," *PLoS One*, vol. 8, no. 5, article e64195, 2013.

[50] M. N. Hebart, K. Görgen, and J. D. Haynes, "The decoding toolbox (TDT): a versatile software package for multivariate analyses of functional imaging data," *Frontiers in Neuroinformatics*, vol. 8, p. 88, 2015.

[51] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state": a practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[52] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, 1971.

[53] B. Calvo-Merino, C. Jola, D. E. Glaser, and P. Haggard, "Towards a sensorimotor aesthetics of performing art," *Consciousness and Cognition*, vol. 17, no. 3, pp. 911–922, 2008.

[54] C. Giacosa, F. J. Karpati, N. E. V. Foster, V. B. Penhune, and K. L. Hyde, "Dance and music training have different effects on white matter diffusivity in sensorimotor pathways," *NeuroImage*, vol. 135, pp. 273–286, 2016.

[55] F. J. Karpati, C. Giacosa, N. E. V. Foster, V. B. Penhune, and K. L. Hyde, "Sensorimotor integration is enhanced in dancers and musicians," *Experimental Brain Research*, vol. 234, no. 3, pp. 893–903, 2016.

[56] D. H. Brainard, "The psychophysics toolbox," *Spatial Vision*, vol. 10, no. 4, pp. 433–436, 1997.

[57] D. G. Pelli, "The VideoToolbox software for visual psychophysics: transforming numbers into movies," *Spatial Vision*, vol. 10, no. 4, pp. 437–442, 1997.

[58] M. Kleiner, D. H. Brainard, D. G. Pelli, A. Ingling, R. Murray, and C. Broussard, "What's new in Psychtoolbox-3," *Perception*, vol. 36, no. 14, pp. 1–6, 2007.

[59] C. Bellebaum, M. Tettamanti, E. Marchetta et al., "Neural representations of unfamiliar objects are modulated by sensorimotor experience," *Cortex*, vol. 49, no. 4, pp. 1110–1125, 2013.

[60] C. Cortes and V. Vapnik, "Support-vector networks," *Machine Learning*, vol. 20, no. 3, pp. 273–297, 1995.

[61] N. Kriegeskorte, *Crossvalidation in Brain Imaging Analysis*, BioRxiv, 2015.

[62] K. R. Muller, S. Mika, G. Ratsch, K. Tsuda, and B. Scholkopf, "An introduction to kernel-based learning algorithms," *IEEE Transactions on Neural Networks*, vol. 12, no. 2, pp. 181–201, 2001.

[63] R. D. Seidler, J. A. Bernard, T. B. Burutolu et al., "Motor control and aging: links to age-related brain structural, functional, and biochemical effects," *Neuroscience & Biobehavioral Reviews*, vol. 34, no. 5, pp. 721–733, 2010.

[64] M. E. Tinetti, "Performance-oriented assessment of mobility problems in elderly patients," *Journal of the American Geriatrics Society*, vol. 34, no. 2, pp. 119–126, 1986.

[65] E. S. Cross, W. Stadler, J. Parkinson, S. Schütz-Bosbach, and W. Prinz, "The influence of visual training on predicting complex action sequences," *Human Brain Mapping*, vol. 34, no. 2, pp. 467–486, 2013.

[66] A. E. Cavanna and M. R. Trimble, "The precuneus: a review of its functional anatomy and behavioural correlates," *Brain*, vol. 129, no. 3, pp. 564–583, 2006.

[67] C. Grefkes, A. Ritzl, K. Zilles, and G. R. Fink, "Human medial intraparietal cortex subserves visuomotor coordinate transformation," *NeuroImage*, vol. 23, no. 4, pp. 1494–1506, 2004.

[68] N. Wenderoth, F. Debaere, S. Sunaert, and S. P. Swinnen, "The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour," *The European Journal of Neuroscience*, vol. 22, no. 1, pp. 235–246, 2005.

[69] P. Linortner, M. Jehna, H. Johansen-Berg et al., "Aging associated changes in the motor control of ankle movements in the brain," *Neurobiology of Aging*, vol. 35, no. 10, pp. 2222–2229, 2014.

[70] T. Wu, K. Kansaku, and M. Hallett, "How self-initiated memorized movements become automatic: a functional MRI study," *Journal of Neurophysiology*, vol. 91, no. 4, pp. 1690–1698, 2004.

[71] S. Higuchi, H. Holle, N. Roberts, S. B. Eickhoff, and S. Vogt, "Imitation and observational learning of hand actions: prefrontal involvement and connectivity," *NeuroImage*, vol. 59, no. 2, pp. 1668–1683, 2012.

[72] P. Vieweg, M. Stangl, L. R. Howard, and T. Wolbers, "Changes in pattern completion—a key mechanism to explain

age-related recognition memory deficits?," *Cortex*, vol. 64, pp. 343–351, 2015.

[73] K. Z. H. Li, U. Lindenberger, A. M. Freund, and P. B. Baltes, "Walking while memorizing: age-related differences in compensatory behavior," *Psychological Science*, vol. 12, no. 3, pp. 230–237, 2016.

[74] J. Carp, J. Park, A. Hebrank, D. C. Park, and T. A. Polk, "Age-related neural dedifferentiation in the motor system," *PLoS One*, vol. 6, no. 12, article e29411, 2011.

[75] J. Carp, J. Park, T. A. Polk, and D. C. Park, "Age differences in neural distinctiveness revealed by multi-voxel pattern analysis," *NeuroImage*, vol. 56, no. 2, pp. 736–743, 2011.

[76] J. Park, J. Carp, A. Hebrank, D. C. Park, and T. A. Polk, "Neural specificity predicts fluid processing ability in older adults," *The Journal of Neuroscience*, vol. 30, no. 27, pp. 9253–9259, 2010.

[77] C. Lustig, P. Shah, R. Seidler, and P. A. Reuter-Lorenz, "Aging, training, and the brain: a review and future directions," *Neuropsychology Review*, vol. 19, no. 4, pp. 504–522, 2009.

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Research Article

Action Observation Treatment Improves Upper Limb Motor Functions in Children with Cerebral Palsy: A Combined Clinical and Brain Imaging Study

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The aim of the present study was to assess the role of action observation treatment (AOT) in the rehabilitation of upper limb motor functions in children with cerebral palsy. We carried out a two-group, parallel randomized controlled trial. Eighteen children (aged 5–11 yr) entered the study: 11 were treated children, and 7 served as controls. Outcome measures were scores on two functional scales: Melbourne Assessment of Unilateral Upper Limb Function Scale (MUUL) and the Assisting Hand Assessment (AHA). We collected functional scores before treatment (T1), at the end of treatment (T2), and at two months of follow-up (T3). As compared to controls, treated children improved significantly in both scales at T2 and this improvement persisted at T3. AOT has therefore the potential to become a routine rehabilitation practice in children with CP. Twelve out of 18 enrolled children also underwent a functional magnetic resonance study at T1 and T2. As compared to controls, at T2, treated children showed stronger activation in a parieto-premotor circuit for hand-object interactions. These findings support the notion that AOT contributes to reorganize brain circuits subserving the impaired function rather than activating supplementary or vicariating ones.

1. Introduction

There is an urgent need in neurorehabilitation of both adults and children of approaches that take into account the progresses of our knowledge in basic neuroscience. These approaches should aim at transferring ideas and facts from basic neuroscience to clinical practice with the final goal to build up tools well-grounded in neurophysiology and to provide a cure for several neurological (and non-neurological) diseases [1, 2]. Such a rehabilitation approach, grounded in basic neuroscience, would also be a model of translational medicine.

The use of such approaches may help to overwhelm a general attitude in neurorehabilitation to focus on ways to circumvent functional deficits, thus leading to a compensation or a reeducation of functions rather than a cure for them through remediation (for a more general discussion on the notion of compensation and remediation, see [3–5]). Although compensation sometimes works and helps patients to recover in daily activities, it does not aim at repairing the

neural circuits underlying specific functions through a direct or indirect restoration. Moving to a translational model in neurorehabilitation would imply to plan specific rehabilitative tools aiming at restoring the neural structures whose damage caused the impaired functions or activating supplementary or related pathways, which may perform the original functions. Last, but not least, rehabilitation tools well-grounded in basic neuroscience allow researchers to plan well-designed randomized controlled trials. This in turn allows clinicians and therapists to measure outcomes not only in terms of functional and/or behavioural gains (as it currently happens by means of functional scales) but also in terms of changes in biological parameters, which researchers can test using neurophysiological and brain imaging techniques. There are indeed some approaches in the neurorehabilitation of children that fit these criteria. For example, constraint-induced movement therapy (CIMT) has a well-established neurophysiological basis grounded on the experimental evidence that monkeys can be induced to use a deafferented limb by restricting movements of the unaffected limb over a period of days [6]. CIMT has been widely applied in patients with acute and chronic stroke and in children with cerebral palsy [7]; similarly, HABIT (hand-arm bimanual intensive training) is a highly structured form of bimanual training, whose goal is to improve the quality and quantity of hand use in bimanual tasks in children with hemiplegic CP [7]. Another example is the mirror therapy [8]. In this treatment, a mirror is placed in the patient's midsagittal plane so that he/she can see her unaffected arm/hand as if it were the affected one. This strategy has been proven to be effective to relieve phantom pain in arm amputees as well as in the recovery of upper limb in chronic stroke patients and in children with cerebral palsy [9, 10]. This approach grounds on a neurophysiological mechanism known as mirror mechanism. Based on this mechanism, the observation of actions performed by other individuals recruits in the observer the same areas involved in the actual execution of those same actions [11]. In the case of mirror therapy, patients have the opportunity to look at their own actions performed with the unaffected arm/hand. More recently, we proposed a novel approach in neurorehabilitation known as action observation treatment (for a review, see Buccino [12]). AOT exploits the mirror mechanism in an even more straightforward manner than mirror therapy, because patients observe daily actions performed by other healthy individuals. During one typical session, patients observe a daily action and afterwards execute it in context. So far, this approach has been successfully applied in the rehabilitation of upper limb motor functions in chronic stroke patients, in motor recovery of Parkinson's disease patients, including those presenting with freezing of gait; interestingly, this approach also improved lower limb motor functions in postsurgical orthopaedic patients [13–16]. Pivotal studies were conducted also in children with cerebral palsy [17–19]. AOT is well-grounded in basic neuroscience, thus representing a valid model of translational medicine in the field of neurorehabilitation. Moreover, the results concerning its effectiveness have been collected in randomized controlled studies, thus being an example of evidence-based clinical practice. The present study aimed at assessing whether this novel rehabilitation approach has the potential to improve the functional recovery of children with CP aged 5–11 (primary school cycle in Italy), within a comprehensive rehabilitation program. The focus was on the recovery of upper limb motor functions. We used the same protocol of an earlier pilot study from our group [17]. We also tested whether this approach may lead to neural changes in the brain by means of a functional magnetic resonance study, in which we asked some of the children that entered the study to manipulate complex objects in the scanner. Control condition was the manipulation of a small sphere.

2. Methods

2.1. Study Design. We used a two-group, parallel randomized controlled trial. Recruitment criteria and methodological procedures were approved by the Ethical Committee of the Hospital of Brescia.

2.2. Participants. All children referred to the Centre of Child Neurology and Psychiatry at the Hospital of Brescia with a diagnosis of cerebral palsy (CP) were eligible. Inclusion criteria were the presence of CP confirmed by neuroimaging techniques (MRI), Manual Ability Classification System (MACS) ≤ 4 [20], verbal IQ > 70, age between 5 and 11 (primary school cycle in Italy), absence of major visual and/or auditory deficits, and no antiepileptic treatment. We enrolled a group of 18 children that met the inclusion/exclusion criteria. Before entering the study, the parents of each child gave written informed consent.

2.3. Allocation and Assessment. Patients were enrolled by one of the authors (Elisa Fazzi); enrolled children were randomly allocated to the treatment ($n = 11$) or the control group ($n = 7$) by means of a dedicated software. Both children and their parents were blind to group allocation. After randomization, children were evaluated clinically with a neurological examination carried out by two expert child neurologists (Elisa Fazzi, Anna Molinaro), while functional assessment was carried out by a physician blind to treatment allocation, using the Melbourne Assessment of Unilateral Upper Limb Function Scale (MUUL) and the Assisting Hand Assessment (AHA). MUUL consists of 16 items involving reaching, grasping, releasing, and manipulation, specifically developed to measure quality of upper limb motor functions in children with CP aged 5 to 16 [21]. It has been shown to have a good reliability on a sample of 20 children with different severity degrees of CP. AHA is a hand function evaluation instrument that measures and describes how children with an upper limb disability in one hand use his/her affected hand collaboratively with the nonaffected hand in bimanual actions [22]. In the present study, children underwent functional evaluation with MUUL and AHA at three different time points: at baseline (T1), at the end of the treatment (T2), and at two months of follow-up (T3).

2.4. Stimuli. We prepared fifteen video clips to be used during AOT in the treatment group, each showing a specific daily action implying the use of the arms/hands, (i.e., grasping an

object, using a pencil, and playing with Lego). All recorded actions were chosen among those which are familiar to children in primary school age. We used the same videos as in a previous study from our group [17]. In that study, we report also a complete list of all seen actions. In the videos, these everyday actions, performed both by normal children and adults, were recorded from different perspectives, to make the video clips more interesting and to sustain the attention of children during the rehabilitation sessions. Each action was subdivided into 3 or 4 constituent motor segments. For instance, eating a candy, one of the shown actions, was subdivided into taking the candy from the table, approaching it to the mouth, and giving back to the therapist. Each motor act was presented for 3 minutes so that the total duration of each video clip was 9–12 minutes. We also prepared the same number of video clips addressing various topics (geography, history, and science adapted for children) but with no motor content, for the control group. Video clips for the control group were also divided into three-four parts, each lasting 3 minutes.

2.5. Treatment Procedure. For 3 weeks, children in the treatment group attended daily rehabilitation sessions from Monday to Friday, during which they were asked to observe one movie showing an actor/an actress performing one specific daily action with the hand. Actions were presented in a fixed order according to their complexity, as judged by the experimenter.

After observation of each motor segment (3-4 per each video clip), children were required to execute for 2 minutes what observed to the best of their ability. They were advised that the quality of their imitation was not the goal of the rehabilitation treatment. Children in the control group viewed short video clips (for the same time as treated participants) showing scenes with no motor content (e.g., geographical documentaries). After observing each part of a video clip (3-4 parts per each video clip), controls were also asked to execute the same actions as treated participants for the same duration. In this way, the total amount of visual stimulation and motor activity following observation was similar in the two groups. The only difference concerned the content of videos: treated participants observed videos with motor content (everyday arm/hand actions), while controls observed videos with no specific motor content. As a whole, each rehabilitation session lasted about half an hour. The physiotherapist devoted up to 10 minutes to explain the task and encourage children to observe carefully the videos and perform the seen actions at their best. Twelve minutes was devoted to observation (motor acts for cases, documentaries for controls) and 8 minutes to the execution of the observed actions (cases) or just execution of the same actions, but without a model (controls).

Both treated participants and controls received written instructions. The physiotherapist read them aloud twice. This was in order to avoid any influence of the physiotherapist in giving instructions.

During the treatment, children continued to follow their routine conventional rehabilitation program that was the same for cases and controls. All children (treated participants and controls) completed the study.

2.6. Outcome Measures. Primary outcome measures were score changes on the MUUL and AHA.

2.7. Statistical Analysis. A mixed linear model, with fixed effects: time (T1, T2, and T3) and group (treatment, control), was carried out on MUUL and AHA scores. The best model was identified using the Akaike information criterion (AIC). The significance level was set at 0.05. Statistical analyses were carried out using SPSS version 23.

2.8. fMRI Study. Twelve children (six treated participants) out of 18 enrolled children also entered an fMRI study to assess a reorganization of brain neural structures following treatment. While being scanned, children with CP from both groups manipulated complex objects with both hands, in order to explore all the motor properties of the manipulated object. As a control condition, children manipulated a simple object, a sphere. All objects used in the scanner were different from those used during the treatment. Figure 1(a) shows the experimental paradigm. fMRI data were collected on a 1.5T Siemens Avanto scanner. The protocol included four EPI sequences (TR/TE 2500/50 ms, $3.3 \times 3.3 \times 3.3$ mm isotropic voxel) and a high resolution T1W 3D MP-RAGE sequence for anatomical reference (TR/TE 2050/2.56 ms, $1 \times 1 \times 1$ mm isotropic voxel). Imaging data were collected before starting treatment (T1) and at the end of treatment (T2). The fMRI paradigm consisted of 14 alternating task-rest blocks (8 volumes/block were acquired) repeated 4 times to increase statistics. fMRI data underwent the following preprocessing. The mean EPI was first computed for each participant and visually inspected to ensure that none showed artifacts. The first 2 EPI volumes of each functional run were discarded to allow for T1 equilibration effects. For each subject, all volumes were spatially realigned to the mean volume of the four runs. Next, the 3D structural data of each subject were normalized to the ANTS standard space, a T1 pediatric template in a standardized MNI space [23]. The normalization matrix was subsequently transferred to the fMRI images, resampled in $1\,\text{mm} \times 1\,\text{mm} \times 1\,\text{mm}$ voxels using trilinear interpolation in space and then the images were spatially smoothed with a 6 mm full width at half maximum isotropic Gaussian kernel for the group analysis. No participant showed head movements greater than 3 mm; thus, none was excluded from further analyses.

Data were analyzed using a random effects model [24], implemented in a two-level procedure. In the first level, single-subject fMRI data entered an independent general linear model (GLM) by design matrixes modelling the onsets and durations of two experimental factors, one related to the experimental task and one related to its corresponding baseline. For each participant, we generated contrast images displaying the effect of the experimental task (manipulating complex objects) contrasted with the respective baseline (manipulating a sphere). Next, each contrast entered a second level GLM to obtain (i) SPM{T} maps (one sample t-test) related to each task at group level and (ii) to test for the

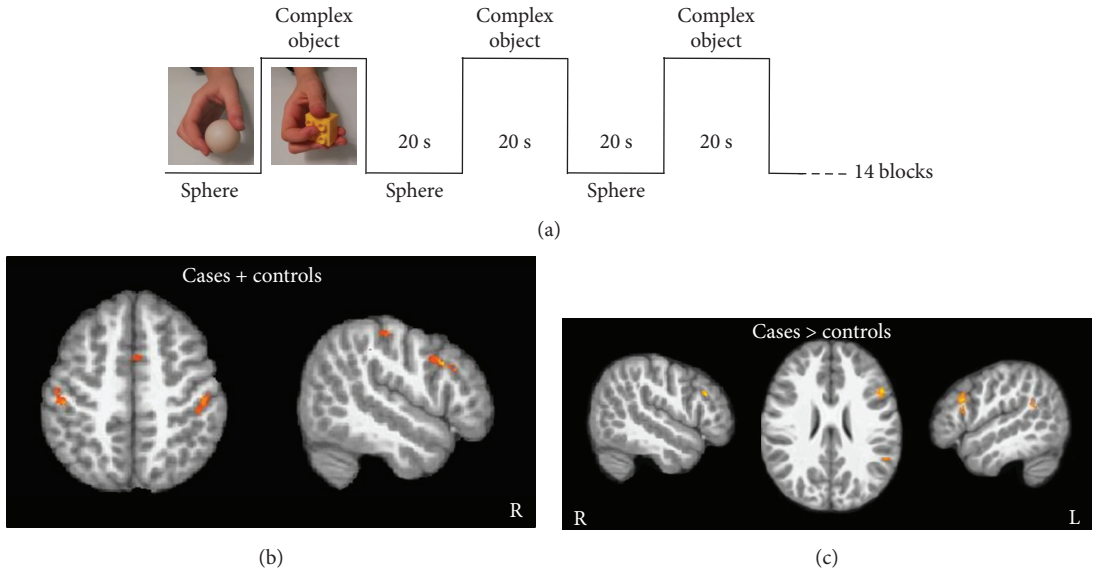

Figure 1: (a) Graphic representation of the fMRI experimental paradigm, alternating manipulation of a simple object (a sphere), and manipulation of complex objects. (b) Clusters of activations transposed on sections from standard pediatric brain (ANTS) before treatment (T1), when comparing manipulation of complex objects versus manipulation of a sphere. Cases and controls are taken as a whole group, $p < 0.001$. Note that at T1, no activation was present when directly comparing cases versus controls. (c) After treatment (T2), direct comparison between cases and controls shows increased activations in frontal and parietal areas known to be involved in hand-object interactions, $p < 0.001$. Clusters of activations transposed on sections from standard pediatric brain (ANTS), as in (b).

existence of brain areas specifically involved in manipulating complex objects. Moreover, we were interested in assessing differences in brain area recruitment between treated children and controls. For all analyses, location of the activation foci was determined in the stereotaxic space of the MNI coordinates system. A significance level of $p < 0.001$ uncorrected and an extended threshold on cluster dimension of 10 voxels was applied.

3. Results

Demographic data, clinical features, and brain imaging findings of children in the two groups are shown in Table 1. Mean scores and SD of AHA and MUUL in treated participants and controls at T1, T2, and T3 are shown in Table 2.

Mixed linear model showed that for MUUL, the best model included the random effects of intercept and the fixed effect of group, time, and interaction. For the AHA, the best model included the random effects of intercept and time and the fixed effects of group and interaction. The mixed linear model analysis disclosed a significant interaction between time and treatment, both for MUUL (b_1 interaction = 2.71, $t_{36} = 3.99$, and $p = 0.000$) and for AHA (b_1 interaction = 2.36, $t_{18} = 3.61$, $p = 0.002$). Score improvements, in both scales, were higher in the treated participants than in the controls; furthermore, in the treatment group, those improvements were not only maintained but became even stronger at T3.

Post hoc analysis showed that for MUUL, results at T2 were significantly different from results at T1 only in cases ($p < 0.001$), but not in controls. As for AHA, results at T2 were significantly different from results at T1 ($p < 0.001$). Even more interestingly, results at T3 were different from results at T2 ($p < 0.001$) for both scales, but again only in cases, but not in controls. Figure 2 shows the results.

4. fMRI Results

For the aim of the present study, we will present results concerning the differences between treated children and controls. It is worth stressing that at baseline (T1), there were no differential activations when comparing cases versus controls. In contrast, after treatment (T2), differential activations were located in the left premotor cortex extending to the inferior frontal gyrus (−49; 19; 26), in the right premotor cortex (53; 14; 31), in the left supramarginal gyrus (−47; −51; 37), and finally a weaker activation in the left superior temporal gyrus (−52; −47; 23). Figures 1(a) and 1(b) shows fMRI findings.

5. Discussion

The results of the present study are relevant within the literature devoted to rehabilitation of children with cerebral palsy. Treated children improved significantly as compared to controls in both MUUL and AHA. These results are in keeping with earlier, pilot studies using AOT as a rehabilitation tool [17, 18]. It is worth stressing that our sample consisted of hemiplegic (both right and left) and tetraplegic children, thus suggesting that AOT may be useful for different clinical presentations of CP. As reported above, AOT exploits a neurophysiological mechanism known as mirror mechanism. The observation of actions performed by other individuals recruits in the observer the same areas involved in the actual execution of those same actions [11], this whatever the biological effector involved in the observed

Table 1: Demographic data, clinical features, and radiological findings in treated participants and controls.

Pt. number	Case/ control	Sex (M, F)	GA (wk)	Age (yr, m)	CP type Hagberg	Motor abnormalities	GMFCS	MACS	CFCS	Associated impairments	Total IQ	Verbal IQ	Performance IQ	Radiological findings (brain MRI)
1	Case	M	33	9 yr, 5 m	Right hemiplegia	Unilateral spastic hypertonia	2	2	1	V: CVI; H: no; M/A: no; LD: no; E: no	85	92	82	Right temporooccipital, left occipitoparietal, bilateral periventricular, and left frontotemporal subdural hematomas
2	Case	F	27	8 yr, 2 m	Right hemiplegia	Unilateral spastic hypertonia	1	2	1	V: ROP; H: no; M/A: no; LD: no; E: no	100	106	107	Mild bilateral periventricular leukomalacia, mild ventricular dilatation
3	Control	M	40	7 yr, 10 m	Right hemiplegia	Unilateral spastic hypertonia	2	2	1	V: no; H: no; M/A: no; LD: no; E: no	99	101	97	Left subdural occipitotemporal hematoma and epidural parietotemporal hematoma; hypoxic ischemic encephalopathy characterized by signal alterations in both putamen tail and anterior thalamus
4	Control	M	34	8 yr, 3 m	Tetraplegia	Bilateral spastic hypertonia, left side more affected	4	3	2	V: CVI; H: no; M/A: yes; LD: no; E: no	73	97	50	Hypoxic ischemic injury with thinning of the corpus callosum, enlargement of CSF spaces, widespread hyperintensity of centrum semiovale, corona radiata, and periventricular white matter, dilation of the ventricles
5	Control	F	40	6 yr, 8 m	Tetraplegia	Bilateral spastic hypertonia, left side more affected	4	2	3	V: CVI; H: no; M/A: yes; LD: no; E: no	114	139	77	Diffuse periventricular hyperintensity with parietal bilateral white matter involvement; mild dilatation of bilateral ventricular trigone
6	Case	F	30	11 yr, 9 m	Tetraplegia	Bilateral spastic hypertonia, left side more affected	4	3	2	V: CVI; H: no; M/A: yes; LD: yes; E: yes	56	89	50	Periventricular leukomalacia, fronto-parieto-occipital white matter reduction, ex vacuo enlargement of bilateral ventricles

Table 1: Continued.

Pt. number	Case/ control	Sex (M, F)	GA (wk)	Age (yr, m)	CP type Hagberg	Motor abnormalities	GMFCS	MACS	CFCS	Associated impairments	Total IQ	Verbal IQ	Performance IQ	Radiological findings (brain MRI)
7	Control	F	37	9 yr, 1 m	Right hemiplegia	Unilateral spastic hypertonia	1	2	1	V: CVI; H: no; M/A: yes; LD: no; E: no	87	84	100	Left periventricular malacic area with gliosis, extended into the corona radiata; left corticospinal projection hyperintensisty with mild cerebellar peduncle hypotrophy (Wallerian degeneration)
8	Control	F	31	8 yr, 9 m	Right hemiplegia	Unilateral spastic hypertonia	2	1	1	V: CVI; H: no; M/A: no; LD: no; E: no	87	99	77	Bilateral parietal cystic periventricular leukomalacia, with centrum semiovale white matter involvement, short distance between cortex and ventricular walls in temporoparietal areas, thinning of the corpus callosum
9	Case	F	Not known	11 yr, 9 m	Left hemiplegia	Unilateral spastic hypertonia	2	2	1	V: no; H: no; M/A: no; LD: no; E: yes	Leiter -R 82			Right fronto-parieto-temporal malacic area, ex vacuo enlargement of the ventricle and Wallerian degeneration of the corticospinal tract
10	Case	M	32	6 yr, 10 m	Tetraplegia	Bilateral spastic hypertonia, right side more affected	3	2	2	V: CVI; H: no; M/A: yes; LD: no; E: no	89	120	70	Periventricular leukomalacia, corpus callosum hypoplasia, hippocampal commissure agenesis
11	Control	M	38	5 yr, 2 m	Right hemiplegia	Unilateral spastic hypertonia	2	3	2	V: CVI; H: no; M/A: no; LD: no; E: no	98	118	87	Cortical laminar necrosis (left insular cortex, left frontoparietal areas, and left temporal lobe). Signal T2 and FLAIR hyperintensity in the left caudate nucleus and in the left corona radiata (ischemic event)

Table 1: Continued.

Pt. number	Case/ control	Sex (M, F)	GA (wk)	Age (yr, m)	CP type Hagberg	Motor abnormalities	GMFCS	MACS	CFCS	Associated impairments	Total IQ	Verbal IQ	Performance IQ	Radiological findings (brain MRI)
12	Case	F	31	10 yr, 1 m	Tetraplegia	Bilateral spastic hypertonia, left side more affected	4	3	3	V: CVI; H: no; M/A: yes; LD: no; E: no	85	92	82	Severe periventricular leukomalacia with major involvement of the posterior area, associated with supra- and subtentorial ventricular dilatation and subarachnoid spaces enlargement, thinning of the corpus callosum
13	Case	F	41	8 yr, 2 m	Right hemiplegia	Unilateral spastic hypertonia	3	2	1	V: CVI; H: no; M/A: no; LD: no; E: yes	87	99	77	Left hemispheric atrophy (previous extensive left frontoparietal intraparenchymal hemorrhage, wide left parietal subdural hematoma), ex vacuo dilatation of the ipsilateral ventricles and midline brain right to left shift, Wallerian degeneration of the corticospinal tract and ipsilateral cerebellar peduncle atrophy
14	Case	M	33	5 yr, 10 m	Right hemiplegia	Unilateral spastic hypertonia	2	3	2	V: strabismus; H: no; M/A: no; LD: no; E: no	85	92	82	Left fronto-parieto-temporo-insular polymicrogyria (perisylvian and perirolandic with cortical infolding), mild left temporal atrophy with subarachnoid spaces enlargement
15	Case	F		6 yr, 8 m	Left hemiplegia	Unilateral spastic hypertonia	4	3	1	V: no; H: no; M/A: yes; LD: no; E: yes	100	106	107	Ischemic right frontoparietal malacic area with focal cortical atrophy, gliosis, subarachnoid space enlargement, and mid ipsilateral ventricular dilatation. Mild controlateral periventricular white matter hyperintensity

Table 1: Continued.

Pt. number	Case/ control	Sex (M, F)	GA (wk)	Age (yr, m)	CP type Hagberg	Motor abnormalities	GMFCS	MACS	CFCS	Associated impairments	Total IQ	Verbal IQ	Performance IQ	Radiological findings (brain MRI)
16	Case	M	38	6 yr, 3 m	Left hemiplegia	Unilateral spastic hypertonia	2	3	2	V: no; H: no; M/A: no; LD: no; E: no	99	101	97	Malacic areas affecting the right middle cerebral artery territory with Wallerian degeneration of the corticospinal tract and of the thalamus, left hemisphere hypotrophy
18	Case	M	40	5 yr, 3 m	Left hemiplegia	Unilateral spastic hypertonia	2	3	1	V: strabismus; H: no; M/A: no; LD: no; E: yes	101	106	100	Right periventricular porencephalic lesion (hemorrhagic venous infarct) with hemosiderin deposition and Wallerian degeneration of the ipsilateral corticospinal tract
18	Control	M	36	6 yr, 4 m	Left hemiplegia	Unilateral spastic hypertonia	1	2	1	V: no; H: no; M/A: no; LD: no; E: no	90	94	93	Supratentorial right malacic areas with right lateral ventricular dilatation; hemosiderin deposition secondary to germinal matrix hemorrhage

M: male; F: female; GA: gestational age; CP: cerebral palsy; GMFCS: Gross Motor Function Classification System; MACS: Manual Ability Classification System; CFCS: Communication Function Classification System; V: vision; CVI: cerebral visual impairment; H: hearing; M/A: memory and attention; LD: learning disabilities (North American usage; mental retardation); E: epilepsy; MRI: magnetic resonance imaging.

Table 2: Mean scores (and SD) of AHA and MUUL in controls and treated participants at different time points.

Group	Score	Time point T1	T2	T3
Control	AHA	65.71 (7.23)	66.86 (7.31)	66.71 (7.52)
	MUUL	96.00 (16.73)	98.00 (16.69)	98.14 (16.52)
Treatment	AHA	57.45 (12.18)	61.09 (10.79)	63.18 (11.06)
	MUUL	81.73 (22.38)	87.27 (22.36)	89.27 (22.41)

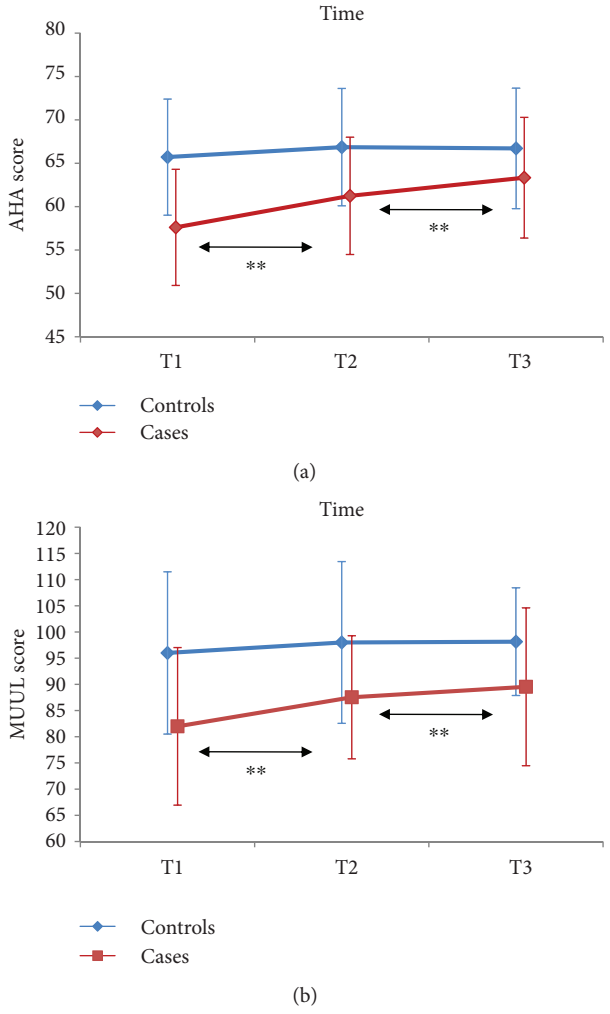

Figure 2: Scores obtained by cases (red line) and controls (blue line) at T1, T2, and T3 in two different functional scales (AHA, MUUL). Statistical analysis (see text for details) showed that only in case scores obtained at T2 differed significantly from scores at T1 in both scales. This was true also when comparing T3 with T2 in both scales (error bars: 95% CI). **refers to statistical significant effects.

action. This mechanism may underlie the capacity to understand and imitate others' actions even at an early stage of life [25, 26] and contribute to interact with other people in an empathic manner (for review see, Hari and Kujala) [27]. This same mechanism may be helpful during learning motor tasks or relearning daily actions following brain lesions and therefore during rehabilitation [28–30]. AOT has the potential to become a routine approach in the rehabilitation of children with CP and could be easily applied by physiotherapists working with children. During the rehabilitation session, physiotherapists have the role to motivate little patients to observe carefully every detail of the observed actions and to push children to use the objects provided at hand, as in the videos, but also to reassure if children fail in performing the observed actions. Patients, even children as in the present study, may follow the rehabilitation program without difficulties. It is worth stressing that AOT may be applied in a very flexible manner: in fact, the trained actions, presented through videos, may vary depending on the real need of patients. For example, children that have more difficulties in performing distal hand/arm actions (i.e., grasping, manipulating) should focus their training on these motor tasks, while children that present with impairment of proximal arm actions (i.e., reaching objects, coding objects in space) should train this kind of motor tasks. Last, but not least, AOT may be used also at home where children may get their rehabilitation session with the help of their parents or even in telerehabilitation with a physiotherapist monitoring from a dedicated position what children perform at home.

In the present study, we collected functional scores on MUUL and AHA also at two months of follow-up. Interestingly, treated children, as compared to controls, maintained and even improved their functional gain at follow-up. In our opinion, these findings may be explained by the fact that during AOT, children learn novel strategies to interact with other people and common objects. They learn to look very carefully at all details present in the scene, they pay attention at the different motor segments of an action, and they spontaneously prepare themselves to imitate a seen action or to interact upon objects available in the environment. Eventually, they transfer these strategies in everyday life situations; thus at the very end, they accomplish the goal of gaining better motor performances.

A main point of interest in the present study is that some of the treated children also underwent an fMRI study aimed at assessing whether AOT may recruit areas within the motor system and eventually contribute to their reorganization. It is worth noting that, while being scanned, children performed an independent task, namely, manipulation of complex objects that were not included in the set of actions trained during the treatment. When comparing treated participants and controls, differential activation was present in a sector of the premotor cortex and parietal cortex also involved in object manipulation in both healthy adults and children [31, 32] and known to be endowed with a motor representation of distal upper limb movements. This premotor sector is strictly connected with a parietal area with which it builds up a sensorimotor circuit allowing individuals to code for the motor properties of objects and the implementation of the most appropriate actions to act upon objects [33]. These findings suggest that the brain target of AOT is exactly a hand motor area possibly involved in executing actions as well as in their processing. It therefore appears that there are not vicariating areas emerging from AOT treatment, but rather a recovery of areas normally involved in a specific

hand motor task. Further studies should assess to what extent this concerns also other biological effectors (e.g., the foot) and contributes to rebuild physiological sensorimotor circuits. Another issue that future studies should help to ascertain is whether there are specific subgroups of children with cerebral palsy that may mostly benefit from AOT, or rather this approach may help clinical conditions in all children affected.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] S. L. Small, G. Buccino, and A. Solodkin, "Brain repair after stroke-a novel neurological model," *Nature Reviews Neurology*, vol. 9, no. 12, pp. 698–707, 2013.

[2] E. Taub, G. Uswatte, and T. Elbert, "New treatments in neurorehabilitation founded on basic research," *Nature Reviews Neuroscience*, vol. 3, no. 3, pp. 228–236, 2002.

[3] A. Roby-Brami, A. Feydy, M. Combeaud, E. V. Biryukova, B. Bussel, and M. F. Levin, "Motor compensation and recovery for reaching in stroke patients," *Acta Neurologica Scandinavica*, vol. 107, no. 5, pp. 369–381, 2003.

[4] M. F. Levin, J. A. Kleim, and S. L. Wolf, "What do motor "recovery" and "compensation" mean in patients following stroke?," *Neurorehabilitation and Neural Repair*, vol. 23, no. 4, pp. 313–319, 2009.

[5] P. S. Lum, S. Mulroy, R. L. Amdur, P. Requejo, B. I. Prilutsky, and A. W. Dromerick, "Gains in upper extremity function after stroke via recovery or compensation: potential differential effects on amount of real-world limb use," *Topics in Stroke Rehabilitation*, vol. 16, no. 4, pp. 237–253, 2009.

[6] R. J. Nudo, "Mechanisms for recovery of motor function following cortical damage," *Current Opinion in Neurobiology*, vol. 16, no. 6, pp. 638–644, 2006.

[7] L. Sakzewski, A. Gordon, and A. C. Eliasson, "The state of the evidence for intensive upper limb therapy approaches for children with unilateral cerebral palsy," *Journal of Child Neurology*, vol. 29, no. 8, pp. 1077–1090, 2014.

[8] V. S. Ramachandran and E. L. Altschuler, "The use of visual feedback, in particular mirror visual feedback, in restoring brain function," *Brain*, vol. 132, no. 7, pp. 1693–1710, 2009.

[9] H. Thieme, J. Mehrholz, M. Pohl, J. Behrens, and C. Dohle, "Mirror therapy for improving motor function after stroke," *Stroke*, vol. 44, no. 1, pp. e1–e2, 2013.

[10] R. Bruchez, M. Jequier Gygax, S. Roches et al., "Mirror therapy in children with hemiparesis: a randomized observer-blinded trial," *Developmental Medicine & Child Neurology*, vol. 58, no. 9, pp. 970–978, 2016.

[11] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[12] G. Buccino, "Action observation treatment: a novel tool in neurorehabilitation," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 369, no. 1644, article 20130185, 2014.

[13] G. Bellelli, G. Buccino, B. Bernardini, A. Padovani, and M. Trabucchi, "Action observation treatment improves recovery of postsurgical orthopedic patients: evidence for a topdown effect?," *Archives of Physical Medicine and Rehabilitation*, vol. 91, no. 10, pp. 1489–1494, 2010.

[14] D. Ertelt, S. Small, A. Solodkin et al., "Action observation has a positive impact on rehabilitation of motor deficits after stroke," *NeuroImage*, vol. 36, Supplement 2, pp. T164–T173, 2007.

[15] E. Pelosin, L. Avanzino, M. Bove, P. Stramesi, A. Nieuwboer, and G. Abbruzzese, "Action observation improves freezing of gait in patients with Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 24, no. 8, pp. 746–752, 2010.

[16] G. Buccino, R. Gatti, M. C. Giusti et al., "Action observation treatment improves autonomy in daily activities in Parkinson's disease patients: results from a pilot study," *Movement Disorders*, vol. 26, no. 10, pp. 1963-1964, 2011.

[17] G. Buccino, D. Arisi, P. Gough et al., "Improving upper limb motor functions through action observation treatment: a pilot study in children with cerebral palsy," *Developmental Medicine & Child Neurology*, vol. 54, no. 9, pp. 822–828, 2012.

[18] G. Sgandurra, A. Ferrari, G. Cossu, A. Guzzetta, L. Fogassi, and G. Cioni, "Randomized trial of observation and execution of upper extremity actions versus action alone in children with unilateral cerebral palsy," *Neurorehabilitation and Neural Repair*, vol. 27, no. 9, pp. 808–815, 2013.

[19] J. Y. Kim, J. M. Kim, and E. Y. Ko, "The effect of the action observation physical training on the upper extremity function in children with cerebral palsy," *Journal of Exercise Rehabilitation*, vol. 10, no. 3, pp. 176–183, 2014.

[20] A. C. Eliasson, L. Krumlinde-Sundholm, B. Rösblad et al., "The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability," *Developmental Medicine & Child Neurology*, vol. 48, no. 7, pp. 549–554, 2006.

[21] M. Randall, J. B. Carlin, P. Chondros, and D. Reddihough, "Reliability of the Melbourne Assessment of Unilateral Upper Limb Function," *Developmental Medicine & Child Neurology*, vol. 43, no. 11, pp. 761–767, 2001.

[22] L. Krumlinde-Sundholm, M. Holmefur, A. Kottorp, and A. C. Eliasson, "The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change," *Developmental Medicine & Child Neurology*, vol. 49, no. 4, pp. 259–264, 2007.

[23] S. S. Ghosh, S. Kakunoori, J. Augustinack et al., "Evaluating the validity of volume-based and surface-based brain image registration for developmental cognitive neuroscience studies in children 4 to 11 years of age," *NeuroImage*, vol. 53, no. 1, pp. 85–93, 2010.

[24] K. J. Friston, A. P. Holmes, C. J. Price, C. Buchel, and K. J. Worsley, "Multisubject fMRI studies and conjunction analyses," *NeuroImage*, vol. 10, no. 4, pp. 385–396, 1999.

[25] A. N. Meltzoff and M. K. Moore, "Imitation of facial and manual gestures by human neonates," *Science*, vol. 198, no. 4312, pp. 75–78, 1977.

[26] T. Falck-Ytter, G. Gredebäck, and C. von Hofsten, "Infants predict other people's action goals," *Nature Neuroscience*, vol. 9, no. 7, pp. 878-879, 2006.

[27] R. Hari and M. V. Kujala, "Brain basis of human social interaction: from concepts to brain imaging," *Physiological Reviews*, vol. 89, no. 2, pp. 453–479, 2009.

[28] P. Celnik, B. Webster, D. M. Glasser, and L. G. Cohen, "Effects of action observation on physical training after stroke," *Stroke*, vol. 39, no. 6, pp. 1814–1820, 2008.

[29] K. Stefan, L. G. Cohen, J. Duque et al., "Formation of a motor memory by action observation," *The Journal of Neuroscience*, vol. 25, no. 41, pp. 9339–9346, 2005.

[30] R. Gatti, A. Tettamanti, P. M. Gough, E. Riboldi, L. Marinoni, and G. Buccino, "Action observation versus motor imagery in learning a complex motor task: a short review of literature and a kinematics study," *Neuroscience Letters*, vol. 540, pp. 37–42, 2013.

[31] F. Binkofski, G. Buccino, S. Posse, R. J. Seitz, G. Rizzolatti, and H. J. Freund, "A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study," *The European Journal of Neuroscience*, vol. 11, no. 9, pp. 3276–3286, 1999.

[32] L. Biagi, G. Cioni, L. Fogassi, A. Guzzetta, G. Sgandurra, and M. Tosetti, "Action observation network in childhood: a comparative fMRI study with adults," *Developmental Science*, vol. 19, no. 6, pp. 1075–1086, 2016.

[33] M. Jeannerod, M. A. Arbib, G. Rizzolatti, and H. Sakata, "Grasping objects: the cortical mechanisms of visuomotor transformation," *Trends in Neurosciences*, vol. 18, no. 7, pp. 314–320, 1995.

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Research Article

Mu Suppression Is Sensitive to Observational Practice but Results in Different Patterns of Activation in Comparison with Physical Practice

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Research has shown the effectiveness of observational practice for motor learning, but there continues to be debate about the mechanisms underlying effectiveness. Although cortical processes can be moderated during observation, after both physical and observational practice, how these processes change with respect to behavioural measures of learning has not been studied. Here we compared short-term physical and observational practice during the acquisition and retention of a novel motor task to evaluate how each type of practice modulates EEG mu rhythm (8–13 Hz). Thirty healthy individuals were randomly assigned to one of three groups: (1) physical practice (PP), (2) observational practice (OP), and (3) no practice (NP) control. There were four testing stages: baseline EEG, practice, postpractice observation, and delayed retention. There was significant bilateral suppression of mu rhythm during PP but only left lateralized mu suppression during OP. In the postpractice observation phase, mu suppression was bilateral and larger after PP compared to that after OP. NP control showed no evidence of suppression and was significantly different to both the OP and PP groups. When comparing the three groups in retention, the groups did not differ with respect to tracing times, but the PP group showed fewer errors, especially in comparison to the NP group. Therefore, although the neurophysiological measures index changes in the OP group, which are similar but moderated in comparison to PP, changes in these processes are not manifest in observational practice outcomes when assessed in a delayed retention test.

1. Introduction

A common instructional method in the teaching of motor skills has been to watch repeated demonstrations with the intention of later reproduction, so termed observational practice or observational learning (for recent reviews regarding its relative efficacy, see [1–6]). Many individuals, perhaps as a result of injury, neurological impairment, or fatigue, cannot engage in physical practice, at least all of the time, such that learning through observation serves as an alternative practice method for motor gains [7]. Despite the potential efficacy of this approach, at least in comparison to no-practice conditions, the mechanisms underpinning its efficacy are still debated, as well as its relative benefits in comparison to actual physical practice. In this paper, we evaluate the similarities and differences between observation and physical practice, in terms of both behavioural performance and learning outcomes as well as neurophysiological processes assessed through EEG and mu rhythm suppression.

We now know that watching others perform skills that are part of their existing motor repertoire engenders similar cortical neural processes to those apparent during actual action execution. There is a considerable body of research pointing towards a motor simulation circuit or mirror-neuron system

in the human brain that responds in a similar way to observed and executed movements, supporting the idea of a shared neural representation between action observation and action execution (for reviews, see [8–11]). There are a wide range of brain areas that are activated during both observation and execution of actions, with the primary regions including the ventral and dorsal premotor cortex (PMC) [12–16], the intraparietal cortex [13, 17] and the superior and inferior parietal lobule [14, 15, 18]. For a recent review of these areas, see a meta-analysis by Caspers et al. [19].

One index of mirror neuron activity that has been extensively studied in humans is mu (8–13 Hz) suppression. At rest, neurons in the sensorimotor area fire synchronously, resulting in large-amplitude EEG and MEG oscillations in the mu frequency band. When participants perform an action, imagine movement, or observe movements, these neurons fire asynchronously, decreasing the power of the mu band [20–25]. This suppression is known as alpha-band or mu-rhythm suppression (also related to event-related desynchronization (ERD)). It has been hypothesized that the mu rhythms reflect downstream modulation of primary sensorimotor areas by mirror neuron activity, representing a critical information processing function translating perception into action [26]. When comparisons have been made across execution and observation conditions, suppression is typically stronger in execution conditions [23]. For very simple movements (e.g., repetitive finger pointing [20]), as well as more functional movements (e.g., reaching and grasping a coffee cup [24]), bilateral suppression, particularly in central electrode sites, has been noted. Importantly, Virji-Babul et al. [27] showed that although both conditions activate similar brain areas, there were distinct differences in the timing and pattern of the activation. During movement execution, the earliest activation was observed in the left premotor and somatosensory regions, followed closely by left primary motor and superior temporal gyrus (STG) at the time of movement onset. In contrast, during observation, there was a shift in the timing of activation with the earliest activity occurring in the right temporal region followed by activity in the left motor areas, suggesting that there are important differences underlying the neural processes of action execution and action observation.

While there is now a significant body of literature linking perception and action in well-learned actions, studies looking at processes underpinning observation practice of new actions are still rather scarce. With respect to behavioural work, generally it has been shown that observation and physical practice can lead to similar behavioural (though weaker in observation) motor outcomes [4, 28, 29] (for a meta-analysis see Ashford et al. [30]). However, notable differences have also been reported. For example, although people learn from watching others perform novel visuomotor adaptation tasks, where people learn to move to radially aligned targets that are rotated from their veridical spatial position, observers do not show after-effects that are nearly always seen in physical practice participants [5, 31]. The absence of after-effects after observational practice has led to conclusions that the two modes of learning implicate distinct brain networks, with an absence or reduction in motor-system (implicit) adaptation following only observation practice.

There is also evidence supporting the idea that observation and physical practice involve similar "motor-related" mechanisms and networks. For example, in studies of sequence learning, observation learning effectiveness was specific to the observed hand [29, 32], suggesting effector-specific modulation of the motor system during observation. In studies where observers watched a learner adapt to a dynamic perturbation controlled by a robot arm, at least some of the observation learning effects appeared to be mediated by the observer's motor system (e.g., [33, 34]). This was shown through dual-task interference effects associated with performing a motor task during the observation practice phase as well as interference from a postobservation practice period of repetitive TMS (transcranial magnetic stimulation) to the primary motor cortex (M1).

There have been two general hypotheses concerning the transfer of information during observation learning [35]. The first is that information is primarily cognitively mediated (also termed late mediation), such that the motor system does not play a role in learning until the later physical enactment stage. The second is a primarily motor-mediated learning (also known as early mediation), whereby observation is thought to automatically activate the motor representations of the observed action in the observer's brain. This motor resonance or simulation is thought to allow for action understanding, and hence learning, to occur [35, 36]. Behavioural studies provide support for both proposals, suggesting that information transfer during observational practice could be a result of either or both processes. There have been no studies to date where measurement of both the neurophysiological and behavioural processes of observation and physical practice of the same task has been determined concurrently during both types of practice.

In relation to observational practice, Nakano et al. [37] recorded EEG signals during the observation, preparation, and execution of five trials of a two-ball-rotation task. Across all three conditions, mu suppression in the fifth trial was significantly greater than that in the first trial. However, no comparisons were made between a pure observation practice-only group and a physical practice group (i.e., after the first trial, the second observation phase was a combination of both observation and execution) and no efforts were made to assess learning, as based on a retention or transfer test [38, 39].

Neurophysiological responses have been probed during action observation under conditions where motor/physical practice experiences have already been attained. For example, EEG was recorded in professional dancers and nondancers while they watched video clips of dance movements and everyday movements. Expert dancers exhibited significantly more mu suppression compared to nondancers, with no difference between the two groups during the observation of everyday movements [40] (see also [41, 42]). However, Babiloni et al. [43] reported that long-term experience was associated with less mu rhythm suppression in action-observation-related areas during the observation of familiar actions.

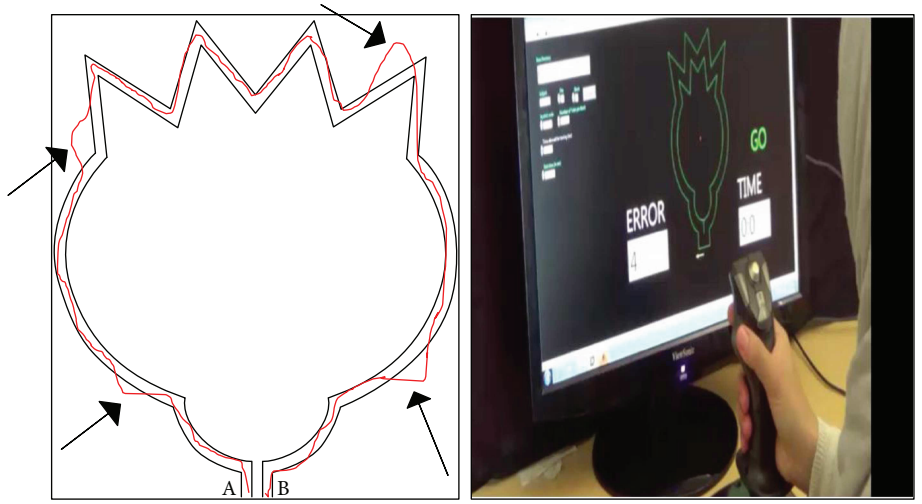

Figure 1: The flower-tracing task. Each arrow represents an error. The total tracing time starts at A and ends at B.

Despite evidence that physical experience modulates a subsequent observation phase with respect to EEG activity, to date, no researchers have studied how visual or physical/motor experiences with a novel motor task modulate EEG activity (specifically mu rhythm) during actual practice. Moreover, there have been no attempts to determine whether cortical activity changes noted in practice are evidenced in behavioural measures of motor learning, as assessed on a retention test. Therefore, in the present study, we compared short-term physical and observation practice during the acquisition and retention of a novel motor tracing task and evaluated how EEG mu rhythm is moderated during each type of practice. Our primary research question related to whether observational practice brings about change in EEG mu rhythm, comparable to that seen during physical practice, during "practice" of a novel motor task, and during a subsequent postpractice observation phase for both groups. To answer this question, EEG measurements were collected during either physical or observational practice across 45 trials of a flower-tracing task performed using a joystick. We also compared these two practice groups to a third, no-practice control group in a postpractice observation-only session. Relative to resting baseline, we hypothesized that mu rhythm would be suppressed at all the central interpolated channels for both the physical practice and the observation practice groups in comparison to the no-practice group, with greater suppression during physical practice.

Our second research question pertained to whether observational practice brings about behavioural evidence of motor learning, based on comparisons of the three groups in a delayed retention test. This delayed testing under the same conditions is regarded as a critical way of assessing motor learning, such that long-term effects of practice can be ascertained, uninfluenced by temporary factors associated with fatigue, motivation, or the conditions of practice [38, 39]. This delayed retention test was conducted without EEG, but all three groups were compared. We predicted that behavioural performance following physical practice would be improved when measured in a retention test compared to observation practice and no practice. However, if there are benefits to be gained from observation practice, we predicted that this group would perform faster and more accurately than the control group would. We expected that any differences in mu rhythm noted during practice and in the postpractice observation session would be evidenced in behavioural measures of motor learning as assessed on the delayed retention test.

2. Materials and Methods

2.1. Participants. Thirty healthy individuals between the ages of 19 and 40 years were recruited from the community. Participants were pseudo-randomly assigned to one of three groups with the constraint of $n = 10$/group and equal distributions of males and females (males = 3/group): physical practice (PP) ($M_{age} = 26.60$ yr, SD = 7.18), observation practice (OP) ($M_{age} = 24.4$ yr, SD = 3.37), and no practice (NP) control group ($M_{age} = 27.70$ yr, SD = 6.0). All participants were right-handed as confirmed by the Edinburgh Handedness Inventory [44]. They reported normal or corrected-to-normal vision, no motor problems, and no known neurological disorders. The experiment was conducted over two days, and informed consent was obtained from all participants according to the ethical guidelines of the University of British Columbia.

2.2. Motor Task. We used a computerized version of the flower-tracing task used in the Movement Assessment Battery for Children (MABC [45]). The flower figure was displayed on a computer screen using custom LabVIEW 7.1 software (National Instruments Co., Austin, TX). Participants were instructed to trace the figure between the two solid lines of the flower figure (Figure 1) as quickly and accurately as possible in a clockwise direction using a joystick. An error was registered each time the participant crossed beyond the two solid lines of the flower. The number of errors and

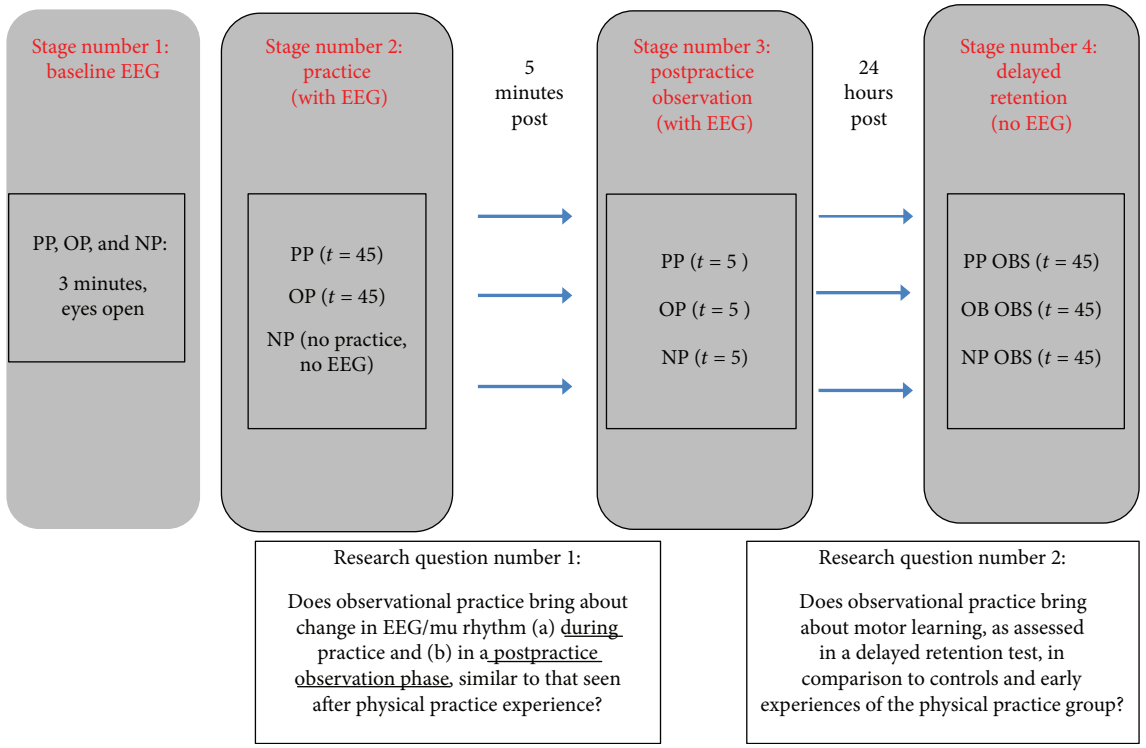

Figure 2: Research design and research questions.

the time it took the participant to complete the trial were displayed on the screen following each trial.

2.3. EEG Recording. EEG was recorded using a 64-channel HydroCel Geodesic Sensor Net with a Net Amps 300 amplifier at a sampling rate of 250 Hz via EGI software (Net Station, Electrical Geodesics Inc., Eugene, OR). At the start of the acquisition, impedance values for all EEG channels were less than 50 kΩ. The collected signals were referenced to the vertex (CZ).

2.4. Procedure. The experiment was divided into four sessions: (1) baseline EEG, (2) practice, (3) postpractice observation, and (4) delayed retention. Figure 2 shows the design of the experiment as well as the primary and secondary research questions related to the design.

2.4.1. Baseline EEG. Baseline EEG data were first collected on all participants for 3 minutes while they were viewing a blank screen. They were asked to keep their eyes open and to sit still without moving their limbs or eyes.

2.4.2. Practice Sessions

(1) Physical Practice (PP) Group. Participants were familiarized with the joystick by tracing a cross on the computer screen for 60 seconds. Once familiar with the movement of the joystick, they performed three blocks of the flower-tracing task for a total of 45 trials. Participants were instructed to trace the flower figure between the two solid lines using the joystick as quickly and accurately as possible. A 2-minute rest was provided between each block of 15 trials. EEG was recorded during all trials.

(2) Observation Practice (OP) Group. Participants in this group observed video clips of a model performing the flower-tracing task. The model in the video clips was right-handed and was a novice to the task. She was selected over several performers as she showed the least trial-to-trial variability in performance, yielding the most typical learning curve.

Each video clip represented one trial, with a total of 45 trials. Similar to the PP group, a 2-minute break was provided between each block of 15 trials. The video clips used in the observation trials were recorded at a resolution of 1280 × 720 pixels and a frame rate of 60 Hz. Additionally, the recording was from a first-person perspective, as this results in improved learning [46] and stronger hemispheric activation [47, 48] compared to the third-person perspective. Observers were instructed to refrain from any movement, and their behaviour was monitored via a video camera. EEG was recorded during all trials.

Participants were instructed to pay attention to the model's movement and were told that they would be doing the same task the following day. To ensure that participants were paying attention to the recordings, each participant was asked to state the tracing time or/and the number of errors made by the model at the end of each trial. These questions were randomized so the observers did not identify the pattern and focus on observing one measure on the screen.

(3) No Practice (NP) Control Group. Participants in this group did not receive physical or observation training. Participants in this group just completed the baseline EEG trials and the postpractice observation stage (as below).

2.4.3. Postpractice Observation Session. Five minutes after the training session, participants in the PP and OP groups viewed a video of the same model observed by the OP group performing the last five trials of the learning experience. The NP group began the session with the postpractice observation. All participants were instructed to pay attention to the model's performance. EEG was recorded as participants observed the model's movements.

2.4.4. Delayed Retention. Twenty-four hours after the training session, participants in all groups performed 45 trials of the motor task (again with 2-minute rests every 15 trials). No EEG was recorded during the retention session.

2.5. EEG Processing and Analysis. EEG data collected from each participant were processed and analyzed using Brain Electrical Source Analysis (BESA) software (MEGIS Software GmbH). Data were first manually screened for eye blinks and eye motion. Trials where eye movement occurred at the time of the task were removed. This resulted in approximately 10% of the total trials from all groups and all conditions being removed from further analysis. Data were filtered at 4–40 Hz and a notch filter of 60 Hz was applied. Independent component analysis (ICA) was then performed on the whole data set using an extended infomax algorithm for mixed sub-Gaussian and super-Gaussian sources in BESA. Using this approach, spatial topographies of the motion artifacts were first defined manually and then the brain signal topographies were determined. The artifact signal at each electrode was reconstructed with a spatial filter taking into account the artifact as well as the brain signal subspace. The reconstructed artifact signal was then subtracted from the original EEG segment.

EEG data were then transformed to a virtual montage using BESA. Virtual montages estimate the voltage at idealized locations of the standard electrodes into 27 channels using spherical spline interpolation. We used the 10-10 virtual standard montage. The average reference was computed for each time point as the mean voltage over the interpolated amplitudes of the standard virtual scalp electrodes. For each clean segment, the power in the 8–13 Hz range was computed using fast Fourier transforms (FFT). The data were segmented into epochs of 2 seconds for each trial in each condition. FFT was performed on the epoched single trials (1024 points) and averaged for each block in each condition to obtain the experimental mu value for each condition. For the baseline mu value, FFT was performed on one minute of the epoched resting state data. Using these values, the Mu suppression index (MSI) was calculated.

2.6. Mu Suppression Index (MSI). We calculated the ratio of the mu power in the experimental condition relative to the mu power in the baseline condition. The ratio is used to control for variability in absolute mu power as a result of individual differences, such as scalp thickness and electrode impedance [49]. Because ratio data are inherently skewed, a log transform was used for the purposes of parametric analysis [49]. The MSI is a change score of absolute mu power (8–13 Hz) between the baseline and experimental conditions. It was calculated as

$$\text{MSI} = \log \frac{\text{mu power experimental}}{\text{mu power baseline}}. \quad (1)$$

A log value below zero in the area of C3, C4, and CZ indicates mu suppression or activation of premotor or sensorimotor neurons and is considered an index of mirror neuron system functioning. A value of zero indicates no suppression or no change from baseline. Values above zero indicate synchronization or deactivation of the premotor or sensorimotor neurons, perhaps indicating inhibition of these premotor regions.

The MSI was calculated for each participant (using rest as baseline) for the electrodes C3, CZ, and C4. These central electrodes record the activity of the left, middle, and right sensorimotor regions, respectively.

For statistical analysis, we first compared MSI for the PP and OP groups in acquisition (stage 2) across 3 practice blocks (t = 15/block) and the three electrode sites. These data were compared in a 2 group × 3 electrode site × 3 block mixed-design ANOVA with repeated measures on the second and third factors. Our primary aim with this first analysis was to assess for group differences as a function of the type of experience (observation versus physical practice) as well as to determine any changes across practice blocks. Second, we compared the MSI values to zero for each electrode site to assess whether there was evidence of suppression for each group. This allowed us to determine at the within-group level, if there was evidence of suppression (and where based on electrode site). As such, we performed single sample t-tests (comparing against zero), with Bonferroni-corrected p values based on the number of electrodes (.05/3 = .017).

A second analysis was performed on the postpractice observation session (stage 3) for all 3 groups. Again, we first compared across groups (PP, OP, and NP) and electrodes in a 3 group × 3 electrode RM ANOVA, with repeated measures on the second factor. We also compared MSI against zero in single sample t-tests for each group and each electrode (again based on Bonferroni-corrected t-tests).

2.7. Behavioural Measures and Analysis. Two behavioural measures were used to assess learning: (1) error, which was denoted as the number of times the participant crossed out of the flower figure's bounds, and (2) total trace time, which was described as the time it took the participant to complete each trace/trial. These two measures were analyzed in retention testing in a 3 group (PP, OP, NP) × 9 block (5 trials/block), mixed-design ANOVA, with repeated measures on the second factor. Greenhouse-Geisser corrections were applied to violations to sphericity associated with the repeated-measures factor. Significant interaction effects were followed up with Tukey HSD post hoc comparisons ($p < .05$). Due to errors in processing, we were missing data from one control group participant (NP) and from one block of a PP

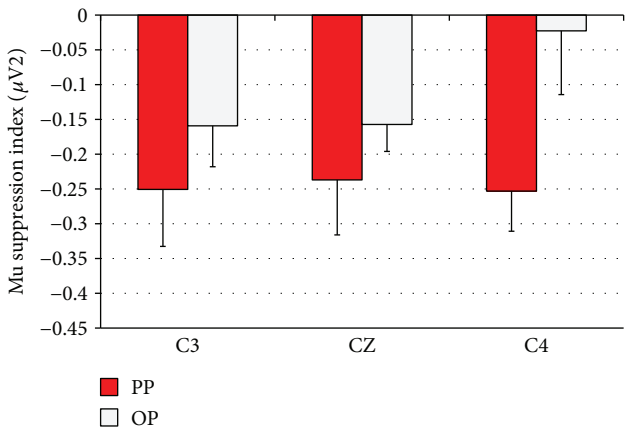

Figure 3: Mu suppression index during physical (PP) and observational practice (OP) (i.e., stage 2 testing) at the central interpolated electrodes C3, CZ, and C4. Values represent the mean log ratio of mu power at the frequency range of 8–13 Hz in the experimental condition compared to baseline. A ratio of negative value indicates suppression. Error bars represent standard error of the mean SE.

participant; these individuals were not included in the reported statistical analyses. As a check, we re-ran the analysis with the PP participant using estimated values (interpolating based on means for surrounding blocks), and this did not affect the behavioural results.

3. Results

3.1. Does Observational Practice Bring about Change in EEG Mu Rhythm Similar to That Seen after Physical Practice?

3.1.1. Mu Suppression during Practice for Both OP and PP Groups. In general, mu suppression across the two groups and across practice blocks and electrodes looked similar. The results of the mixed ANOVA on MSI showed neither significant main effects nor significant interactions (all Fs < 1.37, except the group main effect, where $F(1, 18) = 2.78$, $p = .11$, $\eta_p^2 = 0.13$). In Figure 3, we have plotted the MSI for the PP and OP groups for each of the three electrodes averaged across all trials. Based on comparisons to zero, there was evidence of bilateral mu suppression during PP, but only left lateralized mu suppression during OP. This was confirmed through single sample t-tests for both the PP and OP groups for each electrode, as displayed in Table 1. During PP, the average MSI at C3, CZ, and C4 was significantly less than zero. During OP, the average MSI at C3 and CZ was significantly less than zero, but it was not at C4.

3.1.2. Mu Suppression during the Postpractice Observation Phase. Comparison of the three groups during postpractice observation yielded a significant group main effect, $F(2, 27) = 9.68$, $p = .001$, $\eta_p^2 = 0.42$, but no electrode effect ($F < 1$). In Figure 4, we have plotted the MSI values for each electrode as a function of group. Based on Tukey HSD post hoc comparisons, the PP group showed more overall suppression than both the OP and NP groups and the OP group showed more suppression than the NP control group did. The interaction between group and electrode approached conventional levels of significance, $F(4, 54) = 2.52$, $p = .051$, $\eta_p^2 = 0.26$. As can be seen in Figure 4 and based on Tukey post hoc comparisons, the PP group displayed significantly greater MSI compared to the NP group at all electrodes (i.e., strong bilateral activation across both hemispheres). However, MSI values of the PP group were only significantly higher than were those of the OP group at C4, in the right hemisphere. An additional analysis was run on the baseline mu results for each electrode to test for pre-existing group differences, in a 3 group × 3 electrode RM ANOVA. There were no group differences in baseline mu all group Fs < 1. Group mean values varied from 6.7 to 12.2.

To test for evidence of suppression, single sample t-tests comparing the MSI value to zero for each group and electrode showed that for the PP group, MSI at all three electrodes (C3, CZ, and C4) was significantly less than zero ($p < .006$). For the OP group, only the middle, central electrode, CZ, had a significantly lower MSI value ($p = .004$). For the NP control group, MSI was significantly higher than the baseline at CZ ($p = .003$).

3.2. Does Observational Practice Bring about Motor Learning? In Figure 5(a), we have plotted the average number of errors for the three groups during the nine blocks of testing for the delayed retention test. For illustrative comparison, we have also plotted the acquisition data for the PP group. There does not appear to be any savings associated with previous observational practice for the OP group, when comparing their performance to the PP and NP groups. The PP group had the fewest number of errors in retention, particularly across the first few retention blocks, but across groups, number of errors decreased across blocks. With respect to statistical confirmation of the descriptive data, although the main effect of group was not significant, $F(2, 25) = 2.88$, $p = .075$, $\eta_p^2 = 0.19$, there was a significant block, $F(5.05, 126.23) = 24.04$, $p < .001 \eta_p^2 = 0.49$, and a significant group × block interaction, $F(10.10, 126.23) = 2.21$, $p = .021$, $\eta_p^2 = 0.15$. The block effect comprised significant linear and quadratic trend components ($p < .001$). Tukey's post hoc analysis of the interaction showed significant differences between the PP and NP group for blocks 1, 2, and 3, with the PP group showing fewer errors than the NP group. The PP and OP groups were only significantly different on block 1. However, there was no significant difference between the OP and NP groups for any practice block.

We have also plotted data for the first 10 trials of physical practice for all groups in order to better describe group effects and illustrate how differences in performance were not apparent on these first 10 trials, but rather emerged with practice. These data are shown in Figure 6 (i.e., first 10 trials of retention for all groups in addition to the first 10 trials of acquisition for the PP group). A group × trial ANOVA comparing the PP group during acquisition and the NP and OP groups during retention confirmed the absence of any group effect, $F(2, 26) = 1.30$, $p = .29$, $\eta_p^2 = 0.09$, nor a group × trial interaction ($F < 1$).

Table 1: Single sample t-test results (and Cohen's d), comparing MSI to zero for each electrode site for PP and OP groups during the stage 2 practice session.

	PP				OP			
	df	t_{obs}	d	p	df	t_{obs}	d	p
Electrode								
C3	9	−3.06	0.97	.007*	9	−2.71	0.86	.012*
CZ	9	−3.01	0.95	.008*	9	−4.08	1.2	.002*
C4	9	−4.39	1.3	.001*	9	−0.25	0.08	.405

*Statistical significance based on Bonferroni-corrected alpha values (.05/3 = .017).

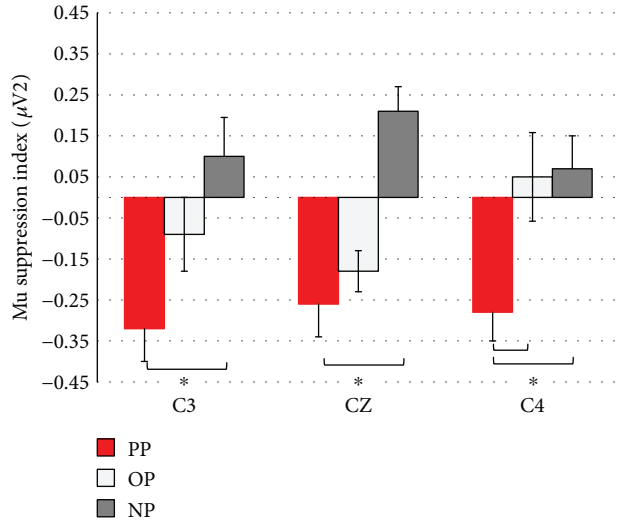

Figure 4: Mu suppression index for the PP, OP, and NP groups during postpractice observation (stage 3 testing). Error bars represent standard error of the mean (SE). Asterisks indicate significant between group differences ($p < .05$).

For tracing time, the data are illustrated in Figure 5(b), again with the PP group's acquisition data illustrated for comparison purposes. Although there was still a main effect of block, $F(3.08, 77.01) = 12.25$, $p < .001$, $\eta_p^2 = 0.33$, which comprised a significant linear trend component ($p < .001$) due to decreasing times as retention testing continued, there was no group or group × block interaction (both Fs < 1).

4. Discussion

This study is the first to investigate how mu suppression changes as a function of both observation and physical practice and what this means in terms of behavioural indices of motor learning. As predicted, the behavioural results showed that during the retention phase, the PP group made the least number of errors compared to the OP and NP control groups. However, the groups did not differ in average tracing time during retention. This suggests that benefits from physical practice were mostly a result of spatial accuracy improvements, rather than speed. Although both the PP and OP groups showed evidence of mu suppression, in both practice and postpractice observation (especially when compared to the control group), the patterns and degree of suppression differed across the groups. Therefore, although there was evidence of suppression in the OP group, suggestive of changes in cortical processing due to observational practice experience, these patterns of activation did not appear to manifest in improved motor learning, when the OP group was compared to the NP control and PP groups on a delayed retention test.

With respect to the behavioural data, there was no evidence of motor learning in the OP group. For tracing times, there were no significant group-related differences. There was no evidence that prior physical practice resulted in tracing time benefits. Rather, there was a trend for the PP group to be slower than the NP and OP groups. However, there was also no evidence that prior observation aided performance times, when comparing the NP and OP groups. The behavioural effects related to prior physical experience were evidenced in tracing errors. The PP group showed fewer errors in retention during the first five trials, when compared to both the NP and OP groups and across the first 15 trials when compared to the NP group. However, the OP group did not differ statistically from the NP group. Because accuracy could be compromised as a function of speed, it may be that the slower tracing times for the PP group (at least descriptively) were compensated for by fewer errors. We do not have a good reason why the PP group might have weighted accuracy more highly than tracing time. We would have expected the NP group in retention to have looked like the PP group in acquisition, but as can be seen from Figures 5(a) and 5(b), the PP group showed fewer errors and longer tracing times right from the start.

The lack of differences between the NP group and the PP and OP groups for the behavioural measures of motor learning might be due to the five 30–40 s observation trials shown during the postpractice observation testing session. It is possible that learners did not need to observe all 45 visual trials to show gains in subsequent execution and that these five trials of "good" performance may have been adequate to bring about performance benefits in retention, at least with respect to tracing time. If so, this suggests that covert practice benefits were likely more strategically mediated, associated with familiarity with the flower shape, rather than a motor-mediated strategy based on action simulation. This does not mean that there was no action simulation, as appeared to be evidenced by the EEG mu suppression data, but that this suppression or simulation was not associated with behavioural indices of motor learning.

The neurophysiological results showed that, compared to baseline, mu rhythm was significantly suppressed over both hemispheres during PP and only over the left hemisphere during OP. However, the magnitude of this suppression did not change, as a function of practice. This result is not consistent with studies that reported changes in the magnitude of MNS activity during practice. Nakano et al. [37], for example, reported a significant difference in suppression between the first and last of 5 trials of observation of a ball rotation task. Although the authors associated this decrease in suppression

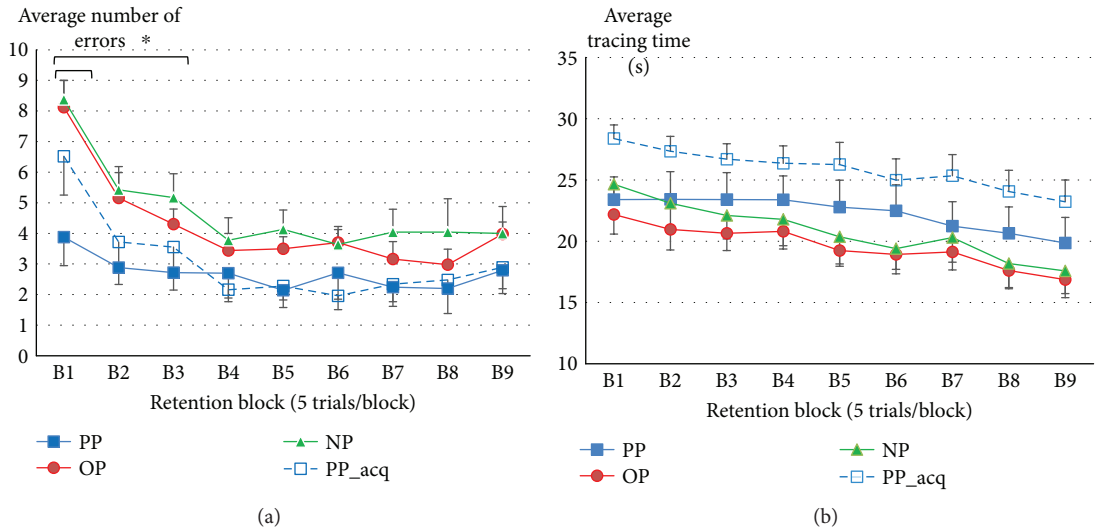

Figure 5: (a) Average number of errors across 9 blocks of retention testing ($t = 9$/blk) for the physical practice (PP), observational practice (OP), and no practice (NP) groups and first-day acquisition trials for the PP group (PP_acq). Error bars represent standard error (SE). *PP group significantly different to NP group B1–B3. PP group significantly different to OP group (B1). (b) Average tracing time across 9 blocks of retention testing ($t = 9$/blk) for the physical practice (PP), observational practice (OP), and no practice (NP) groups and first-day acquisition trials for the PP group (PP_acq). Error bars represent standard error (SE). There was no interaction.

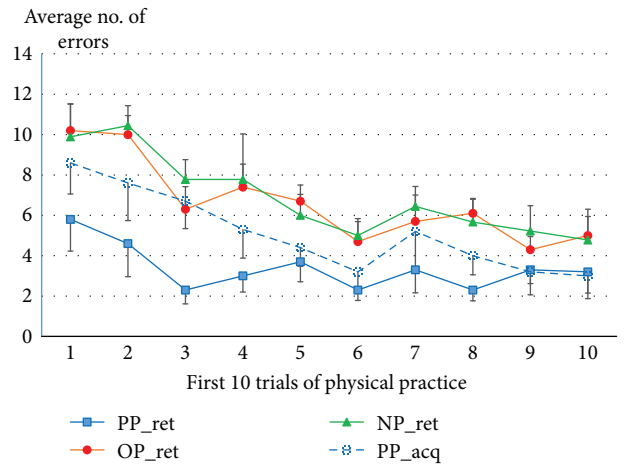

Figure 6: Average number of errors across the first 10 trials of physical practice in retention for the physical practice (PP), observational practice (OP), and no practice (NP) groups as well as during first-day acquisition for the PP group (PP_acq). Error bars represent standard error (SE). There were no group differences comparing PP_acq to the OP_ret and NP_ret.

with motor learning, it is difficult to draw a conclusion about motor learning based on so few trials (in our study, there were 45 trials of practice). The unchanged magnitude of mu suppression is also not in line with the neural efficiency hypothesis, which associates improved learning with less cortical activation [50]. Several lines of evidence show that experts exhibit less suppression during the execution and observation of motor skills, suggesting that more experience eventually leads to a more efficient neural processing [43]. However, contrary to our study, which focused on short-term practice, these studies tested individuals with years of experience and researchers have identified different brain networks, with different activation patterns, involved in short-term and long-term motor practice [51].

As expected, mu suppression during physical practice was bilateral, showing that both hemispheres were active during movement performance. Contrary to our hypothesis, however, mu suppression during observational practice was higher in magnitude in the left hemisphere compared to the right hemisphere and hence did not show a similar bilateral suppression as noted for physical practice. Given that both the model and the study participants were right-handed and that the observers watched the movement from a first-person perspective, bilateral suppression of mu rhythm would be expected based on previous work [52].

Despite this research above, which was primarily based on observation of already experienced actions, there is evidence that action observation can lead to a more lateralized activation pattern. For example, Perry and Bentin [53] showed that when they examined right-handed participants while observing movements of both right and left hands from a first-person perspective, mu suppression was evidenced at the frequency range of 8–13 Hz. This suppression was stronger in the hemisphere contralateral to the hand being observed compared to the hemisphere ipsilateral to the observed hand (similar to our data). Similarly, when Quandt et al. [54, 55] presented video clips of a right-handed model from a first-person perspective, action observation was associated with greater suppression at the alpha frequency range in the left hemisphere compared with the right hemisphere. In a different study, when a third-person, action-observation paradigm was employed, suppression was greater over the right hemisphere compared with the left hemisphere [55]. The left-lateralized activation reported in this study is also consistent with fMRI studies. These studies have revealed

that watching right-hand reaching-and-grasping movements from a first-person, egocentric perspective elicited larger BOLD responses in the left anterior intraparietal cortex of right-handed observers [17]. This contralateral effect, however, was replaced by an ipsilateral response (i.e., the right hemisphere) in the anterior superior parietal lobule when the right-handed observers viewed the right-handed movements from an allocentric perspective (i.e., facing the model) [56].

Complementing the EEG differences in practice between OP and PP, the postpractice observation testing session also yielded differences between groups based on experience. Although for the OP group, these postobservation trials had already been viewed, whereas these were novel videos for the PP and NP groups, there was no suggestion that the patterns of activation were affected by novelty. There was no significant block effect in acquisition, such that the patterns of activation shown in the first block of practice were maintained throughout practice. Moreover, patterns of activation seen for the PP group while acting were also maintained for this group while observing. Again, this suggests that prior experience, rather than novelty or familiarity, was responsible for these effects.

For the PP group, postpractice observation was characterized by bilateral suppression. For the OP group, observing the same stimuli as the PP group, action observation was characterized by left-lateralized suppression. It appears that observation without any physical practice activates only a subset of brain regions, which also explains the lateralized effect during observation practice. The absence of suppression for the NP group, however, suggests that more than 5 trials of observation are needed for this suppression to be evidenced or that a learning model who shows improvement across trials is necessary for suppression. The model shown in the postpractice observation session only was of near perfect performance (i.e., the last five trials from practice). Behavioural studies that have compared expert and learning models have provided evidence that watching learning models engages the observer in a problem-solving mode in which he/she considers all the relations between the movement patterns and their outcomes to optimize performance [57]. Given the association between the left hemisphere and relational reasoning [58], the left-lateralized suppression during visual training could be moderated by model type, which continues to influence patterns of activation during near-perfect performance. In light of this explanation, it is possible that the bilateral effect during observation reported in other studies in this area was because the observers viewed error-free hand movements, with no learning component.

What is important from the postpractice observation data is the fact that differences existed between the groups based on the types of experience, despite the fact that all three groups were watching the same action stimuli and that we only collected data from 5 trials in practice (each trial lasting ~60 s). Differences in activation between the OP and PP groups might simply be a carryover effect from practice, such that whatever areas of the brain were activated during initial exposure continued to be activated during a subsequent observation phase. Because the observe-only group never physically practiced and did not show bilateral suppression, there was no reason to think that this would be observed postpractice as nothing had changed. For the PP group, it appears that it was able to resonate and engage in action simulation, based on previous physical experience with the task, such that the patterns of activations resembled these early learning physical practice experiences. In comparing the size of suppression and making conclusions about motor-mediated learning in observation conditions, the PP group exhibited the strongest suppression compared to the OP and NP control groups. This suggests that for observation to induce significant suppression, it has to be preceded by active motor experience with the motor skill of interest. This result corroborates with EEG studies that have stressed the role of prior active motor experience (long- or short-term) in modulating mu responses during observation [59].

Although previous PP in this study involved both hemispheres and led to the strongest suppression, comparable suppression between OP and PP groups was shown at the medial central site (i.e., CZ), especially in comparison to the NP control group. Interestingly, although the NP control was not that different to the PP and OP group with respect to their behavioural performance in retention, at least with respect to tracing times, the five trials of EEG collected during the observation-testing session revealed significant differences between these groups. No suppression was observed at all three central sites (in fact, there was significant synchronization in comparison to baseline). Even though the participants in the control group were observing a motor task, their preceding lack of experience with this task either covertly or overtly moderated any motor system suppression at this central location. Therefore, action-observation does not always induce suppression, supporting the suggestion that the MNS and mu suppression more specifically is sensitive to previous experiences with the task, both visual and physical (see also [60]). Prior physical and observation practice experiences caused mu suppression in our study, but to different degrees and in qualitatively different ways.

This study has some limitations that deserve mention. One of these concerns potential accuracy-speed trade-offs. Any improvement in one measure could be attributed to a decrease in the other. Although not reported, correlations between these two measures in retention were all small ($rs < 0.25$) and nonsignificant. However, in future work, fixing one measure of the task to examine the changes in the other would rule out any possible trade-off influences and narrow down alternative explanations for the observed effects (e.g., requiring zero-error performance).

Monitoring the observers' motion only via a video camera, without a stringent control for muscle activation, introduced another limitation. Although the activation during PP was different from that during OP, there is still a possibility that any mu suppression could be due to muscle activation. To avoid such confounding effects, electromyography (EMG) should be used to accurately detect any possible movement.

The lack of change in the magnitude of mu suppression throughout both types of practice could be a result of the

number of training trials (i.e., 45 trials). This number was used because in pilot testing, it was shown that behavioural measures of performance leveled out (i.e., plateaued) around the 45th trial. Increasing the number of trials could also cause participants possible discomfort with the EEG net, which in turn could negatively impact performance. Nevertheless, in future work it would be important to increase the amount of practice, especially as behavioural plateaus do not indicate the absence of learning [61]. Moreover, it may be that for observational learning benefits to be realized in this task, observational practice trials should be increased. Although behaviourally, the OP group did not look different to the NP group, which might suggest that five observation trials were enough to bring about some performance gains, watching 45 trials of practice from a learning model did lead to differences in cortical activation. In future work, it will be important to test motor performance of a no-practice control group in the absence of any observational practice trials to better appreciate the short-term effects of watching and the volume of practice which is needed to bring about observational-related changes.

Finally, although mu rhythm is mainly described as EEG oscillations at the frequency range of 8–13 Hz, some authors limited mu rhythm to the frequency band of 8–10 Hz (e.g., [26]). EEG researchers have identified two frequency ranges within the alpha range (8–13 Hz): the lower alpha (8–10) Hz and the upper alpha (10–13) Hz. The lower alpha emanates from the somatosensory cortex and is modulated by motor activity, showing a more anterior and asymmetrical hemispheric effect. The upper band, in contrast, consists of posterior bilateral waves, which cluster mainly around the parietooccipital cortices and is primarily modulated by visual stimulation [62]. Given that the observed suppression in this study could be a result of visual stimulation or motor activation or both, examining each component separately would shed more light on both the hemispheric activation and the source of stimulation. It may also be of interest in future work to conduct time frequency analysis on the EEG, to help provide more information about the complex network dynamics underlying observational practice [63].

In conclusion, we have demonstrated that observation practice induces neurophysiological changes as indexed by mu suppression at central sites, which provides evidence for motor-based processes during observational practice. However, there was no evidence that these motor-related processes were related to motor learning and behavioural measures of learning in retention. The lateralized suppression during observation practice suggests that cortical processes involved in this covert type of practice might not be entirely motor-based and that the lateralized activation during OP and the bilateral activation during PP at the central sites suggest that OP does not trigger all brain areas activated during PP. Therefore, observation practice cannot replace physical practice, even though in some instances there may be benefits to be gained behaviourally from this type of practice (at least in comparison to not practicing). Because of EEG differences between OP and NP control conditions during a postpractice observation phase, there is evidence that OP is leading to neurophysiological changes, although we did not have evidence that this suppression was linked to motor learning outcomes.

Importantly, we confirm the vital role of previous motor experience in modulating mu responses during observation, suggesting that employing movements that are within the observer's motor repertoire (i.e., prior physical exposure) is more likely to result in optimal activation during a subsequent practice phase. To a lesser extent, observers without this experience could benefit from watching movements where they have only had previous visual experience. Although both physical and observational practice might share some similarities, the underlying mechanisms by which each of them operates appears to be different both qualitatively and quantitatively. To better understand the relationship between mu responses and motor learning during observational practice, researchers should address other factors that could influence this relationship, such as handedness, observation perspective, the amount of visual familiarity, model's expertise, and the type of motor task. Further study of the relation between these types of practice and their neurophysiology would help to elucidate on the dominant mechanisms underpinning observation practice and the conditions which maximize motor-mediated learning under these conditions. It has yet to be shown that an increase in motor-related areas during observation practice is responsible for better learning. One possible future method to help determine how cortical activation in motor-related areas of the brain relates to learning is to use methods to stimulate the brain either during or before a period of observational practice, potentially through transcranial direct current stimulation (tDCS).

Disclosure

The manuscript is based on the Masters' thesis of the first author, Najah Alhajri (June 2017), comparing motor learning and mu suppression under short-term physical and observational practice in adults (University of British Columbia).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] N. J. Hodges and D. Ste-Marie, "Observation as an instructional method," in *Developing Sport Expertise: Researchers and Coaches put Theory into Practice*, D. Farrow, J. Baker, and C. MacMahon, Eds., pp. 115–128, Routledge, Abingdon, UK, 2nd edition, 2013.

[2] N. J. Hodges, "Observations on action-observation research: an autobiographical retrospective across the past two decades," *Kinesiology Review*, vol. 6, no. 3, pp. 240–260, 2017.

[3] N. J. Hodges, A. M. Williams, S. J. Hayes, and G. Breslin, "What is modelled during observational learning?," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 531–545, 2007.

[4] D. Maslovat, S. J. Hayes, R. Horn, and N. J. Hodges, "Motor learning through observation," in *Vision and Goal-Directed Movement: Neurobehavioral Perspectives*, D. Elliott and M.

Khan, Eds., pp. 315–340, Human Kinetics, Champaign, IL, USA, 2010.

[5] N. T. Ong and N. J. Hodges, "Mixing it up a little: how to schedule observational practice," in *Skill Acquisition in Sport: Research, Theory and practice*, N. J. Hodges and A. M. Williams, Eds., pp. 48–65, Routledge, London, UK, 2nd edition, 2012.

[6] D. M. Ste-Marie, B. Law, A. M. Rymal, O. Jenny, C. Hall, and P. McCullagh, "Observation interventions for motor skill learning and performance: an applied model for the use of observation," *International Review of Sport and Exercise Psychology*, vol. 5, no. 2, pp. 145–176, 2012.

[7] M. Bassolino, G. Sandini, and T. Pozzo, "Activating the motor system through action observation: is this an efficient approach in adults and children?," *Developmental Medicine and Child Neurology*, vol. 57, Supplement 2, pp. 42–45, 2015.

[8] P. Molenberghs, R. Cunnington, and J. B. Mattingley, "Is the mirror neuron system involved in imitation? A short review and meta-analysis," *Neuroscience and Biobehavioral Reviews*, vol. 33, no. 7, pp. 975–980, 2009.

[9] L. Cattaneo and G. Rizzolatti, "The mirror neuron system," *Archives of Neurology*, vol. 66, no. 5, pp. 557–560, 2009.

[10] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[11] K. Zentgraf, J. Munzert, M. Bischoff, and R. D. Newman-Norlund, "Simulation during observation of human actions–theories, empirical studies, applications," *Vision Research*, vol. 51, no. 8, pp. 827–835, 2011.

[12] G. Buccino, S. Vogt, A. Ritzl et al., "Neural circuits underlying imitation learning of hand actions: an event-related fMRI study," *Neuron*, vol. 42, no. 2, pp. 323–334, 2004.

[13] I. Dinstein, U. Hasson, N. Rubin, and D. J. Heeger, "Brain areas selective for both observed and executed movements," *Journal of Neurophysiology*, vol. 98, no. 3, pp. 1415–1427, 2007.

[14] F. Filimon, C. A. Rieth, M. I. Sereno, and G. W. Cottrell, "Observed, executed, and imagined action representations can be decoded from ventral and dorsal areas," *Cerebral Cortex*, vol. 25, no. 9, pp. 3144–3158, 2015.

[15] V. Gazzola and C. Keysers, "The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data," *Cerebral Cortex*, vol. 19, no. 6, pp. 1239–1255, 2009.

[16] M. Iacoboni, I. Molnar-Szakacs, V. Gallese, G. Buccino, J. C. Mazziotta, and G. Rizzolatti, "Grasping the intentions of others with one's own mirror neuron system," *PLoS Biology*, vol. 3, no. 3, article e79, 2005.

[17] L. Shmuelof and E. Zohary, "Dissociation between ventral and dorsal fMRI activation during object and action recognition," *Neuron*, vol. 47, no. 3, pp. 457–470, 2005.

[18] T. T.-J. Chong, R. Cunnington, M. A. Williams, N. Kanwisher, and J. B. Mattingley, "fMRI adaptation reveals mirror neurons in human inferior parietal cortex," *Current Biology*, vol. 18, no. 20, pp. 1576–1580, 2008.

[19] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[20] C. Babiloni, F. Babiloni, F. Carducci et al., "Human cortical electroencephalography (EEG) rhythms during the observation of simple aimless movements: a high-resolution EEG study," *NeuroImage*, vol. 17, no. 2, pp. 559–572, 2002.

[21] S. Cochin, C. Barthelemy, B. Lejeune, S. Roux, and J. Martineau, "Perception of motion and qEEG activity in human adults," *Electroencephalography and Clinical Neurophysiology*, vol. 107, no. 4, pp. 287–295, 1998.

[22] S. D. Muthukumaraswamy, B. W. Johnson, and N. A. McNair, "Mu rhythm modulation during observation of an object-directed grasp," *Cognitive Brain Research*, vol. 19, no. 2, pp. 195–201, 2004.

[23] J. A. Pineda, B. Z. Allison, and A. Vankov, "The effects of self-movement, observation, and imagination on mu rhythms and readiness potentials (RP's): toward a brain-computer interface (BCI)," *IEEE Transactions on Rehabilitation Engineering*, vol. 8, no. 2, pp. 219–222, 2000.

[24] N. Virji-Babul, A. Moiseev, T. Cheung, D. Weeks, D. Cheyne, and U. Ribary, "Changes in mu rhythm during action observation and execution in adults with Down syndrome: implications for action representation," *Neuroscience Letters*, vol. 436, no. 2, pp. 177–180, 2008.

[25] C. C. Woodruff and S. Maaske, "Action execution engages human mirror neuron system more than action observation," *Neuroreport*, vol. 21, no. 6, pp. 432–435, 2010.

[26] J. A. Pineda, "The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing"," *Brain Research Reviews*, vol. 50, no. 1, pp. 57–68, 2005.

[27] N. Virji-Babul, A. Moiseev, T. Cheung, D. Weeks, D. Cheyne, and U. Ribary, "Spatial-temporal dynamics of cortical activity underlying reaching and grasping," *Human Brain Mapping*, vol. 31, no. 1, pp. 160–171, 2010.

[28] R. Gatti, A. Tettamanti, P. M. Gough, E. Riboldi, L. Marinoni, and G. Buccino, "Action observation versus motor imagery in learning a complex motor task: a short review of literature and a kinematics study," *Neuroscience Letters*, vol. 540, pp. 37–42, 2013.

[29] C. M. Heyes and C. L. Foster, "Motor learning by observation: evidence from a serial reaction time task," *The Quarterly Journal of Experimental Psychology*, vol. 55, no. 2, pp. 593–607, 2002.

[30] D. Ashford, S. J. Bennett, and K. Davids, "Observational modeling effects for movement dynamics and movement outcome measures across differing task constraints: a meta-analysis," *Journal of Motor Behavior*, vol. 38, no. 3, pp. 185–205, 2006.

[31] N. T. Ong and N. J. Hodges, "Absence of after-effects for observers after watching a visuomotor adaptation," *Experimental Brain Research*, vol. 205, no. 3, pp. 325–334, 2010.

[32] G. Bird and C. Heyes, "Effector-dependent learning by observation of a finger movement sequence," *Journal of Experimental Psychology: Human Perception and Performance*, vol. 31, no. 2, pp. 262–275, 2005.

[33] L. E. Brown, E. T. Wilson, and P. L. Gribble, "Repetitive transcranial magnetic stimulation to the primary motor cortex interferes with motor learning by observing," *Journal of Cognitive Neuroscience*, vol. 21, no. 5, pp. 1013–1022, 2009.

[34] A. A. G. Mattar and P. L. Gribble, "Motor learning by observing," *Neuron*, vol. 46, no. 1, pp. 153–160, 2005.

[35] S. Vogt and R. Thomaschke, "From visuo-motor interactions to imitation learning: behavioural and brain imaging studies," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 497–517, 2007.

[36] S. Vogt, "Visuomotor couplings in object-oriented and imitative actions," in *The Imitative Mind: Development, Evolution,*

and Brain Bases, A. N. Meltzoff and W. Prinz, Eds., pp. 206–220, CUP, Cambridge UK, 2002.

[37] H. Nakano, M. Osumi, K. Ueta, T. Kodama, and S. Morioka, "Changes in electroencephalographic activity during observation, preparation, and execution of a motor learning task," *The International Journal of Neuroscience*, vol. 123, no. 12, pp. 866–875, 2013.

[38] S. S. Kantak and C. J. Winstein, "Learning-performance distinction and memory processes for motor skills: a focused review and perspective," *Behavioural Brain Research*, vol. 228, no. 1, pp. 219–231, 2012.

[39] R. A. Schmidt and T. D. Lee, *Motor Control and Learning: a Behavioral Emphasis*, Human Kinetics, Champaign, IL, USA, 2005.

[40] G. Orgs, J. H. Dombrowski, M. Heil, and P. Jansen-Osmann, "Expertise in dance modulates alpha/beta event-related desynchronization during action observation," *The European Journal of Neuroscience*, vol. 27, no. 12, pp. 3380–3384, 2008.

[41] L. P. Behmer Jr and K. J. Jantzen, "Reading sheet music facilitates sensorimotor mu-desynchronization in musicians," *Clinical Neurophysiology*, vol. 122, no. 7, pp. 1342–1347, 2011.

[42] E. S. Cross, D. J. M. Kraemer, A. F. . C. Hamilton, W. M. Kelley, and S. T. Grafton, "Sensitivity of the action observation network to physical and observational learning," *Cerebral Cortex*, vol. 19, no. 2, pp. 315–326, 2009.

[43] C. Babiloni, C. del Percio, P. M. Rossini et al., "Judgment of actions in experts: a high-resolution EEG study in elite athletes," *NeuroImage*, vol. 45, no. 2, pp. 512–521, 2009.

[44] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, 1971.

[45] S. E. Henderson, D. A. Sugden, and A. L. Barnett, *Movement Assessment Battery for Children*, Psychological Corporation, London, UK, 1992.

[46] T. Ishikura and K. Inomata, "Effects of angle of model-demonstration on learning of motor skill," *Perceptual and Motor Skills*, vol. 80, no. 2, pp. 651–658, 1995.

[47] P. L. Jackson, A. N. Meltzoff, and J. Decety, "Neural circuits involved in imitation and perspective-taking," *NeuroImage*, vol. 31, no. 1, pp. 429–439, 2006.

[48] S. Pilgramm, B. Lorey, R. Stark, J. Munzert, D. Vaitl, and K. Zentgraf, "Differential activation of the lateral premotor cortex during action observation," *BMC Neuroscience*, vol. 11, no. 1, p. 89, 2010.

[49] A. Perry, N. F. Troje, and S. Bentin, "Exploring motor system contributions to the perception of social information: evidence from EEG activity in the mu/alpha frequency range," *Social Neuroscience*, vol. 5, no. 3, pp. 272–284, 2010.

[50] R. J. Haier, B. V. Siegel Jr, K. H. Nuechterlein et al., "Cortical glucose metabolic rate correlates of abstract reasoning and attention studied with positron emission tomography," *Intelligence*, vol. 12, no. 2, pp. 199–217, 1988.

[51] A. Floyer-Lea and P. M. Matthews, "Distinguishable brain activation networks for short- and long-term motor skill learning," *Journal of Neurophysiology*, vol. 94, no. 1, pp. 512–518, 2005.

[52] A. Streltsova, C. Berchio, V. Gallese, and M. A. Umilta', "Time course and specificity of sensory-motor alpha modulation during the observation of hand motor acts and gestures: a high density EEG study," *Experimental Brain Research*, vol. 205, no. 3, pp. 363–373, 2010.

[53] A. Perry and S. Bentin, "Mirror activity in the human brain while observing hand movements: a comparison between EEG desynchronization in the μ-range and previous fMRI results," *Brain Research*, vol. 1282, pp. 126–132, 2009.

[54] L. C. Quandt, P. J. Marshall, C. A. Bouquet, and T. F. Shipley, "Somatosensory experiences with action modulate alpha and beta power during subsequent action observation," *Brain Research*, vol. 1534, pp. 55–65, 2013.

[55] L. C. Quandt, P. J. Marshall, T. F. Shipley, S. L. Beilock, and S. Goldin-Meadow, "Sensitivity of alpha and beta oscillations to sensorimotor characteristics of action: an EEG study of action production and gesture observation," *Neuropsychologia*, vol. 50, no. 12, pp. 2745–2751, 2012.

[56] L. Shmuelof and E. Zohary, "Mirror-image representation of action in the anterior parietal cortex," *Nature Neuroscience*, vol. 11, no. 11, pp. 1267–1269, 2008.

[57] C. B. Black and D. L. Wright, "Can observational practice facilitate error recognition and movement production?," *Research Quarterly for Exercise and Sport*, vol. 71, no. 4, pp. 331–339, 2000.

[58] S. A. Bunge, E. H. Helskog, and C. Wendelken, "Left, but not right, rostrolateral prefrontal cortex meets a stringent test of the relational integration hypothesis," *NeuroImage*, vol. 46, no. 1, pp. 338–342, 2009.

[59] L. C. Quandt, P. J. Marshall, C. A. Bouquet, T. Young, and T. F. Shipley, "Experience with novel actions modulates frontal alpha EEG desynchronization," *Neuroscience Letters*, vol. 499, no. 1, pp. 37–41, 2011.

[60] N. N. Rüther, E. C. Brown, A. Klepp, and C. Bellebaum, "Observed manipulation of novel tools leads to mu rhythm suppression over sensory-motor cortices," *Behavioural Brain Research*, vol. 261, pp. 328–335, 2014.

[61] J. A. Adams, "Historical review and appraisal of research on the learning, retention, and transfer of human motor skills," *Psychological Bulletin*, vol. 101, no. 1, pp. 41–74, 1987.

[62] G. Pfurtscheller and C. Neuper, "Motor imagery activates primary sensorimotor area in humans," *Neuroscience Letters*, vol. 239, no. 2-3, pp. 65–68, 1997.

[63] A. M. Cebolla, E. Palmero-Soler, A. Leroy, and G. Cheron, "EEG spectral generators involved in motor imagery: a swLORETA Study," *Frontiers in Psychology*, vol. 8, p. 2133, 2017.

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Clinical Study

Effect of Group-Based Rehabilitation Combining Action Observation with Physiotherapy on Freezing of Gait in Parkinson's Disease

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Freezing of gait (FoG) is among the most disabling symptoms of Parkinson's disease (PD) patients. Recent studies showed that action observation training (AOT) with repetitive practice of the observed actions represents a strategy to induce longer-lasting effects compared with standard physiotherapy. We investigated whether AOT may improve FoG and mobility in PD, when AOT is applied in a group-based setting. Sixty-four participants with PD and FoG were assigned to the experimental (AO) or control groups and underwent a 45-minute training session, twice a week, for 5 weeks. AOT consisted in physical training combined with action observation whereas the control group executed the same physical training combined with landscape-videos observation. Outcome measures (FoG questionnaire, Timed Up and Go test, 10-meter walking test, and Berg balance scale) were evaluated before training, at the end of training, and 4 weeks later (FU-4w). Both groups showed positive changes in all outcome measures at posttraining assessment. Improvements in FoG questionnaire, Timed Up and Go test, and Berg balance scale were retained at FU-4w evaluation only in the AOT group. AOT group-based training is feasible and effective on FoG and motor performance in PD patients and may be introduced as an adjunctive option in PD rehabilitation program.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease, characterized by dopaminergic and nondopaminergic degeneration, causing severe motor and nonmotor symptoms [1]. The motor manifestations of PD are manifold (tremor, rigidity, bradykinesia, and postural instability), but gait and balance disorders have a great impact on autonomy and quality of life.

Freezing of gait (FoG), defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk" [2], is one of the most disabling symptoms that severely impacts quality of life [3] and increases risk of falls [4] in subjects with PD. This phenomenon, commonly occurring in confined spaces or under time constraints, may be already present in the early stage of the disease and can affect up to 80% of patients in the later stages [5].

To date, both pharmacological and surgical (deep brain stimulation) treatments have been proposed to ameliorate FoG; however, the evidence of effectiveness is unsatisfying, and clear treatment protocols are still not available [6].

Regarding alternative therapeutic options (i.e. rehabilitative approaches), treatments based on behavioural strategies,

requiring patients to evoke a more goal-directed type of motor control, have demonstrated to reduce freezing severity in PD patients. In this scenario, cue-augmented training surely represents one of the most effective methods for improving FoG and ameliorating gait and upper limb movements in freezers [7]. However, to date, findings are not univocal, and long-term consolidation of performance improvement needs to be investigated in future studies.

Among emerging approaches, action observation training (AOT) has been proposed as an innovative and effective method for improving gait disturbances [8, 9], bradykinesia [10], and functional independence [11] in people with PD.

Briefly, this training consists in observing and imitating specific motor actions. AOT aims to facilitate motor learning processes through the activation of the so-called "mirror neuron system" (MNS) [12]. Crucially, for the link between action observation and memory formation to be established, observed movements must be promptly executed after video observation [13].

The majority of the studies tested AOT efficacy in PD with a one-to-one (physiotherapist-patient) intervention context [14], and only one trial evaluated the feasibility of this treatment as a home-based intervention [15]. To our knowledge, no study investigated the possibility to apply AOT in a group-based rehabilitative setting. Previous data from our group have shown that AOT significantly reduced FoG episodes, producing larger and longer-lasting improvements in comparison to a control condition [8]. Interestingly, in a recent paper, clinical improvements reached after 4 weeks of AOT were also associated to functional brain changes in freezers and these changes were also able to predict clinical evolution at 8-week follow-up [9]. Based on these encouraging results and taking advantage of positive aspects related to community-based exercise programs, here, we investigated whether the AOT program may improve FoG and mobility in subjects with PD, when AOT is applied in a group-based setting. Further, by comparing the AOT program with a control program (same physical training combined with landscape-videos observation), we wanted to explore whether AOT offers beneficial effects in long-term retention of performance skills even if delivered in a group-based setting.

2. Methods

2.1. Participants. A total of 70 participants with PD were recruited at the outpatient Movement Disorders Clinic of the University of Genoa for participating in this pilot study. Patients were included in the study if they had the following inclusion criteria: (i) idiopathic PD, according to the United Kingdom Parkinson's Disease Society Brain Bank criteria [16]; (ii) Hoehn and Yahr stage II to III; (iii) able to walk unassisted despite FoG. In order to select PD subjects for those FoG severely impacted gait, patients were enrolled if the occurance of freezing was at least once a week (minimum score of 1 on item 2 in the new FoG Questionnaire (FoG-Q)) [17] and the longest episodes was >2 seconds (minimum score of 2 on item 4 of the FoG-Q).

Table 1: Demographic and clinical characteristics of participants.

	AOT	LOT	p
Age (years)	70.4 ± 4.5	72.8 ± 3.1	0.31
Sex (M/F)	16/17	15/16	0.61
Education (years)	9.2 ± 3.5	10.1 ± 2.2	0.77
Disease duration (years)	10.7 ± 3.9	9.5 ± 4.2	0.75
Hoehn and Yarh (stage)	2.4 ± 0.5	2.6 ± 0.3	0.73
UPDRS part III	31.6 ± 6.1	30.9 ± 7.2	0.88
LEDD (mg)	435.2 ± 158.5	383.1 ± 270.2	0.42
MMSE score	27.3 ± 2.1	28.2 ± 1.7	0.11

AOT: action observation training; LOT: landscape observation training; M: male; F: female; UPDRS: unified Parkinson's disease rating scale; LEDD: levodopa equivalent daily dose; Mg: milligrams; MMSE: Mini-Mental State Examination.

Participants were excluded if they had (i) diagnosis of a neurological disease (other than PD), (ii) presence of a deep brain stimulator, (iii) Mini-Mental State Examination score < 25, (iv) visual or acoustic limitations, and (v) severe orthopedic problems in the lower limbs.

Disease severity was assessed by means of section III (motor) of the Italian version of the MDS-unified Parkinson's disease rating scale (UPDRS). All patients were under treatment with dopaminergic therapy and were evaluated during the ON state (approximately 1 hour after taking their antiparkinsonian medications). Prior to any procedure, written informed consent was obtained from each participant according to our institutions' policy and was carried out in agreement with international regulations (Declaration of Helsinki, 1964) and all the subjects gave written informed consent after receiving a comprehensive explanation. Demographic and clinical characteristics of participants are reported in Table 1.

2.2. Training Protocol. At the end of the recruitment phase, 6 patients were excluded for not satisfying the inclusion criteria, then 64 participants were randomized to the action observation (AOT) or to the landscape observation (LOT) training by using a computerized random-number generator by an independent researcher. After the randomization process, participants were assembled in groups consisting of 5/6 patients each. Patients enrolled in the AO group-based training ($n = 32$; 14 males and 18 females; mean age ± SD: 70.4 ± 4.5) were required to carefully watch six videos (each lasting 6 minutes), in which strategies for circumventing FoG were presented and then to execute the observed actions according to the instructions given by the physiotherapist. During each group-based training session, two different video clips were presented twice and the complexity of the actions increased progressively over the sessions. Precisely, the six actions recorded in the video clips were the following: (1) shifting the body weight from one foot to the other; (2) shifting the body weight from one foot to the other making a step forward, backward and to the side; (3) walking straight with long steps; (4) turning around a chair; (5) stepping over an obstacle after shifting the body weight from one foot to the other; (6)

walking through a doorway (for further details, see [8] Appendix 1). All actions shown in the video clips were performed by a physiotherapist and then projected in third-person perspective.

Participants enrolled in the LOT group ($n = 32$; 15 males and 17 females; mean age ± SD: 72.8 ± 3.1) watched six videos containing sequences of static pictures (without any human or animal representation). Precisely, during each training session LOT participants watched 2 video clips (each lasting 6 minutes and presented twice) displaying landscape scenes (e.g., pictures of mountains and seaside, countryside, and desert scenes). Then, following the physiotherapist's instructions, they performed the same actions, in the exact order and for an identical amount of time, as for the AOT group. Great care was taken to ensure that the intervention was equal across groups; thus, actions were performed following a prefixed order in both AOT and LOT groups. Therefore, the training can be considered identical for the two groups and was done by the same physiotherapist. Training sessions were scheduled 2 times per week for 5 weeks and each session lasted 45 minutes. In both group-based training, each session started with the observation of video-clips (actions or landscape images) displayed on a projector screen on the wall. To ascertain that participants focus proper attention during the video presentation, they were specifically required concentrating on what was displayed on the screen. In addition, those included in the AO group-based training were not allowed to imitate any action while observing the videos and they were not allowed to take the videos at home.

2.3. Outcome Measures. The objective of the study was to verify the effectiveness of group-based AOT in improving FoG and mobility. The primary outcome measure was FoG severity measured with the new FoG questionnaire. Secondary outcome measures included the effect of intervention on gait and balance performances measured by means of the Timed Up and Go (TUG), the 10-meter walking test (10 M-WT), and the Berg balance scale (BBS). Patients were always tested in their best medical condition (ON state). Assessments were performed one week before the physical therapy program (PRE), within one week after the end of the training (POST) and four weeks later (FU-4w) by an independent researcher.

3. Statistical Analysis

Normal distribution of data at baseline was detected by means of the Shapiro-Wilk test. Gender differences between the groups were assessed by chi-square test. Differences between groups (AOT and LOT) for age an education were assessed by the nonparametric Mann-Whitney U test. For UPDRS III, FoG-Q score TUG, 10 M-WT, and BBS, an unpaired t-test was used to compare data between groups at baseline.

To evaluate changes in the outcome measures (FoG-Q, TUG, 10 M-WT, and BBS), a repeated measure analysis of variance (RM-ANOVA) was performed with the groups (AOT and LOT) as a between-subject factor and time (PRE, POST, and FU-w4) as a within-subject factor. Post hoc analysis was performed using t-tests. p values < 0.05 were considered as a threshold for statistical significance. All statistical analyses were performed using SPSS22.

4. Results

All participants ($n = 64$) completed the entire cycle of group-based training; one subject from the AOT group and two participants from LOT group withdrew during the follow-up due to personal problems, and thus the adherence rate was 95.5%. At the baseline, the two groups were comparable for demographics (age, $p = 0.31$; gender, $p = 0.61$; years of education, $p = 0.77$), clinical characteristics (disease duration, $p = 0.75$; UPDRS part III, $p = 0.88$), dopaminergic daily intake (LEDD, $p = 0.42$), FoG severity (FoG-Q, $p = 0.91$), and motor performance (TUG, $p = 0.68$; 10 M-WT, $p = 0.34$; BBS, $p = 0.33$). Baseline values related to FoG severity and motor performance are reported in Table 2.

Overall results showed that both groups achieved significant improvements in all the outcome measures at posttreatment (POST) assessment, but the improvement was retained up to the FU evaluation only in AO group-based training. Indeed, statistical analysis showed a significant effect of TIME for FoG-Q score ($F_{2,59} = 41.92$, $p < 0.001$), for TUG test ($F_{2,59} = 27.65$, $p < 0.001$), and BBS ($F_{2,59} = 17.20$, $p < 0.001$) and significant group × time interactions for FoG-Q ($F_{2,59} = 9.49$, $p < 0.001$) and gait and balance performances (TUG, $F_{2,59} = 3.52$, $p = 0.033$; BBS, $F_{2,59} = 3.24$, $p = 0.043$). Further, post hoc analysis revealed that improvements in these outcome measures were retained up to the FU-4w evaluation only in the AOT group (FU-4w versus PRE: FoG-Q, $p < 0.001$; TUG, $p < 0.001$; BBS, $p < 0.001$) (Figures 1(a)–1(d)).

Differently, for the 10 M-WT data, RM-ANOVA revealed a main effect of TIME ($F_{2,59} = 35.95$, $p < 0.001$) with no significant GROUP X TIME interaction ($F_{2,59} = 0.77$, $p = 0.46$), showing that these improvements were maintained in both training arms at FU-4w (PRE versus POST, $p < 0.01$; PRE versus FU-4w, $p < 0.01$). Details of the results and statistical significances are reported in Table 2.

5. Discussion

The main aim of the present study was to investigate whether an AOT program delivered in a group-based setting may improve FoG and mobility in subjects with PD. Further, we wanted to explore whether AOT was more effective than standard physical therapy in long-term consolidation of rehabilitation-induced improvements, even if AOT is delivered in a group-based setting.

Here, we demonstrated, for the first time, that AOT applied in a group-based setting is feasible and more effective for long-term benefit retention than physiotherapy alone. Our results showed that the reduction of FoG severity seen after the training period in both the AOT and the control groups was maintained up to the follow-up evaluation only in PD patients trained with AOT. Indeed, improvements achieved by participants who received physiotherapy alone

Table 2: Outcome measures tested before and after training and at follow-up evaluation.

Outcome measures	Action observation training group			Landscape observation training group			Repeated measure analysis of variance	
	PRE	POST	FU-4w	PRE	POST	FU-4w	Time	Time × group
FoG-Q (score)	12.3 ± 5.8	9.7 ± 5.8 #	9.4 ± 5.7 §	12.6 ± 5.3	10.5 ± 4.8 #	12.0 ± 5.7	($F_{2,59} = 41.92$; $p < 0.001$)	($F_{2,59} = 9.49$; $p < 0.001$)
TUG (sec.)	16.1 ± 7.2	12.2 ± 4.9 #	12.9 ± 4.1 §	17.3 ± 8.1	13.4 ± 6.1 #	15.5 ± 6.8	($F_{2,59} = 27.65$; $p < 0.001$)	($F_{2,59} = 3.52$; $p = 0.033$)
BBS (score)	46.3 ± 8.5	51.3 ± 5.7 #	51.5 ± 5.5 §	48.3 ± 7.1	52.4 ± 4.5 #	49.6 ± 5.7	($F_{2,59} = 17.20$; $p < 0.001$)	($F_{2,59} = 3.24$; $p = 0.043$)
10 M-WT (sec.)	13.9 ± 4.0	10.7 ± 3.9 #	12.3 ± 4.3 §	15.4 ± 5.5	12.9 ± 4.3 #	13.9 ± 5.4§	($F_{2,59} = 35.95$; $p < 0.001$)	($F_{2,59} = 0.77$; $p = 0.464$)

The mean ± standard deviation and details of statistical analysis are reported. FOG-Q: freezing of gait questionnaire; TUG: Timed Up and Go; BBS: Berg balance scale; 10 M-WT, 10-meter walking test; PRE: baseline evaluation; POST: after training evaluation; FU-4w: follow-up 4-weeks evaluation. Post hoc analysis: # PRE versus POST and § PRE versus FU-4w significant changes.

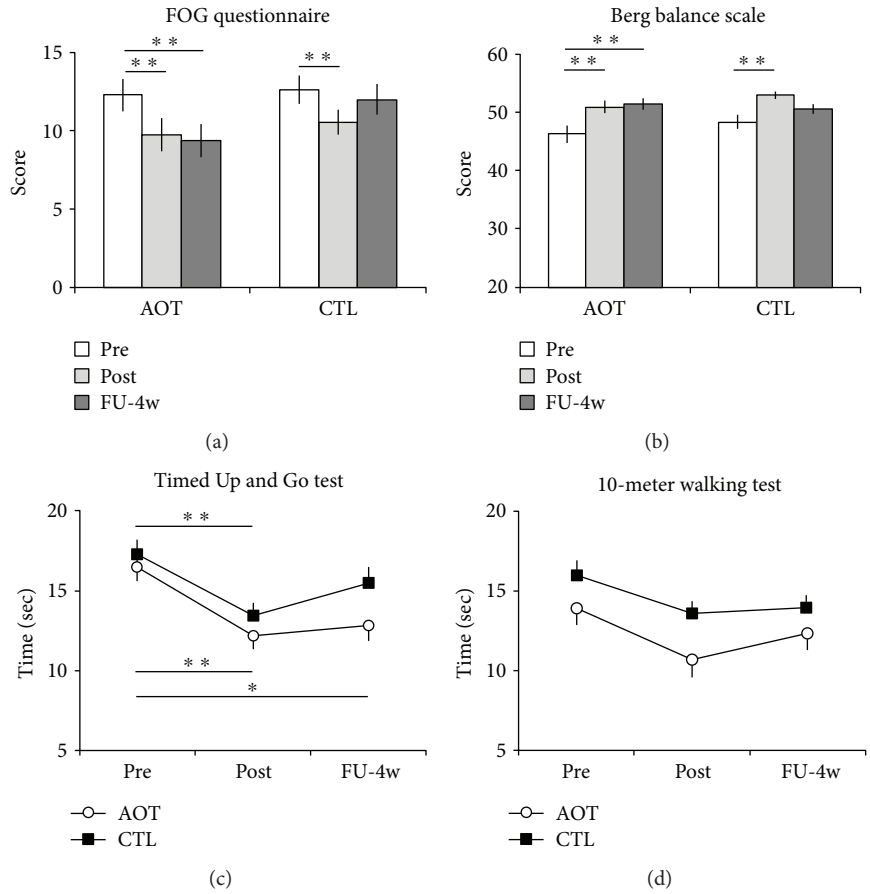

Figure 1: (a-b) FoG-Q and BBS mean scores (±SE). (c-d) TUG and 10 M-WT mean times (±SE). Baseline (PRE), end of training (POST), and 4-weeks follow-up (FU-4w) results are shown. Asterisks indicate when statistical significant differences within testing time evaluations emerged at post hoc analysis when the interaction term GROUP X TIME was significant ($^{*}p < 0.05$; $^{**}p < 0.001$). AOT: action observation training arm; LOT: landscape observation training arm; FoG-Q: new freezing of gait questionnaire; BBS: Berg balance scale; 10 M-WT: 10-meter walking test; TUG: Timed Up and Go.

(LOT group) were lost after 4 weeks. Further, the long-lasting effect of AO training was seen not only for FoG severity but also for gait and balance performances.

First, we can exclude that differences in disease severity and medication intake might have exerted an impact on motor learning induced by AOT, since no differences emerged between groups related to UPDRS III score, disease duration, and Levodopa equivalent dose (LEDD).

Thus, since patients in both groups practiced exactly the same physical training and were exposed to learning the same strategies to circumvent FoG, we may postulate that the long-term retention of benefits (reduction of FoG severity at 4-weeks FU) observed only in the AOT group is likely to be related to the action observation component of training, fostering a more effective learning, possibly through a plastic effect on the MNS.

To date, a large amount of evidence has demonstrated that AOT can enhance the beneficial effects of physiotherapy by reinforcing high-level brain networks involved in motor planning and execution, by promoting imitation learning and motor control relearning [13, 18] in the elderly [19] and in patients with orthopaedic [20] and neurological diseases [21].

Regarding PD, although the number of the studies is still limited, it has been consistently showed that AOT has a beneficial effect on motor performance, especially when actions represent meaningful tasks pertaining to the patients' motor repertoire, already after a single session of AOT and to a larger extent when AOT is administered in a long-term rehabilitative program [8, 10, 11]. In line with our results, in a recent paper, it has been demonstrated that combining AO with the execution of the observed action was able to induce a positive effect on motor disability, walking speed, balance, and quality of life with a trend toward a persisting reduced freezing of gait severity up to 8 weeks after the end of the training [9] only in patients enrolled in the AOT group.

Noteworthy, these authors adopted the same video clips and identical exercises (for patients enrolled in the AOT group and control group) used in our study.

To our knowledge, only one study reported significant improvements in self-perceived mobility but no objective changes in walking performance after home-based AOT in PD [15]. Crucially, participants were not instructed to watch and repeat the observed actions although it has been reported that in AOT learning it is promoted when the task consists explicitly in "observation-execution" [13]. In addition to that,

in order to achieve some benefits and foster retention effect, it seems to be fundamental teaching behavioural strategies that are suggested to shift patients' habitual motor control to a goal-directed one. Thus, the choice of actions to be displayed during AOT plays a key role in the effectiveness of this specific approach.

Freezing of gait (FoG) is a common and disabling phenomenon in PD patients [2], and it is recognized as one of the main risk factors for falls [22]. The management of FoG is complex and to date evidence is inadequate for identifying the most effective treatments [6, 7]. Developing innovative rehabilitative approaches and further reinforcing available evidence with larger studies is important for supporting both clinicians and patients in FoG management. Although the pathophysiology of FoG is still uncertain, imaging studies in PD patients with FoG pointed out the importance of cortical areas, particularly the supplementary motor area, as well as subcortical structures, including the striatum and brainstem locomotors centres [23]. A unifying idea for this network dysfunction has recently been proposed [23] suggesting a dynamic cerebral substrate for FoG. In PD patients with FoG during continuous movement (like locomotion), cortical activity in areas such as the supplementary motor area is decreased and subcortical activity is increased, perhaps to compensate the decreased cortical activity. During FoG episodes, activity in the supplementary motor area is still reduced, but subcortical hyperactivity breaks down to hypoactivity. This faulty dynamic process in cortical-subcortical activity, leading to "freezing," might become particularly evident during challenging events that require precise regulation of step length and gait timing.

Noteworthy, a recent fMRI study [9] in PD patients with FoG showed that a 4-week AOT program was able to increase the activation of premotor cortex, inferior frontal gyrus, and left inferior parietal lobule (all areas involved in the MNS) and to influence the recruitment of frontoparietal areas that are usually involved in controlled attention and goal-directed processing in response to shifting environmental factors. Overall, these results support the idea that AOT fosters the building of motor memories, thus improving motor learning. Further, AOT is likely to interact with the faulty dynamic process involving the cortex and subcortical structures, likely through the engagement of neural circuits subserving external focus of attention. Indeed, it is well known that focused attention and external stimuli can help PD patients to overcome FoG episodes. However, this hypothesis should be confirmed in an ad hoc study testing whether AOT can interfere with cortical-subcortical activations during continuous movements in PD patients with FoG.

Finally, it is also likely that group activity facilitates adherence and stimulates the participation of subjects. Indeed, receiving exercise training in a group context may be useful for PD patients who are at higher risk of daily life and health care stigmatization [24] compared to age-matched subjects who are not suffering from the neurological disease. However, a limitation in using group-based training is that it does not allow an intervention tailored on the subjects' individual needs according to the type of freezing or other clinical features. This suggests that group-based treatment should contemplate the inclusion of patients sufficiently homogeneous for clinical features, in order to build the training program on a group's need. On the other side of the coin, our results demonstrated also that group-based training experience did not compromise the attentional capacity of participants and enabled effective learning (observational learning) of motor skills.

Some limitations of our study need to be pointed out. First, we focused on motor performance not reporting data regarding quality of life or nonmotor symptoms; second, the long-lasting effects induced by AOT were tested only 4 weeks after training; third, the screening of patients' cognitive function was limited to MMSE. Related to the latter limitation, a more comprehensive cognitive evaluation would be recommended especially in PD patients with FoG, as several studies documented a strict link between freezing and cognitive status (in particular, executive functions) [25, 26]. However, in a previous study, it has been shown that PD patients with FoG who performed worse on tests assessing visuospatial abilities, problem-solving, shifting attention, and verbal comprehension compared to controls were able to follow an AOT protocol with beneficial effects on long-term motor performance [9]. Further, it has been demonstrated that action observation triggers preserved automatic [27] and voluntary [28] imitation mechanisms even in patients with cognitive deficits due to Alzheimer's disease, particularly when patients observed a human demonstrator respect to when the stimulus was abstract. However, a recent fMRI study also showed a progressive weakening of the mirror neurons network with respect to the neurodegenerative process by comparing neural activity induced by AO in normal elderly subjects, people with amnestic mild cognitive impairment and Alzheimer's disease patients [29]. In this scenario, we think that future studies should investigate the impact of patients' cognitive profile on the immediate and long-lasting effects of AOT.

6. Conclusions

To conclude, our results support the efficacy of AOT, as an explicit learning process, in improving FoG in patients with PD. We demonstrated that this training is feasible and safe and can be administered even in a group-based setting thus representing an adjunctive strategy for clinicians and physiotherapists.

Conflicts of Interest

All the authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] J. Jankovic, "Parkinson's disease: clinical features and diagnosis," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 79, no. 4, pp. 368–376, 2008.

[2] N. Giladi and A. Nieuwboer, "Understanding and treating freezing of gait in Parkinsonism, proposed working definition, and setting the stage," *Movement Disorders*, vol. 23, no. S2, Supplement 2, pp. S423–S425, 2008.

[3] T. Ellis, J. T. Cavanaugh, G. M. Earhart, M. P. Ford, K. B. Foreman, and L. E. Dibble, "Which measures of physical function and motor impairment best predict quality of life in Parkinson's disease?," *Parkinsonism & Related Disorders*, vol. 17, no. 9, pp. 693–697, 2011.

[4] B. R. Bloem, J. M. Hausdorff, J. E. Visser, and N. Giladi, "Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena," *Movement Disorders*, vol. 19, no. 8, pp. 871–884, 2004.

[5] D. M. Tan, J. L. McGinley, M. E. Danoudis, R. Iansek, and M. E. Morris, "Freezing of gait and activity limitations in people with Parkinson's disease," *Archives of Physical Medicine and Rehabilitation*, vol. 92, no. 7, pp. 1159–1165, 2011.

[6] J. Nonnekes, A. H. Snijders, J. G. Nutt, G. Deuschl, N. Giladi, and B. R. Bloem, "Freezing of gait: a practical approach to management," *The Lancet Neurology*, vol. 14, no. 7, pp. 768–778, 2015.

[7] P. Ginis, E. Nackaerts, A. Nieuwboer, and E. Heremans, "Cueing for people with Parkinson's disease with freezing of gait: a narrative review of the state-of-the-art and novel perspectives," *Annals of Physical and Rehabilitation Medicine*, 2017.

[8] E. Pelosin, L. Avanzino, M. Bove, P. Stramesi, A. Nieuwboer, and G. Abbruzzese, "Action observation improves freezing of gait in patients with Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 24, no. 8, pp. 746–752, 2010.

[9] F. Agosta, R. Gatti, E. Sarasso et al., "Brain plasticity in Parkinson's disease with freezing of gait induced by action observation training," *Journal of Neurology*, vol. 264, no. 1, pp. 88–101, 2017.

[10] E. Pelosin, M. Bove, P. Ruggeri, L. Avanzino, and G. Abbruzzese, "Reduction of bradykinesia of finger movements by a single session of action observation in Parkinson disease," *Neurorehabilitation and Neural Repair*, vol. 27, no. 6, pp. 552–560, 2013.

[11] G. Buccino, R. Gatti, M. C. Giusti et al., "Action observation treatment improves autonomy in daily activities in Parkinson's disease patients: results from a pilot study," *Movement Disorders*, vol. 26, no. 10, pp. 1963-1964, 2011.

[12] G. Rizzolatti, L. Fogassi, and V. Gallese, "Neurophysiological mechanisms underlying the understanding and imitation of action," *Nature Review Neuroscience*, vol. 2, no. 9, pp. 661–670, 2001.

[13] X. Zhang, T. T. de Beukelaar, J. Possel et al., "Movement observation improves early consolidation of motor memory," *The Journal of Neuroscience*, vol. 31, no. 32, pp. 11515–11520, 2011.

[14] D. Caligiore, M. Mustile, G. Spalletta, and G. Baldassarre, "Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis," *Neuroscience & Biobehavioral Reviews*, vol. 72, pp. 210–222, 2017.

[15] A. Jaywant, T. D. Ellis, S. Roy, C. C. Lin, S. Neargarder, and A. Cronin-Golomb, "Randomized controlled trial of a home-based action observation intervention to improve walking in Parkinson disease," *Archives of Physical Medicine and Rehabilitation*, vol. 97, no. 5, pp. 665–673, 2016.

[16] A. J. Hughes, S. E. Daniel, L. Kilford, and A. J. Lees, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 55, no. 3, pp. 181–184, 1992.

[17] A. Nieuwboer, L. Rochester, T. Herman et al., "Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers," *Gait & Posture*, vol. 30, no. 4, pp. 459–463, 2009.

[18] G. Buccino, "Action observation treatment: a novel tool in neurorehabilitation," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 369, no. 1644, article 20130185, 2014.

[19] B. Tia, F. Mourey, Y. Ballay, C. Sirandré, T. Pozzo, and C. Paizis, "Improvement of motor performance by observational training in elderly people," *Neuroscience Letters*, vol. 480, no. 2, pp. 138–142, 2010.

[20] J. H. Villafañe, M. Isgrò, M. Borsatti, P. Berjano, C. Pirali, and S. Negrini, "Effects of action observation treatment in recovery after total knee replacement: a prospective clinical trial," *Clinical Rehabilitation*, vol. 31, no. 3, pp. 361–368, 2017.

[21] G. Abbruzzese, L. Avanzino, R. Marchese, and E. Pelosin, "Action observation and motor imagery: innovative cognitive tools in the rehabilitation of Parkinson's disease," *Parkinson's Disease*, vol. 2015, Article ID 124214, 9 pages, 2015.

[22] C. G. Canning, S. S. Paul, and A. Nieuwboer, "Prevention of falls in Parkinson's disease: a review of fall risk factors and the role of physical interventions," *Neurodegenerative Disease Management*, vol. 4, no. 3, pp. 203–221, 2014.

[23] A. H. Snijders, K. Takakusaki, B. Debu et al., "Physiology of freezing of gait," *Annals of Neurology*, vol. 80, no. 5, pp. 644–659, 2016.

[24] L. Tickle-Degnen, L. A. Zebrowitz, and H. I. Ma, "Culture, gender and health care stigma: practitioners' response to facial masking experienced by people with Parkinson's disease," *Social Science & Medicine*, vol. 73, no. 1, pp. 95–102, 2011.

[25] M. Amboni, A. Cozzolino, K. Longo, M. Picillo, and P. Barone, "Freezing of gait and executive functions in patients with Parkinson's disease," *Movement Disorders*, vol. 23, no. 3, pp. 395–400, 2008.

[26] S. Vercruysse, H. Devos, L. Munks et al., "Explaining freezing of gait in Parkinson's disease: motor and cognitive determinants," *Movement Disorders*, vol. 27, no. 13, pp. 1644–1651, 2012.

[27] A. Bisio, M. Casteran, Y. Ballay, P. Manckoundia, F. Mourey, and T. Pozzo, "Motor resonance mechanisms are preserved in Alzheimer's disease patients," *Neuroscience*, vol. 222, pp. 58–68, 2012.

[28] A. Bisio, M. Casteran, Y. Ballay, P. Manckoundia, F. Mourey, and T. Pozzo, "Voluntary imitation in Alzheimer's disease patients," *Frontiers in Aging Neuroscience*, vol. 8, no. 48, pp. 1–10, 2016.

[29] E. Farina, F. Baglio, S. Pomati et al., "The mirror neurons network in aging, mild cognitive impairment, and Alzheimer disease: a functional MRI study," *Frontiers in Aging Neuroscience*, vol. 9, no. 371, pp. 1–13, 2017.

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Clinical Study

Functional Brain Connectivity during Multiple Motor Imagery Tasks in Spinal Cord Injury

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Reciprocal communication of the central and peripheral nervous systems is compromised during spinal cord injury due to neurotrauma of ascending and descending pathways. Changes in brain organization after spinal cord injury have been associated with differences in prognosis. Changes in functional connectivity may also serve as injury biomarkers. Most studies on functional connectivity have focused on chronic complete injury or resting-state condition. In our study, ten right-handed patients with incomplete spinal cord injury and ten age- and gender-matched healthy controls performed multiple visual motor imagery tasks of upper extremities and walking under high-resolution electroencephalography recording. Directed transfer function was used to study connectivity at the cortical source space between sensorimotor nodes. Chronic disruption of reciprocal communication in incomplete injury could result in permanent significant decrease of connectivity in a subset of the sensorimotor network, regardless of positive or negative neurological outcome. Cingulate motor areas consistently contributed the larger outflow (right) and received the higher inflow (left) among all nodes, across all motor imagery categories, in both groups. Injured subjects had higher outflow from left cingulate than healthy subjects and higher inflow in right cingulate than healthy subjects. Alpha networks were less dense, showing less integration and more segregation than beta networks. Spinal cord injury patients showed signs of increased local processing as adaptive mechanism. This trial is registered with NCT02443558.

1. Introduction

Reciprocal communication of the central and peripheral nervous systems is compromised during spinal cord injury (SCI), a condition that often causes permanent disability due to massive neurotrauma of ascending and descending pathways [1, 2]. While changes in brain activity and brain organization may seem trivial, when compared to the underlying injury of the pathways, they have nevertheless been consistently associated with SCI [3–5]. Such changes have also been observed at the early stages after the injury and have been associated with differences regarding the prognosis of SCI patients' recovery [4–6]. Demonstrated structural changes of the brain include atrophy of afferent neural pathways, microstructural changes of efferent axons, and disorder of white matter integrity in multiple nodes of the sensorimotor cortex that involve the primary motor and somatosensory areas [7] and also diffuse neuronal degeneration [8].

Functional connectivity (FC) after SCI has been studied by means of electroencephalography (EEG) [9–15] and functional magnetic resonance imaging (fMRI) [6, 16–21]. Poor recovery after SCI has been associated with decreased FC strengths between midline sensorimotor network nodes during resting state, while the opposite pattern has been associated with good recovery [6]. Supplementary and cingulate motor areas have been shown to play important roles during the sensorimotor neurophysiological process [9, 11], while

unique interactions and temporal dynamics have been identified in the functional networks of SCI patients [12, 14]. Connectivity changes have been hypothesized to be able to serve as injury biomarkers [22] while novel methods have been developed and have been proposed in order to study the brain's connectome following SCI in hopes of providing more reliable evidence of these changes [23].

Most studies on functional connectivity after SCI have focused on patients with chronic complete injury, including the majority of EEG studies. Only a couple of studies employing fMRI as a modality to detect brain activity have assessed patients with incomplete injury but those have only studied connectivity during resting-state condition so far [6, 16–18]. Moreover, the pioneer EEG studies on functional cortical connectivity of SCI patients during motor imagery have employed a robust but rather limited study design [9]. In this design, the motor imagery task involved an attempt to move the paralyzed right foot and was performed simultaneously with one motor execution task (lip protrusion), while the functional networks were subsequently analyzed using a variety of tools. So far, to the authors' best knowledge, no study has been performed employing multiple motor imagery tasks, especially of the upper extremities, aiming to analyze differences in the formed networks. Moreover, incomplete injury at the chronic phases remains understudied compared to chronic complete injury with regard to functional connectivity networks. Despite the clinical and social impact of SCI, so far published studies have been unable to form a complete model regarding the effect of the injury on brain networks, although effort has been made into modeling-specific aspects, like resting-state connectivity and chronic injury [3, 22]. It can be hypothesized—and there are also indications—that even incomplete spinal cord injury may show measurable effects on the functional sensorimotor network [24] that could be important for modeling the condition in relation to prognosis [3, 6, 16].

Motor imagery, apart from its importance to the study of brain activity after neurotrauma, has shown great potential in motor skill learning and in rehabilitation of upper and lower limb paralysis [25, 26]. It has been established that motor imagery produces patterns of brain activation and brain connectivity similar to those of motor execution [27, 28], while the visual motor imagery class also activates a distinct task-dependent neural system [29, 30]. Motor imagery has been used as a modality to induce plasticity and recovery in a range of conditions [31], including complete cervical spinal cord injury [32] and stroke [33]. Moreover, motor imagery has been also used as a control modality for brain-computer interface implementations of exoskeletons for complete [34] and incomplete spinal cord injury [35]. Functional recovery has been induced even in the case of complete injuries using such an approach [34]. Such results demonstrate the importance of motor imagery functional networks studies to accurately model the plastic changes that occur after SCI.

In our previous work, we have presented our study with a cohort of SCI patients and healthy control subjects that exercised motor imagery to achieve control of anthropomorphic robotic arms in various movement tasks. We have accounted for development [36], pilot experiments, and brain network analysis [37, 38], and we have presented a detailed user perception and performance assessment study, based on neurological and psychometric evaluation [39]. In the current paper, we present an elaborate analysis of the functional connectivity networks formed on the sensorimotor cortex during visual motor imagery of multiple motor tasks performed by subjects with SCI and healthy controls. In Materials and Methods, we briefly present the experimental setup and detail our signal processing computational workflow, network analysis, and statistical comparisons. In Results, we detail important findings with regard to the effect of injury, motor imagery category, brainwave rhythm, and timing of imagery. In Discussion, we attempt to interpret our results in the context of already published studies in the field, and we note the limitations of this approach.

2. Materials and Methods

2.1. Experimental Setup

2.1.1. Recruitment and Subject Assessment. The experimental setup has been previously described in detail, including subject assessment [39] and procedures [36, 37], so we will hereby provide only a brief overview. Our experimental protocol was approved by the institutional ethical committee [40], and all subjects signed an informed consent form. We recruited 8 male and 2 female patients with SCI (age: mean 46.0, SD 17.64, range 28–74 years) and ten gender- and age-matched healthy controls. All participants were right-handed and reported no prior experience in mental imagery (Table 1).

For both groups, we collected demographics and medical history; also, a specialist physician performed neurological examination using the International Standards for Neurological Classification of Spinal Cord Injury, to document classification in American Spinal Injury Association Impairment Scale (AIS) and the Neurological Level of Injury (NLI). Subject assessment also included subjective reporting of imagery capacity, using Vividness of Visual Imagery Questionnaire (VVIQ) [41] with eyes open (Table 1). Within the SCI group, 60% of the patients were grouped into positive outcome based on the neurological assessment (4 AIS D, 2 AIS E), and 40% of the patients were grouped into negative outcome (1 AIS A, 2 AIS B, and 1 AIS C).

2.1.2. Experimental Procedure. The experiment took place inside a magnetic shielded room for EEG recording, specially designed for presentation capability and audiovisual monitoring of the participants. The subjects sat at a 1 m distance across a 21″ computer monitor. They wore an active electrode cap (Brain Products, Germany) and were connected to a 128-channel EEG (Nihon-Kohden, Japan) according to the high-resolution EEG 10–5 international electrode system [42]. Recordings were taken at a sampling rate of 1000 Hz and an impedance threshold of 10 kohm [36]. Initially, we recorded resting-state activity, 1.5 min with open eyes and 1.5 min with closed eyes.

Table 1: Demographic data and reported imagery capacity of subject groups (SCI and healthy).

(a)

SCI group	Age	Gender	Cause	AIS	NLI	VVIQ
CSI-02-001	28	f	MVA	C	C4	54
CSI-02-002	52	m	MVA	D	C4	69
CSI-02-003	42	m	MVA	D	C8	68
CSI-02-004	70	m	Fall	D	C5	76
CSI-02-005	60	m	Fall	E	C6	70
CSI-02-006	28	m	MVA	D	C5	56
CSI-02-007	30	m	MVA	E	C5	67
CSI-03-001	47	m	Fall	A	T7	72
CSI-03-002	29	f	MVA	B	T4	60
CSI-03-003	74	m	Other	B	T4	65
Mean (SD)	*46.00 (17.64)*					*65.70 (7.04)*

(b)

Healthy group	Age	Gender	VVIQ
CSI-04-001	27	f	77
CSI-04-007	51	m	75
CSI-04-003	43	m	56
CSI-04-006	71	m	70
CSI-04-009	63	m	70
CSI-04-004	28	m	46
CSI-04-005	31	m	58
CSI-04-008	47	m	80
CSI-04-002	27	f	75
CSI-04-010	74	m	63
Mean (SD)	*46.20 (18.27)*		*67.00 (10.09)*

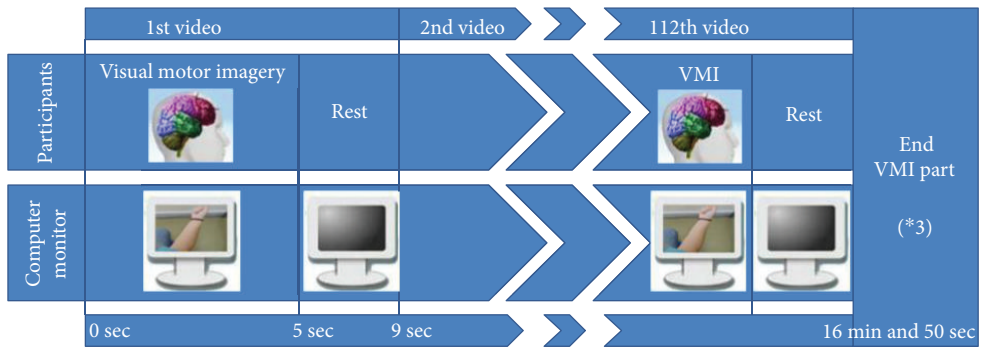

Figure 1: Flow diagram of the experimental procedure of one part of the visual motor imagery presentation. Each presented video lasted 5 seconds and was followed by 4 seconds of black resting screen. The videos were presented 9 times each, in a random order. The presentation was divided into three parts, lasting approximately 17 minutes each, with an intermission between them.

In the main experimental part, the subjects watched videos of 32 different arm motor tasks, a walking task video, and an oddball video. The videos were presented in random order. All arm motor task videos were presented from the perspective of the participant watching his or her own arms and were gender-matched. The walking task video presented a pair of gender-matched legs walking, while seeing them from the perspective of watching one's own legs. The oddball video showed a wildlife documentary. The videos lasted 5 sec, each followed by a black screen with duration of 4 sec. A trigger channel was recorded at the onset of each visual cue (the start of each video) through an optic diode. The presentation was separated in three parts of about 17 min each, with 5 min of rest between them (Figure 1). At conclusion, each task had

been presented 9 times in total. The subjects were asked to perform visual motor imagery (VMI), while watching a motor task, without actually moving their limbs (regardless of neurological status or group) and were instructed to rest while watching the black screen. They already knew that the videos would be presented at random but not of the presence of an oddball video (video showing wildlife). Moreover, the subjects' arms, torso, and legs were covered with a black curtain during the whole procedure in order to facilitate mental registration of the presented arms and legs into their perceived body schema [43].

The 32 upper extremity motor tasks consisted of 8 independent movements (degrees of freedom) * 2 directions of movement * 2 extremities, comprising the full range of motion of the human arms and were classified into categories for further analysis [39]. In short, the 8 categories of motor tasks were "Hands," "Left," "Right," "Proximal," "Distal," "Rotational," "Linear," and "Walking."

The "Hands" category included all 32 tasks of both upper extremities. The "Left" and "Right" categories included 16 motor tasks each of the respective upper extremity (left or right). The "Proximal" category included 16 motor tasks of the shoulder and elbow joints of both extremities, while the "Distal" category included the remaining 16 motor tasks of wrist joints and fingers. Further, the "Rotational" category included those 8 motor tasks that result in rotational motion, and the "Linear" category included those 24 motor tasks of both extremities that resulted in linear motion (Table 2). Finally, the "Walking" category was also defined as a separate category of motor imagery, consisting only of the walking motor imagery task, for a total of 8 categories. Table 2 lists in summary all presented motor tasks of one upper extremity (16 tasks), for each showing the degree of freedom, direction of movement, classification by proximity, and resulted motion.

Table 2: Presented motor tasks for one upper extremity (left or right): 16 motor tasks were presented (8 independent movements (degrees of freedom) * 2 directions of movement) and were then classified by proximity (proximal or distal tasks) and resulting motion (linear or rotational). For both upper extremities, the subjects watched and performed visual imagery of 32 motor tasks in total.

Independent movement	Direction	Proximal/ distal	Linear/ rotational
Shoulder	Arm down	Proximal	Linear
Shoulder	Arm up	Proximal	Linear
Shoulder	Arm left	Proximal	Linear
Shoulder	Arm right	Proximal	Linear
Elbow	Forearm down	Proximal	Linear
Elbow	Forearm up	Proximal	Linear
Forearm	External rotation	Proximal	Rotational
Forearm	Internal rotation	Proximal	Rotational
Wrist	Hand down	Distal	Linear
Wrist	Hand up	Distal	Linear
Wrist	External rotation	Distal	Rotational
Wrist	Internal rotation	Distal	Rotational
Thumb	Open	Distal	Linear
Thumb	Close	Distal	Linear
Fingers	Open	Distal	Linear
Fingers	Close	Distal	Linear

2.2. Signal Analysis

2.2.1. Signal Preprocessing. Signal analysis was performed on a subset of the 10–5 international electrode system that is overlying the cortical sensorimotor areas [44] that were later defined as regions of interest (ROIs) for this study (Figure 2). This subset included 64 electrodes: AFF5h, AFF3h, AFF1h, AFz, AFF2h, AFF4h, AFF6h, F5, F3, F1, Fz, F2, F4, F6, FFT7h, FFC3h, FFC1h, FFC2h, FFC4h, FFT8h, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, FTT7h, FCC5h, FCC3h, FCC1h, FCC4h, FCC6h, FTT8h, C5, C3, C1, Cz, C2, C4, C6, CCP3h, CCP1h, CCP2h, CCP4h, CP5, CP3, CP1, CPz, CP2, CP4, CP6, CPP3h, CPP1h, CPP2h, CPP4h, P3, P1, Pz, P2, P4, PPO1h, and PPO2h. As scalp electrodes capture mixed activity from unknown cortical and subcortical brain sources, recording brain activity related to motor tasks only from the sensors overlying the sensorimotor area presents some risk for loss of information but also presents certain advantages. This approach has been used in EEG source imaging studies regarding motor tasks with good results [45–48], as the signal of interest is less attenuated and signal to noise ratio is higher than in distant sensors, while contaminated channels closer to muscular artifact generators are excluded.

All signal preprocessing was performed using a custom script on the FieldTrip toolbox for MATLAB [49]. Raw data from those selected channels was band-pass filtered at 0.5–30 Hz using a zero-phase FIR filter and subsequently downsampled at 100 Hz. We visually examined continuous EEG signal time series of each subject to detect bad electrodes that showed large drifts from their mean value and then removed these electrodes. Epochs were then initially extracted from −2000 msec to +5000 msec centered on the trigger (visual cue). Subsequently, independent component analysis was performed on the concatenated continuous data (of each session) using the second-order blind identification method [50]. Independent components corresponding to eye blinks and muscle artifacts were identified and removed from the epoched data. Bad electrodes were then interpolated using spherical splines interpolation [51]. Finally, the epoched data were split into two time intervals (Figure 3), which will be referred to as "early" (early onset imagery from −1000 msec to +2000 msec around the trigger) and "late" (late continuous imagery from +2000 msec to +5000 msec after the trigger). While shorter time windows have also been used in similar analyses [52], differences in the behavior of alpha and beta rhythms between the window around the imagery onset and later windows have been identified with regard to networks [53], relative power [54], and

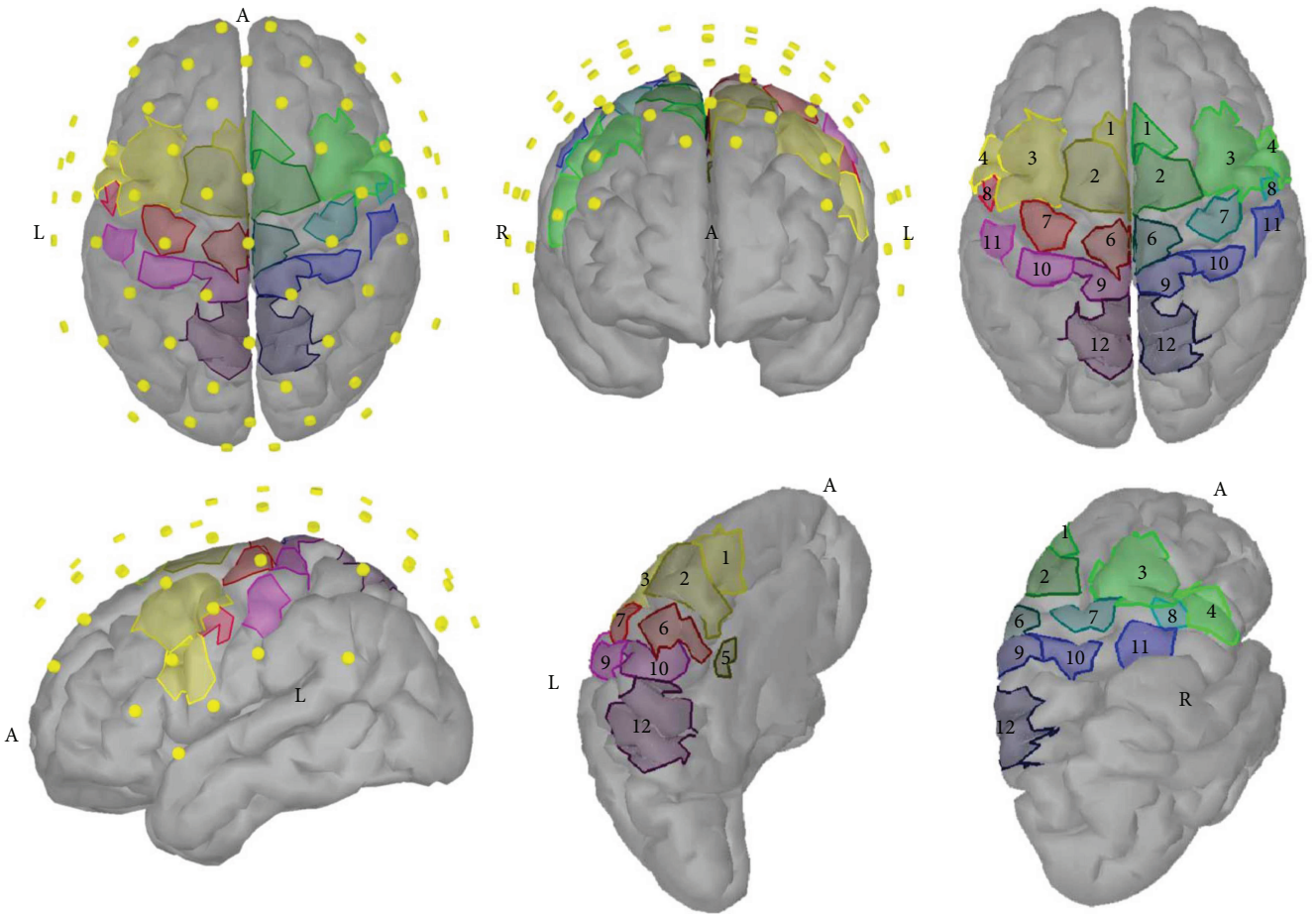

Figure 2: Regions of interest (ROIs) of the sensorimotor cortex and the overlying subset of electrodes that was used for signal analysis in our study. 1: presupplementary motor area (pSMA); 2: supplementary motor area (SMA); 3: dorsal premotor area (PMd); 4: ventral premotor area (PMv); 5: cingulate motor area (CMA); 6: primary foot motor area (M1F); 7: primary hand motor area (M1H); 8: primary lip motor area (M1L); 9: primary foot somatosensory area (S1F); 10: primary hand somatosensory area (S1H); 11: secondary somatosensory area (S2); 12: somatosensory association area (SAC).

event-related desynchronization [55]. The data from one subject (from the healthy group) was exempted from further analysis, as this preprocessing methodology did not result in sufficiently clean epoched data.

2.2.2. Current Cortical Density. The solution of the forward problem, the lead field matrix that best describes the conduction from the current cortical density (CCD) source model (Table 3) to scalp potentials, is based on the following equation:

$$m = Ld + b, \tag{1}$$

where m refers to the M simultaneous electrode voltage recordings, d refers to the N current dipoles in the current cortical density model, b is the noise vector, and L is the abovementioned lead field matrix [56]. We used the solution applied in eConnectome toolbox for MATLAB [57, 58] of the forward problem which is a high-resolution lead field matrix relating 2054 scalp triangles to 7850 cortical dipoles. The lead field matrix is derived using a three-layer block element modifier model based on the Colin27 Montreal Neurological Institute brain [59]. The dipoles were constrained to the gray matter with orientations perpendicular to the local cortical surface, under the assumption that the primary source of measured EEG signal is local groups of pyramidal neurons of the cortex firing synchronously and is arranged perpendicular to its surface [60]. In our case, a subset of the lead field matrix was used for the 64 selected EEG electrodes.

Weighted minimum norm estimate was used to solve the ill-posed inverse problem (Table 3) by minimizing the source space energy based on the fact that the power of the source dipoles is limited by the cortex physiology [61]. Minimum norm estimate aims at minimizing the following equation:

$$J(d) = \|m - Ld\|^2 + \lambda \|d\|^2, \tag{2}$$

where m refers to the actual recordings from the scalp, d is the simultaneous current dipoles to be calculated, L is the lead field matrix, λ is the regularization parameter, and $|d|^2$ is the regularization term which in our case refers to the energy of the solution's dipoles. The first term in the above equation represents the error between the actual and predicted electrode recordings. The second term is the penalization term, which aims at enforcing the abovementioned

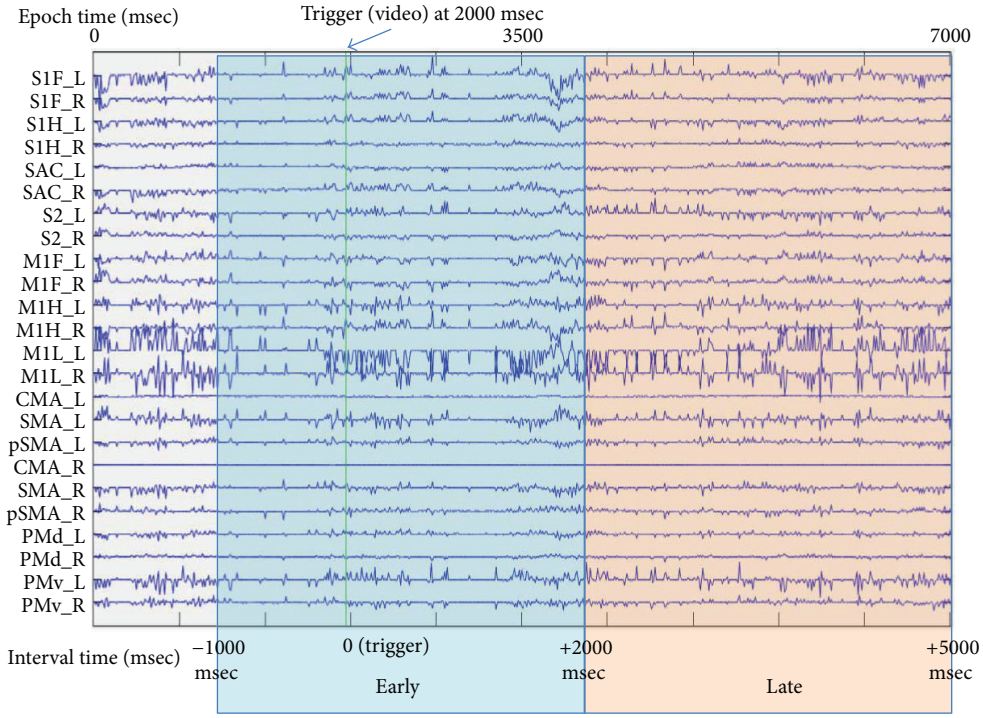

Figure 3: Activation time series of all regions of interest (ROIs) of the sensorimotor cortex during a random epoch and definition of time intervals around the trigger (onset of the video presenting the motor imagery task).

Table 3: Summary presentation and description of the most important models and connectivity metrics or measures that were used in the methodological section of this study.

Metric or model name	Acronym		Description
Current cortical density	CCD	Forward problem solution	A model that aims to explain the correspondence of cortical source activity to scalp electrical potentials, taking account of skull and scalp conductivity.
Weighted minimum norm estimate	wMNE	Inverse problem solution	An estimation of how signals captured at the scalp correspond to source activations, with their power limited by the cortical physiology.
Directed transfer function	DTF	Granger causality measure	A metric of effective network connectivity (functional connectivity that incorporates causal relations instead of statistical inference alone) that produces directed networks with weighted edges.
Characteristic path length	CPL	Network integration	A representative measure of shortest distances between network nodes that are connected to each other.
Clustering coefficient	CC	Network segregation	A measure of the tendency of network nodes to become organized into functionally separated clusters.
Density	D	Network density	A measure of existing connections against the theoretical maximum number of possible connections if the network was fully connected.
Small-worldness	SW	Overall network effectiveness	A model of network behavior, where short paths and increased forming of functional clusters lead to optimization and resilience of information transfer.
Out-strength and in-strength	OS and IS		The total nodal sum of weights from outgoing and incoming connections, respectively.

energy restriction. Lastly, λ, which balances the effect of the penalization term, was calculated using the L-curve method [62]. The solution of minimum norm estimate was derived using Tikhonov regularization in the regularization toolbox [63]. 24 custom-defined ROIs were created at the surface of the cortex model, in order to proceed to connectivity analysis, as illustrated in Figure 2. The ROI time series signal (Figure 3) was calculated by averaging the amplitude from all included cortical current dipoles.

2.2.3. Functional Connectivity. In total, 24 ROIs were defined on the cortical source model, consisting of the following areas bilaterally: presupplementary motor area (pSMA), supplementary motor area (SMA), dorsal premotor

area (PMd), ventral premotor area (PMv), cingulate motor area (CMA), primary foot motor area (M1F), primary hand motor area (M1H), primary lip motor area (M1L), primary foot somatosensory area (S1F), primary hand somatosensory area (S1H), secondary somatosensory area (S2), and somatosensory association area (SAC) (Figure 2). Their average activation time series were computed for every time interval.

Directed transfer function (DTF) [64] was used (Table 3) in order to calculate functional cortical connectivity of the sensorimotor network consisting of the 24 ROIs as nodes [44], computing causal relations among the nodal activation time series. The produced connectivity matrices were thresholded, using the surrogate data method with testing of significance of connections, instead of using absolute or relative thresholding [65–67]. During computation of DTF, a number of 1000 surrogate permutations and a significance level of 0.05 were set, resulting in partially connected matrices with only the most significant causal connections. DTF is a measure based on Granger causality [68] that uses the multivariate autoregressive model described by the following function:

$$X(t) = \sum_{j=1}^{p} A(j)X(t-j) + E(t), \tag{3}$$

where p is the model order, $X(t)$ contains the ROIs values at time t, $E(t)$ is the residual noise vector, and A is a coefficient k × k-sized matrix [44]. Using the above equation, the A matrices are computed by means of the minimalization of the residual noise E.

The order of the multivariate autoregressive model [69] was chosen to be 8 after considering the following criterions [70]: (a) tests that demonstrated an optimal order of 10 for a sampling rate of 128 Hz for modeling EEG spectra [71, 72]; (b) the model order should be smaller than $\tau \times \mathrm{Fs}$, where τ is the expected lag between two brain processes and Fs the sampling rate; (c) better to err on the side of selecting a larger model order, (d) using the same model order for all DTF computations.

Equation (3) is described in the frequency domain as

$$\begin{aligned} E(f) &= A(f)X(f), \\ X(f) &= A^{-1}(f)E(f) = H(f)E(f), \end{aligned} \tag{4}$$

where $H(f)$ is a transfer matrix of the system, and it contains information about the relationships between signals. It is nonsymmetric, so it allows for finding causal dependencies. DTF is then computed by the equation:

$$\mathrm{DTF}^2_{j\to i}(f) = \frac{\left\|H_{ij}(f)\right\|^2}{\sum_{m=1}^{k}\left\|H_{im}(f)\right\|^2}. \tag{5}$$

DTF describes casual influence of channel j on channel i at frequency f. For our analysis, DTF was computed for the networks formed at the frequency bands of alpha rhythm at 8–12 Hz ("alpha networks") and beta rhythm at 13–30 Hz ("beta networks"), as those are considered the brainwaves most relevant to the sensorimotor processes [73].

2.2.4. Network Analysis. Network analysis in terms of descriptors of the weighted directed graphs ("network properties") was performed with the brain connectivity toolbox for MATLAB [74] for the *alpha* and *beta* networks formed during *early* and *late* time intervals. Out-strength (OS), in-strength (IS), and clustering coefficient were computed for each of the 24 nodes of the network during each task of imagery. Characteristic path length (CPL), mean clustering coefficient (CC), and density (D) were also computed at the level of graphs of each task of imagery. Topology of small-worldness (SW) was then derived from these network properties for each task of imagery [44]. To facilitate further analysis, all properties were averaged for the 8 imagery categories mentioned in Experimental Procedure. A summary of the interpretation of these network properties is also presented in Table 3.

CPL, a measure of integration, calculates the sum of the shortest distances among connected graph nodes, divided by the number of nodes [75, 76]. It is described by (6), where Li is the average distance between node i and the other node, and d_{ij} is the shortest path between nodes i and j. The distance matrix was computed using the logarithmic conversion of weights by the Floyd-Warshall algorithm [77], as implemented in the BCT [78].

$$\mathrm{CPL} = \frac{1}{n}\sum_{i\in N} Li = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}}{n-1}. \tag{6}$$

Global CC, a measure of segregation, estimates the tendency of the graph nodes to organize into clusters [79, 80]. It is described by (7), where Ci is the clustering value for a node i, k_i is the node's degree, and t_i is the number of neighboring nodes that connect to each other in triangles around node i.

$$\mathrm{CC} = \frac{1}{n}\sum_{i\in N} Ci = \frac{1}{n}\sum_{i\in N}\frac{2t_i}{k_i(k_i-1)}. \tag{7}$$

D is the ratio of a network's actual connections to the maximum possible connections. In our example, the graphs were only partially connected, and the connection weights were ignored, since all connections were considered significant as computed by DTF with testing for statistical significance ($p = 0.05$) by surrogate data. It is therefore described by (8), where E is the ensemble of the network's connections, and V is the ensemble of the network's nodes.

$$D = \frac{|E|}{|V|(|V|-1)}. \tag{8}$$

SW is defined as the combination of short paths and high clustering in a network, when compared to random networks with comparable paths constructed by the same number of nodes and connections. This property has commanded attention as an important brain network characteristic that models the brain's effective communication patterns [81–83]. It is described by (9), and in our study, the comparison of CPL and CC was made against 10,000 random networks. These random networks were directed graphs, with the same number of nodes and edges as the original, and they were generated using the brain connectivity toolbox [84]. CPL and CC were

computed for each random network and compared against the original, in a process that was iterated 10,000 times to produce a range of SW values. The range of values was then averaged to produce a single robust value of the SW property for each original network.

$$\mathrm{SW} = \frac{\mathrm{CC}/\mathrm{CC}_{\mathrm{rand}}}{\mathrm{CPL}/\mathrm{CPL}_{\mathrm{rand}}}. \quad (9)$$

The strength of node strength is the sum of the weights of connections to or from that node. The IS, therefore, is the sum of incoming connection weights, and the OS is the sum of outgoing connection weights [74]. They are described by (10) and (11), respectively, where C_{ij} is the weighted directed N^*M connectivity matrix, with a direction of $i \to j$, N is the number of columns, and M is the number of rows.

$$\mathrm{IS} = \sum_{j=1}^{N} C_{ij}, \quad (10)$$

$$\mathrm{OS} = \sum_{i=1}^{M} C_{ij}. \quad (11)$$

2.3. Statistical Analysis. Adjacency matrices computed by directed transfer function were compared between healthy and patient groups using the network-based statistic toolbox for MATLAB [85]. We performed the statistical analysis using the false discovery rate on the general linear model with t-test [86], a significance level of 0.05 and 50,000 permutations. Using a between-group design, we compared alpha and beta networks of healthy subjects to alpha and beta networks of SCI subjects for each imagery category, elaborating the comparisons for the effect of early and late intervals. We also compared alpha to beta networks of each category and time interval using a within-group design. Differences in networks were visualized using the BrainNet Viewer for MATLAB [87].

Statistical analysis of age, imagery capacity, and computed network properties was performed in IBM SPSS Statistics (version 23), and we set a significance level of 0.05 for all statistical tests. All variables were explored for normality assumption (healthy and SCI groups as grouping factor) using visual inspection of histograms, normal Q-Q plots and boxplots, skewness and kurtosis [88–90], and normality tests (Shapiro-Wilk test and Kolmogorov-Smirnov test) [91, 92]. Depending on normality assumption, different analyses were performed (paired t-tests or Wilcoxon signed-rank tests). Normality assumption was met for the variable age and for the VVIQ score for both groups. Independent sample t-tests were performed to reveal significant age and VVIQ differences between the two groups. As the groups did not differ either for age distributions (healthy-skewness: 0.407 (SE = 0.687), kurtosis: −1.418 (SE = 1.334); SCI-skewness: 0.651 (SE = 0.687), kurtosis: −0.752 (SE = 1.334)) or for their reported imagery capacity (VVIQ: $t = -1.094$, df = 8, and $p = 0.306$), the rest of the statistical analysis was planned accordingly.

We planned within-group comparisons of brain network properties using as grouping factor the rhythm (alpha, beta). Differences of variables between the two rhythms were calculated for the categories of visual motor imagery tasks, separately at early and late time intervals. Subsequently, we calculated within-group comparisons of brain network properties using as grouping factor the time interval (early, late). Between-group comparisons were performed using the calculated differences of variables at the two time intervals with either independent samples t-tests or Mann–Whitney U tests.

Nodal strengths, both incoming and outgoing, were averaged across different motor imagery tasks, rhythms, and time intervals, and total nodal strengths were calculated. They were tested for normality assumption for both groups and analyzed within groups using descriptive statistics and between groups (SCI, healthy) using Mann–Whitney U test. Targeted differences between nodes CMA_L and CMA_R were tested for statistical significance using either Pearson or Spearman correlation coefficient depending on normality assumption.

3. Results

3.1. Functional Connectivity. Visualizations of connectivity maps for the two groups (SCI, healthy) were made using the eConnectome toolbox for alpha and beta networks during both time intervals averaged across the motor imagery categories (Figure 4). The highest information transfer in all examined networks came from the bilateral cingulate motor areas including their reciprocal communication. In both groups, the maximum incoming nodal strength was observed in right CMA (Table 4), whereas the maximum outgoing nodal strength was found in left CMA (Table 5). Between-group comparisons revealed significant differences in total nodal strengths, both incoming and outgoing.

More precisely, significant differences in incoming strengths were found bilaterally in CMA, SMA, S1H, PMd, and PMv as well as in the left S1F. Healthy participants showed higher incoming strengths in all aforementioned nodes apart from the left CMA (Figure 5) compared to the SCI participants (Table 4).

Outgoing strengths were found to be significantly different between groups in all nodes (Table 5) apart from the right S1F. In more detail, SCI group showed considerably higher outgoing strengths in the S1F and SAC in the left hemisphere, in S1H and CMA in the right hemisphere as well as in S2, PMd and PMv bilaterally. In the remaining nodes, healthy participants were found to have increased outgoing strengths compared to SCI participants.

When calculating differences of group averages (healthy group-SCI group) of in-strength (IS) and out-strength (OS) of cingulate motor areas (CMAs) during all motor imagery categories, a possible trend was revealed. OS of CMA_R was consistently higher in the healthy group, while OS of CMA_L was consistently higher in the SCI group. The opposite held true for IS of those nodes (Figure 6). Between-group differences in CMA_R were negatively correlated to those in CMA_L in targeted imagery categories (early alpha walking ($r = -0.867$, $p = 0.002$), late alpha walking ($r = -0.250$ $p = 0.517$), early beta walking ($r = -0.502$, $p = 0.169$), and late beta walking ($r = -0.827$, $p = 0.006$)).

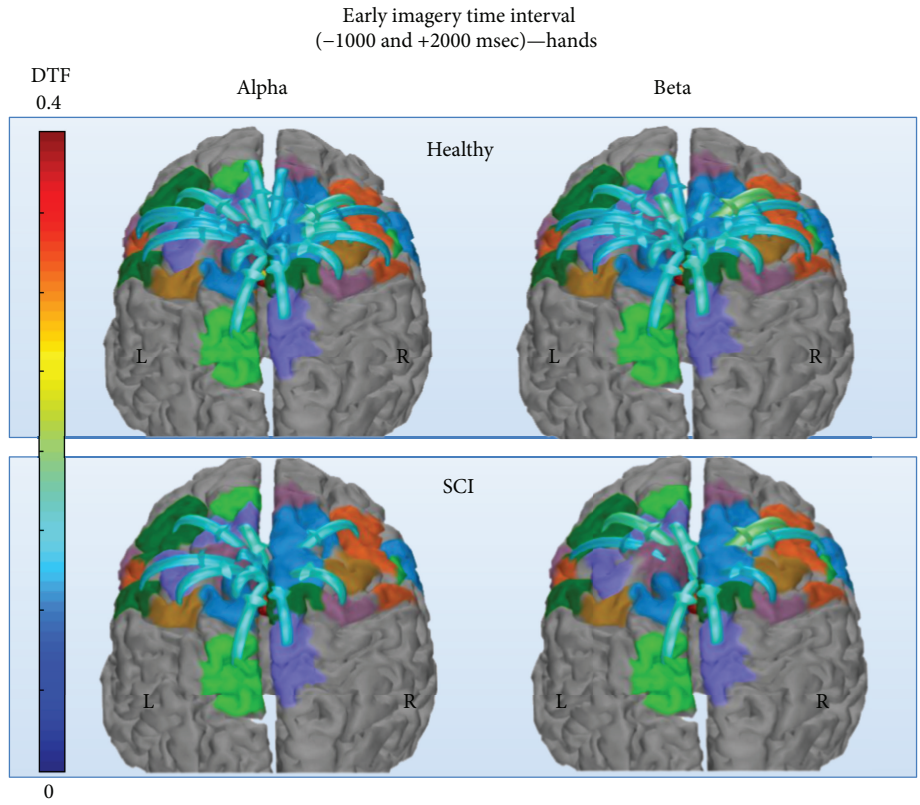

Figure 4: Average information transfer (calculated by directed transfer function) of healthy and SCI groups calculated for alpha (left) and beta (right) rhythm networks during the early imagery time interval, for the hands motor imagery category. Connections between the bilateral cingulate motor areas (CMA_R ← → CMA_L) presented the highest information transfer. Only connections with at least 25% of max information transfer among all statistically significant connections are displayed.

Table 4: Descriptive statistics of nodal incoming strengths with statistically significant differences between healthy and SCI participants and between-group comparison results.

Nodes	Median		Mean ranks		IQR: $[Q_1, Q_2]$		Healthy versus SCI
	Healthy	SCI	Healthy	SCI	Healthy	SCI	
SIF L	**0.235**	0.230	37.72	27.28	[0.231, 0.253]	[0.226, 0.238]	$U = 345.0$, $p = 0.025$
SIH L	**0.263**	0.246	44.13	20.88	[0.258, 0.270]	[0.239, 0.256]	$U = 140.0$, $p < 0.001$
SIH R	**0.256**	0.233	40.94	24.06	[0.243, 0.265]	[0.229, 0.248]	$U = 242.0$, $p < 0.001$
CMA L	0.410	**0.438**	18.84	46.16	[0.402, 0.419]	[0.431, 0.445]	$U = 75.0$, $p < 0.001$
CMA R	**0.486**	0.473	38.38	26.63	[0.475, 0.509]	[0.458, 0.489]	$U = 324.0$, $p = 0.012$
SMA L	**0.236**	0.217	41.34	23.66	[0.230, 0.243]	[0.213, 0.229]	$U = 229.0$, $p < 0.001$
SMA R	**0.305**	0.289	39.50	25.50	[0.296, 0.314]	[0.281, 0.297]	$U = 288.0$, $p = 0.003$
PMd L	**0.309**	0.272	46.84	18.16	[0.296, 0.320]	[0.260, 0.278]	$U = 53.0$, $p < 0.001$
PMd R	**0.299**	0.284	37.78	27.22	[0.290, 0.304]	[0.274, 0.299]	$U = 343.0$, $p = 0.023$
PMv L	**0.252**	0.232	40.53	24.47	[0.236, 0.259]	[0.220, 0.243]	$U = 255.0$, $p = 0.001$
PMv R	**0.262**	0.247	41.81	23.19	[0.254, 0.267]	[0.240, 0.255]	$U = 214.0$, $p < 0.001$

3.2. Network-Based Statistics between Groups and within Groups. Important differences of connectivity were found only in between groups (SCI against healthy), where a subset of connections had significantly higher FC in the healthy group than in the SCI group in the hands motor imagery category (Figure 7). This subset included connections with lower FC in the SCI group of M1H_R to bilateral primary foot motor areas (M1F), primary foot and hand sensory areas (S1H, S1F), the somatosensory association areas (SAC), and the secondary sensory areas (S2). This finding persisted in both alpha and beta networks when testing with *t*-test.

Table 5: Descriptive statistics of nodal outgoing strengths with statistically significant differences between healthy and SCI participants and between-group comparison results.

Nodes	Median		Mean ranks		IQR: $[Q_1, Q_2]$		Healthy versus SCI
	Healthy	SCI	Healthy	SCI	Healthy	SCI	
S1F L	0.073	**0.084**	21.34	43.66	[0.080, 0.095]	[0.080, 0.095]	$U = 155.000$, $p < 0.001$
S1F R	0.131	0.133	31.81	33.19	[0.123, 0.146]	[0.123, 0.146]	$U = 490.000$, $p = 0.768$
S1H L	**0.090**	0.084	38.38	26.63	[0.084, 0.100]	[0.077, 0.091]	$U = 324.000$, $p = 0.012$
S1H R	0.091	**0.166**	16.50	48.50	[0.086, 0.096]	[0.153, 0.181]	$U = 0.000$, $p < 0.001$
SAC L	0.071	**0.087**	18.28	46.72	[0.069, 0.074]	[0.084, 0.092]	$U = 57.000$, $p < 0.001$
SAC R	**0.025**	0.015	47.41	17.59	[0.023, 0.027]	[0.014, 0.016]	$U = 35.000$, $p < 0.001$
S2 L	0.010	**0.022**	17.41	47.59	[0.009, 0.012]	[0.020, 0.024]	$U = 29.000$, $p < 0.001$
S2 R	0.128	**0.148**	20.91	44.09	[0.124, 0.138]	[0.139, 0.159]	$U = 141.000$, $p < 0.001$
M1F L	**0.078**	0.073	38.13	26.88	[0.072, 0.088]	[0.069, 0.076]	$U = 332.000$, $p = 0.016$
M1F R	**0.294**	0.236	47.69	17.31	[0.286, 0.324]	[0.230, 0.263]	$U = 26.000$, $p < 0.001$
M1H L	**0.311**	0.170	47.59	17.41	[0.283, 0.339]	[0.163, 0.181]	$U = 29.000$, $p < 0.001$
M1H R	**0.061**	0.059	38.34	26.66	[0.059, 0.066]	[0.058, 0.061]	$U = 325.000$, $p = 0.012$
M1L L	**0.003**	0.003	26.25	38.75	[0.003, 0.003]	[0.003, 0.004]	$U = 312.000$, $p = 0.007$
M1L R	**0.011**	0.010	42.78	22.22	[0.010, 0.013]	[0.009, 0.010]	$U = 183.000$, $p < 0.001$
CMA L	**2.927**	2.519	47.28	17.72	[2.805, 3.008]	[2.404, 2.581]	$U = 39.000$, $p < 0.001$
CMA R	0.879	**1.156**	18.41	46.59	[0.784, 0.973]	[1.082, 1.261]	$U = 61.000$, $p < 0.001$
SMA L	**0.350**	0.276	46.25	18.75	[0.326, 0.375]	[0.267, 0.295]	$U = 72.000$, $p < 0.001$
SMA R	**0.206**	0.187	41.72	23.28	[0.191, 0.226]	[0.176, 0.194]	$U = 217.000$, $p < 0.001$
pSMA L	**0.044**	0.031	46.50	18.50	[0.040, 0.048]	[0.030, 0.035]	$U = 64.000$, $p < 0.001$
pSMA R	0.026	**0.031**	19.28	45.72	[0.024, 0.027]	[0.030, 0.033]	$U = 89.000$, $p < 0.001$
PMd L	0.149	**0.187**	21.13	43.88	[0.141, 0.167]	[0.179, 0.201]	$U = 148.000$, $p < 0.001$
PMd R	0.484	**0.577**	18.25	46.75	[0.448, 0.521]	[0.559, 0.606]	$U = 56.000$, $p < 0.001$
PMv L	0.014	**0.024**	16.50	48.50	[0.013, 0.014]	[0.022, 0.025]	$U = 0.000$, $p < 0.001$
PMv R	0.016	**0.032**	17.91	47.09	[0.014, 0.018]	[0.028, 0.035]	$U = 45.000$, $p < 0.001$

When we further tested the networks of our participants by grouping the SCI subjects by outcome (positive and negative), no differences were found between the networks of the two groups. During all permutations, the p value of the false discovery rate did not approach statistical significance ($p > 0.05$). Also, testing for other imagery categories did not reveal significant differences, with the exception of the walking category. Comparing the networks of healthy and patients during the walking imagery category, significantly greater S2_L-PMv_R connectivity was found in the SCI group.

Furthermore, when testing for main effect of within time interval and brainwave rhythm within the healthy and patient groups, no further statistical significant differences of the connectivity weights of the network were observed.

3.3. Analysis of Network Properties

3.3.1. Within-Group Comparisons of Graph Properties between Alpha and Beta Showed Less Segregation, Less Integration, Greater Density, and Less Effectiveness of Beta Networks. When exploring within-group differences of graph properties using as grouping factor the rhythm (alpha, beta), beta networks showed *less segregation*, *less integration*, and *less overall effectiveness* compared to alpha networks. CPL, CC, and SW showed significantly lower values in beta compared to alpha networks, *in both early and late time intervals*. These findings were observed during nearly all imagery categories in both SCI and healthy group.

On the opposite, beta networks showed *greater density* compared to alpha networks. D was significantly greater in beta networks in both early and late time intervals of all imagery categories in both SCI and healthy group (Figure 8). Aggregated statistical test results and p values for abovementioned findings can be found in supplementary material (available here). Specific exemptions are detailed below, as differences of graph properties in beta network compared to alpha did not reach statistical significance only in walking category, in the following cases: (a) in SCI group, CPL during the late interval, (b) in SCI group, CC and SW during the early interval, and (c) in healthy group, CC during the late interval.

3.3.2. Within-Group Comparisons of Graph Properties between Early and Late Time Intervals Showed (1) Less SCI Network Integration during Late Walking Imagery, (2)

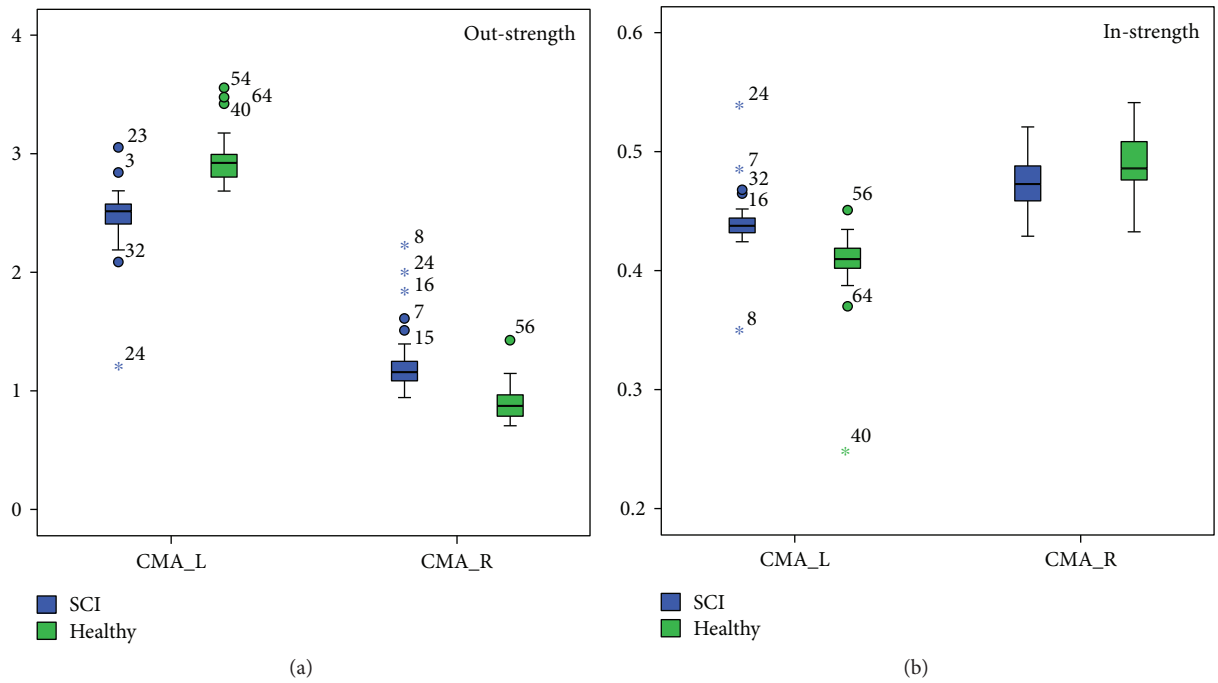

Figure 5: Nodal strengths (a: out-strength, b: in-strength) of bilateral cingulate motor areas for both subject groups. Left cingulate motor area (CMA_L) showed the highest out-strength and right cingulate motor area (CMA_R) showed the highest in-strength in the network. SCI subjects presented significantly higher CMA_R out-strength and CMA_L in-strength than healthy subjects. " ∗ " represent extreme values and "o" represent outliers.

Greater SCI Network Segregation and Stable Effectiveness for Distal Tasks during Late Imagery, and (3) Less Healthy Network Segregation and Effectiveness for Distal Tasks during Late Imagery. When exploring within-group differences of graph properties using as grouping factor the time interval (early, late), few significant differences were observed.

Regarding network integration, significant difference of CPL values was shown only SCI group's alpha networks during the *walking* task ($t = 2.743$, df = 9, and $p = 0.023$). More precisely, SCI subjects were characterized by lower path lengths at the second stage of the task (late) (early alpha walking CPL: 7.809; late alpha walking CPL: 7.032). Changes in the CPL in the beta rhythm comparing the two time intervals were not observed. Also, no significant difference was found for healthy subjects.

Regarding network segregation, significantly higher CC values in the SCI group were observed in the alpha band of *distal* imagery category ($t = -2.574$, df = 9, and $p = 0.030$; early alpha distal CC: 0.0076; late alpha distal CC: 0.0082). Considerable differences in mean CC at the beta band were not found. In healthy participants, considerably lower CC value was found only in alpha band of the *left* category ($t = 2.435$, df = 8, and $p = 0.041$; early alpha left CC: 0.0094; late alpha left CC: 0.0086).

Regarding network density, healthy group showed significantly higher D values at the late stage of *linear* imagery tasks in alpha rhythm ($t = -2.543$, df = 8, and $p = 0.035$; early alpha linear D: 0.3595; late alpha linear D: 0.3713), whereas density was considerably less at the late stage of *proximal* tasks in beta rhythm ($t = 3.038$, df = 8, and $p = 0.016$; early beta proximal D: 0.5904; late beta proximal D: 0.5784). SCI group showed greater density when comparing the two time intervals of *right* imagery category in alpha band ($t = -2.962$, df = 9, and $p = 0.016$; early alpha right D: 0.3663; late alpha right D: 0.3801), but no alterations were found in beta networks.

Regarding overall network effectiveness, significant results of SW were found for healthy subjects at *distal* imagery tasks in both alpha and beta rhythms (alpha: $t = 2.201$, df = 8, and $p = 0.059$; beta: $t = 3.044$, df = 8, and $p = 0.016$). In more detail, significantly lower values of SW were observed in distal imagery tasks between the two time intervals (early alpha distal SW: 1.553; late alpha distal SW: 1.406; early beta distal SW: 1.159; late beta distal SW: 1.137). For the SCI group, considerable differences were not observed.

3.3.3. Between-Group Comparisons of Graph Properties Showed Not Only Similar Network Integration and Density But Also Greater Segregation and Effectiveness of Alpha Band Networks in Some Imagery Categories for the Patients. When exploring between-group differences of graph properties, few significant differences were observed. Comparisons of CPL and D did not reveal any considerable difference across any imagery category (supplementary material), showing similar network integration and network density of the networks of healthy and patient subjects.

Regarding network segregation, significant changes in CC were observed at the *left* imagery tasks ($t = 2.672$, df = 17, and $p = 0.016$), at the *rotational* imagery tasks ($t = 2.104$, df = 17, and $p = 0.051$), and at *distal* imagery tasks ($U = 20.00$, $p = 0.041$), all appearing in alpha band. In more detail, SCI subjects seem to show greater CC of alpha networks in the

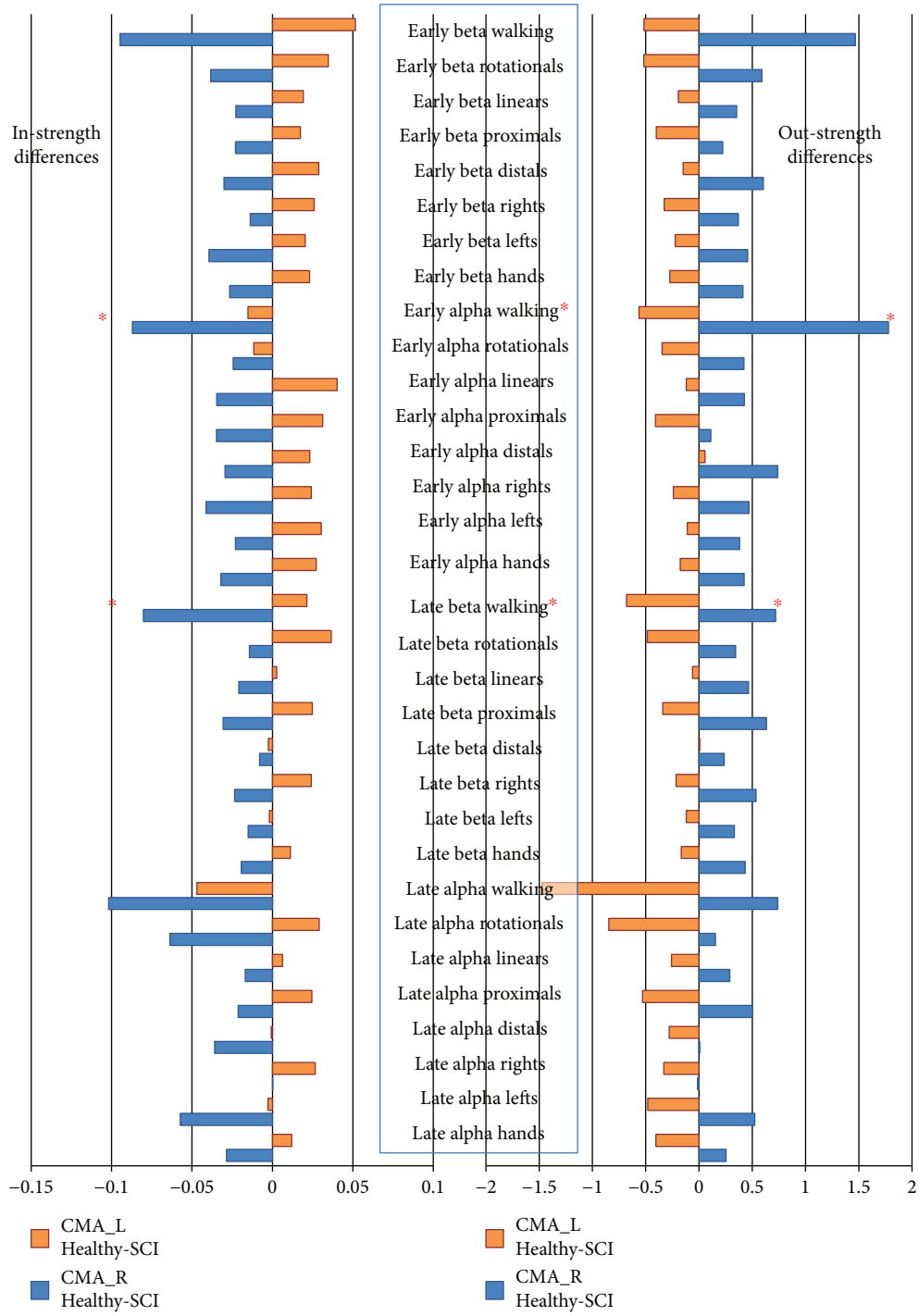

Figure 6: Differences of group averages (healthy-SCI) of in-strength (IS) and out-strength (OS) of cingulate motor areas (CMAs) during all motor imagery categories. A trend was revealed, in which OS of CMA_R was consistently higher in the healthy than the SCI group. OS of CMA_L was consistently lower in the healthy than the SCI group. The opposite held true for IS of those nodes. This trend reached statistical significance only for early alpha walking ($p = 0.002$) and late beta walking ($p = 0.006$) tasks.

late part of the aforementioned imagery tasks (alpha left dif (mean)—SCI: 0.00019, healthy: −0.00084; alpha distal dif (median)—SCI: 0.00049, healthy: −0.00075; alpha rotational dif (mean)—SCI: 0.00061, healthy: −0.0010). Significant differences were not found between groups in the beta networks of all tasks.

Regarding overall network effectiveness, the SCI group seems to have only a significant change in mean SW of alpha network while performing VMI on *distal* imagery tasks compared to healthy ($t = 2.365$, df = 17, and $p = 0.030$). More precisely, SCI group seems to show greater SW of alpha networks in the late part of the distal tasks (alpha distal dif (mean)—SCI:

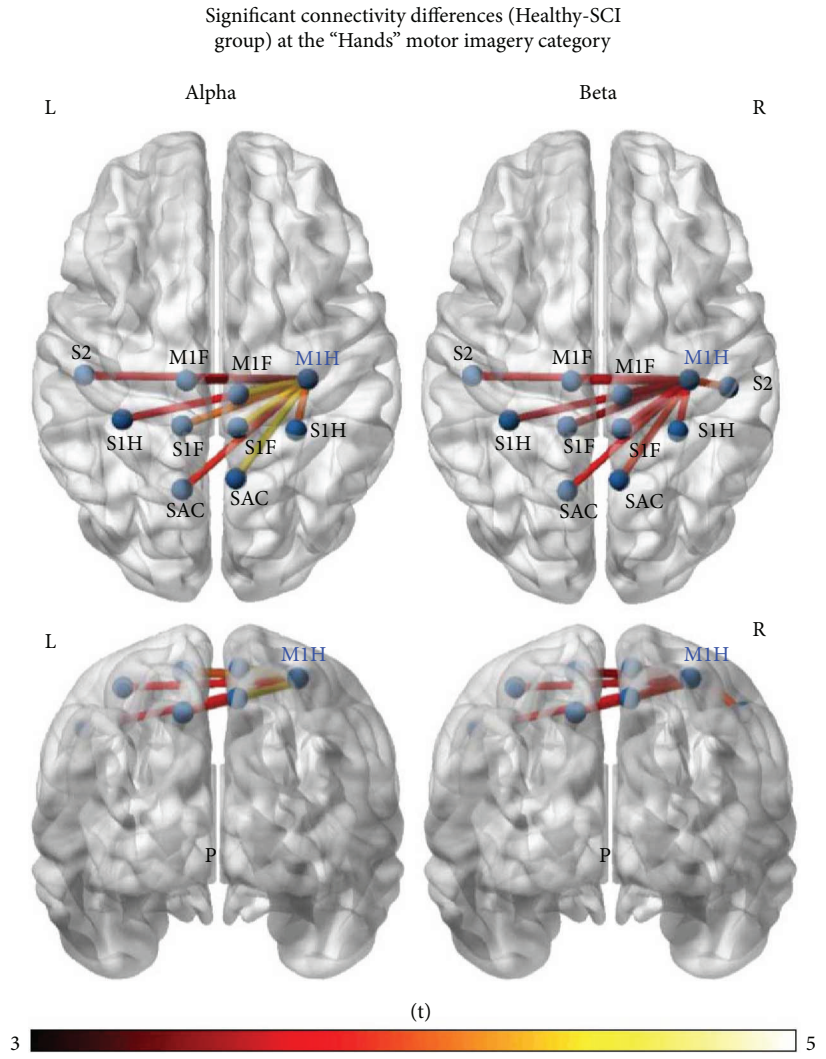

Figure 7: From the comparison of the networks of healthy and SCI subjects, a subset of network connections emerged as significantly stronger in the healthy group than in the SCI group for both the alpha and beta networks of "hands" motor imagery category, as calculated by network-based statistics—false discovery rate methodology.

0.0253, healthy: −0.1467). Other between-group differences were not observed (supplementary material).

4. Discussion

4.1. Functional Connectivity. A subset of the sensorimotor network during hands motor imagery was shown to have significantly lower functional connectivity power in the SCI group compared to the healthy group, a finding from analyses of the general linear model. This subset included connections of the M1H_R cortical area (theoretically the nondominant hand primary motor area for right-handed subjects) with other motor and sensory cortical areas. This subset also excluded the "assistive" motor nodes (CMA/SMA/pSMA/PMv/PMd). Interestingly, among these excluded nodes were also the ones that were shown to have consistently higher OS and IS, for all imagery categories, as we will discuss later on. The subset of connected nodes to M1H_R included bilateral primary foot motor areas (M1F), primary foot and hand sensory areas (S1H, S1F), the somatosensory association areas (SAC) located in superior parietal cortex (SPC), and the secondary sensory areas (S2). Small differences between alpha and beta rhythm networks can be observed, whereas most of those connections' lower FC reached statistical significance for either rhythm. These cortical areas can be identified as the point of origin of the pyramidal tract and the point of conclusion of the major somatosensory tracts. This finding could suggest that chronic disruption of reciprocal communication between the brain and spinal cord, even in noncomplete injuries, could result in permanent significant decrease of connectivity between a subset of the functional sensorimotor network at the cortical level. This effect was observed regardless of positive or negative neurological outcome since grouping SCI subjects by outcome did not reveal any differences regarding this finding. While the lack of difference between those two clinically and functionally different subgroups of patients could be affected by a lack of statistical power when comparing small samples,

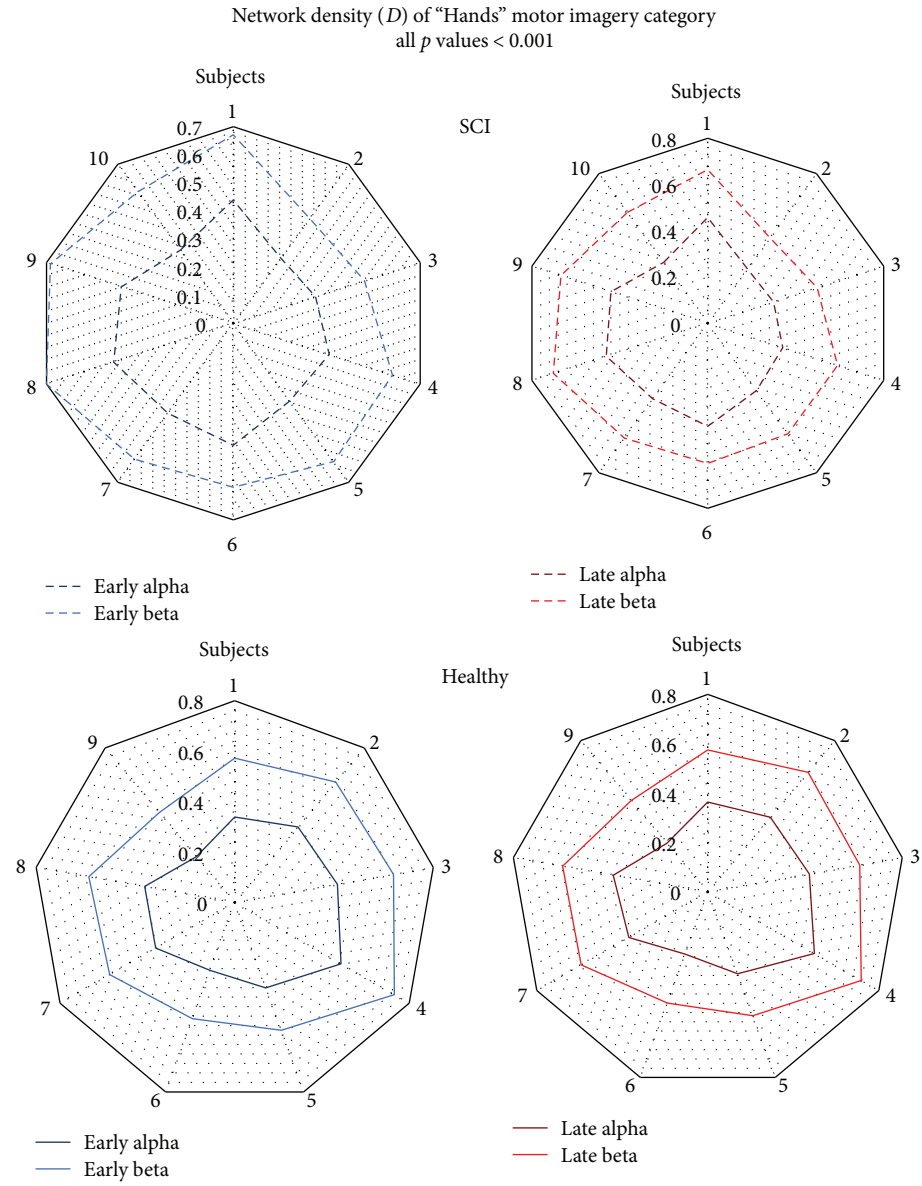

Figure 8: Network density was significantly higher in beta than alpha networks (all p values < 0.001) of the "hands" motor imagery category during both early and late time intervals for all subjects of both the SCI and the healthy group (all p values < 0.001). This finding was also consistent across every other motor imagery categories in both groups (all p values < 0.001).

a possible explanation could also be explored along the lines of mental imagery capacity. Motor execution and motor imagery do present differences in the level of neural networks that are affected by the subjects' quality and intensity of imagination [93]. In our study, the patients did not report differences in vividness of visual imagery to that of the healthy participants, as measured by the VVIQ questionnaire at the time of the experimental procedure. A degree of "though extinction process" has been reported in chronic paralysis [94], but since this is not the case in our investigation, it is possible that the lack of difference in the networks of patients with positive and negative outcomes could be due to the unaffected mental capacity of the participants.

Further significant differences between the healthy and patient groups were found with regard to nodal strengths. Almost all nodes had significantly different out-strength between the two groups. An interesting pattern can be identified. Primary motor areas, supplementary motor areas, left presupplementary motor area, and left cingulate motor area show significantly higher out-strength in the healthy group. On the contrary, premotor areas, right presupplementary motor area, and right cingulate motor area show significantly higher out-strength in the SCI group. Incoming connection strengths to primary somatosensory areas, premotor areas, supplementary motor areas, and right cingulate motor area are higher for healthy participants, while in-strength of left cingulate motor area is higher for SCI participants. Despite

the differences in strengths of those nodes, similar patterns of connectivity were found for both groups [12, 13]. The significantly reduced nodal strengths could reflect the disconnection itself and the reduced input and output of the sensorimotor pathways in spinal cord injury. Nonetheless, the higher in-strengths of left cingulate motor area and out-strengths of premotor areas and right pSMA and CMA in SCI group could indicate an attempt of the sensorimotor network to compensate for the impaired function [10, 11, 95].

CMA areas have been previously identified as important information hubs for sensorimotor networks, especially those of beta rhythm [9, 11]. In our study, this attribute is confirmed, since bilateral CMA areas consistently received the greater inflow and contributed the greater outflow in terms of connection strengths for all categories of motor imagery. Moreover, their reciprocal communication constituted the most powerful connections of every examined network. On the other hand, an important role has been identified for the SMAs [11–13] that have been shown to present notable outflow during motor imagery tasks and form clusters with the CMAs. Their role was asserted in our work previously too [44, 96], but it is not so apparent in our current study, where the SMAs were not among the top contributors in either outflow or inflow. Although not easily explained, the meaning of this finding can be explored along possible factors: (a) the random-oddball (unexpected imagery task) paradigm of presentation, (b) the MVAR model order set, and (c) the definitions of the midline network nodes themselves. The degree that each factor possibly contributed to this finding is an issue for further investigation. An example of SMAs and primary motor areas not presenting the greatest strength during hands motor imagery has also been recently reported in a study [97] where the authors used transcranial direct current stimulation to affect the connectivity of a broader definition of sensorimotor ROIs.

With regard to differentiating different upper limb motor imagery tasks, our results did not produce significant differences in terms of spatial patterns specific to certain tasks. Moreover, network-based differences between healthy and patients, although significant for the all-inclusive upper limb imagery category, did not reach statistical significance for specific categories, suggesting possibly a lack of statistical power for these categorical differences. This is not unexpected, since connectivity features, in general, have so far shown only moderate success in classification of motor imagery tasks [98, 99]. It should be also noted that some effort has been made in analyzing effective networks of compound motor imagery tasks [100]. Differentiating anatomical levels and consecutive classification should perhaps be better explored along the lines of time-varying connectivity [95, 101–103] instead of spatial pattern analysis.

Walking motor imagery, while it also did not reveal specific connectivity patterns, produced the most promising results in terms of classification, in accordance to previous studies suggesting that maximally different conditions should be explored [98]. Walking motor imagery category was the only one where the negative correlation between-group differences of the two cingulate motor area strengths reach statistical significance in half of the studied cases, those of early alpha rhythm walking networks ($p = 0.002$) and of late beta walking networks ($p = 0.006$). Moreover, the comparison of networks of healthy and patient subjects produced at least one significantly stronger connection, between the right ventral premotor area and the left secondary somatosensory area, although it is unclear whether this can be attributed to plasticity or merely to SCI-induced disconnection sequelae. To the best of the authors' knowledge, this is the first electroencephalographic study of functional cortical connectivity after incomplete spinal cord injury, and it is also the first functional cortical connectivity study examining multiple motor imagery tasks in those patients regardless of recording modality.

4.2. Analysis of Network Properties. Analysis of within-group effect of rhythm produced the most consistent results. According to the revealed pattern, alpha networks present lower integration (as measured by CPL), higher segregation (as measured by CC), while being less dense and more "effective" (as measured by SW) than beta networks. These findings are present across all motor imagery categories and they closely match findings from our previous study on the role of alpha and beta rhythms in sensorimotor networks [44, 104]. Our previous work suggested a pattern where alpha rhythm engaged local information processing using greater wiring costs [105], and that beta rhythm assumes a coordinative role during the sensorimotor process [106]. These findings were then observed on different ROI models and during simpler but far more repetitive motor imagery and motor execution tasks. They are also now replicated on a wider definition of the model of ROIs and during multiple, more complex, random motor imagery tasks. More importantly, these findings have now also been confirmed on networks of SCI patients with incomplete injury, allowing us to attempt to model the behavior of other between-group and within-group findings based on this pattern of alpha and beta organization.

Between the two groups, the fact that CPL and D were not significantly different, neither in alpha nor in beta networks, allows us to make direct comparisons of their sensorimotor network organization since they reach the same level of wiring costs and node integration. Moreover, the few between-group differences were observed mostly in alpha rhythm, which could be interpreted as differences only in local processing in the sensorimotor network of SCI patients. Increased functional segregation (CC in left, rotational and distal categories) and increased "effectiveness" of the network (SW in distal) were found for certain categories of motor imagery. More importantly, they were observed for *distal* arm imagery tasks, those that correspond to spinal cord levels below the level of injury, as the majority of the SCI subjects included in our study suffered from mid to low cervical SCI (C4–C8). As those differences were also observed during the late time interval, they can possibly be interpreted as an effect for delayed adaptation (compensation) of the sensorimotor network at the cortical level. This could possibly fall

in line with reported increased network fault tolerance [10] and an increase of local efficiency and communication between closest cortical areas [15] during paralyzed foot motor imagery that has been reported in chronic complete SCI subjects.

Regarding the walking imagery category in our study, walking networks were the only where alpha and beta rhythm differences did not reach statistical significance in certain cases. Indeed, this previously reported increase of local efficiency and close communication in complete SCI appears to also be possible in incomplete injuries as well. The walking beta networks did not show less segregation and effectiveness than the walking alpha networks of incomplete SCI subjects during the early imagery part and also did not show less integration during the late imagery part, as was the case with the upper limb imagery categories. These findings suggest the presence of a phenomenon that has been attributed to adaptive plasticity and compensation when it regards patients with complete injuries [10, 15]. Within-group effect of time interval for upper limb motor imagery categories was far more sporadic, showing greater network segregation and less network integration of the alpha rhythm network in the patient group during the late imagery in some categories. What could interestingly fall into place with the rest of the interpretation is that healthy subjects display a drop of overall network effectiveness (as depicted by SW) in both alpha and beta networks during the late imagery part. In the SCI group, such a difference was not observed, an observation that could possibly be attributed to the same delayed compensatory effect induced by the injury. Since indeed the rest of the observed effects are not consistent, our reported findings cannot be obligatory attributed to neuroplasticity effects. Therefore, it is evident that more investigation in the direction of modeling the effect of spinal cord injury on the effective connectivity of the brain during different time points and injury severity conditions is needed before drawing accurate conclusions.

4.3. Limitations and Future Work. Among limitations of our study, one investigating functional connectivity should remain wary when the analysis reveals significant differences between the groups, as those differences are usually very small and not always clear if functionally or clinically meaningful. As such, it remains difficult to identify compelling advantages of graph theory-based analysis of brain activity over other approaches to provide additional important insight into the effects of SCI on brain activity. Functional connectivity at the source level also suffers from certain disadvantages including localization error, smoothing effect, and a degree of uncertainty of the connectivity between spatially close nodes [107]. There are several factors contributing to source localization errors, induced most importantly by the forward model but also by the inverse. The resolution of the source reconstruction is determined by the source space, with 4.69 mm of average source spacing and 22.04 mm^2 average surface area per source. Nonetheless, resolution of the source space is considered sufficient for the purpose of the study, and the same model has been previously used by similar studies [9–15]. The 3-layer block element modifier forward model introduces errors through the use of a general template anatomy, modeling of skull conductivity as isotropic, not modeling cerebrospinal fluid and conductivity ratios. Moreover, it is known that EEG boasts great temporal but suffers from low spatial resolution and has been traditionally considered able to detect rapid brain dynamics in a trade-off with source estimation and low signal to noise ratio due to volume conduction effect [108, 109]. EEG in general greatly suffers from anisotropic conductivity of skull leading to signals blurring and to low EEG spatial resolution. In accordance, the localization error of deeper sources is considered greater than swallower ones. An interesting approach to address these problems would be the investigation of time-adaptive connectivity with a focus on temporal alterations of important connections rather than spatial [64], while using individual subject anatomy, an approach that we aim to explore in our future work.

5. Conclusions

We observed that chronic disruption of reciprocal communication between the brain and spinal cord, even in the context of incomplete injuries, could result in permanent significant decrease of connectivity between a subset of the functional sensorimotor network at the cortical level. This effect was observed regardless of positive or negative neurological outcome since grouping SCI subjects by outcome did not reveal any further difference. Cingulate motor areas were identified as important information hubs in different categories of motor imagery as they consistently showed the highest in-strengths (CMA_L) and out-strengths (CMA_R) in both groups of participants. While SCI subjects also followed the same pattern, they had higher outflow from left CMA and higher inflow to right CMA than healthy subjects. For both groups, alpha networks were less dense while having both longer average paths and more clustering than beta networks in almost all imagery categories. SCI patients showed signs of increased local processing in the late part of imagery, possibly an adaptive compensatory mechanism of injury-induced neuroplasticity.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki (1964) and its following amendments. The Bioethics & Ethics Committee of Faculty of Medicine, Aristotle University of Thessaloniki, approved the study.

Consent

All experiments were conducted with the subjects' understanding and written informed consent.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Supplementary Materials

Statistical analysis: methodology and results for CPL, CC. D, SW, and correlations. Figure 1: SCI group shows increase in mean global clustering coefficient compared to healthy group in late time interval of the alpha networks, during "left," "distal," and "rotational" motor imagery categories. Figure 2: SCI group shows increased small-worldness (SW) compared to healthy group in the late time interval of alpha networks for "distal" imagery category. Figure 3: between-group differences in CMA_L were negatively correlated to those in CMA_R in early alpha walking and late beta walking. Table 1: descriptive statistics of total nodal out-strengths and in-strengths of the networks of the SCI subjects. Table 2: descriptive statistics of total nodal out-strengths and in-strengths of the networks of the healthy subjects. *(Supplementary Materials)*

References

[1] K. D. Anderson, M. E. Acuff, B. G. Arp et al., "United States (US) multi-center study to assess the validity and reliability of the spinal cord independence measure (SCIM III)," *Spinal Cord*, vol. 49, no. 8, pp. 880–885, 2011.

[2] R. Nardone, Y. Höller, F. Brigo et al., "Descending motor pathways and cortical physiology after spinal cord injury assessed by transcranial magnetic stimulation: a systematic review," *Brain Research*, vol. 1619, pp. 139–154, 2015.

[3] A. Athanasiou, M. A. Klados, N. Pandria et al., "A systematic review of investigations into functional brain connectivity following spinal cord injury," *Frontiers in Human Neuroscience*, vol. 11, p. 517, 2017.

[4] R. Nardone, Y. Höller, F. Brigo et al., "Functional brain reorganization after spinal cord injury: systematic review of animal and human studies," *Brain Research*, vol. 1504, pp. 58–73, 2013.

[5] P. Freund, N. Weiskopf, J. Ashburner et al., "MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study," *The Lancet Neurology*, vol. 12, no. 9, pp. 873–881, 2013.

[6] J. Hou, Z. Xiang, R. Yan et al., "Motor recovery at 6 months after admission is related to structural and functional reorganization of the spine and brain in patients with spinal cord injury," *Human Brain Mapping*, vol. 37, no. 6, pp. 2195–2209, 2016.

[7] W. Zheng, Q. Chen, X. Chen et al., "Brain white matter impairment in patients with spinal cord injury," *Neural Plasticity*, vol. 2017, Article ID 4671607, 8 pages, 2017.

[8] T. Ilvesmäki, E. Koskinen, A. Brander, T. Luoto, J. Öhman, and H. Eskola, "Spinal cord injury induces widespread chronic changes in cerebral white matter," *Human Brain Mapping*, vol. 38, no. 7, pp. 3637–3647, 2017.

[9] L. Astolfi, H. Bakardjian, F. Cincotti et al., "Estimate of causality between independent cortical spatial patterns during movement volition in spinal cord injured patients," *Brain Topography*, vol. 19, no. 3, pp. 107–123, 2007.

[10] F. D. V. Fallani, L. Astolfi, F. Cincotti et al., "Cortical functional connectivity networks in normal and spinal cord injured patients: evaluation by graph analysis," *Human Brain Mapping*, vol. 28, no. 12, pp. 1334–1346, 2007.

[11] F. De Vico Fallani, L. Astolfi, F. Cincotti et al., "Extracting information from cortical connectivity patterns estimated from high resolution EEG recordings: a theoretical graph approach," *Brain Topography*, vol. 19, no. 3, pp. 125–136, 2007.

[12] D. Mattia, F. Cincotti, L. Astolfi et al., "Motor cortical responsiveness to attempted movements in tetraplegia: evidence from neuroelectrical imaging," *Clinical Neurophysiology*, vol. 120, no. 1, pp. 181–189, 2009.

[13] R. Sinatra, F. de Vico Fallani, L. Astolfi et al., "Cluster structure of functional networks estimated from high-resolution EEG data," *International Journal of Bifurcation and Chaos*, vol. 19, no. 2, pp. 665–676, 2009.

[14] L. Astolfi, F. Cincotti, D. Mattia et al., "Time-varying cortical connectivity estimation from noninvasive, high-resolution EEG recordings," *Journal of Psychophysiology*, vol. 24, no. 2, pp. 83–90, 2010.

[15] F. De Vico Fallani, F. A. Rodrigues, L. da Fontoura Costa et al., "Multiple pathways analysis of brain functional networks from EEG signals: an application to real data," *Brain Topography*, vol. 23, no. 4, pp. 344–354, 2011.

[16] J.-M. Hou, T.-S. Sun, Z.-M. Xiang et al., "Alterations of resting-state regional and network-level neural function after acute spinal cord injury," *Neuroscience*, vol. 277, pp. 446–454, 2014.

[17] Y.-S. Min, J. W. Park, S. U. Jin et al., "Alteration of resting-state brain sensorimotor connectivity following spinal cord injury: a resting-state functional magnetic resonance imaging study," *Journal of Neurotrauma*, vol. 32, no. 18, pp. 1422–1427, 2015.

[18] Y.-S. Min, Y. Chang, J. W. Park et al., "Change of brain functional connectivity in patients with spinal cord injury: graph theory based approach," *Annals of Rehabilitation Medicine*, vol. 39, no. 3, pp. 374–383, 2015.

[19] A. Oni-Orisan, M. Kaushal, W. Li et al., "Alterations in cortical sensorimotor connectivity following complete cervical spinal cord injury: a prospective resting-state fMRI study," *PLoS One*, vol. 11, no. 3, article e0150351, 2016.

[20] M. Kaushal, A. Oni-Orisan, G. Chen et al., "Evaluation of whole-brain resting-state functional connectivity in spinal cord injury: a large-scale network analysis using network-based statistic," *Journal of Neurotrauma*, vol. 34, no. 6, pp. 1278–1282, 2017.

[21] M. Kaushal, A. Oni-Orisan, G. Chen et al., "Large-scale network analysis of whole-brain resting-state functional connectivity in spinal cord injury: a comparative study," *Brain Connectivity*, vol. 7, no. 7, pp. 413–423, 2017.

[22] A. H. Hawasli, J. Rutlin, J. L. Roland et al., "Spinal cord injury disrupts resting-state networks in the human brain," *Journal of Neurotrauma*, vol. 35, no. 6, pp. 864–873, 2018.

[23] H. Luo, W. Dou, Y. Pan et al., "Joint analysis of multi-level functional brain networks," in *2016 9th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI)*, pp. 1521–1526, Datong, China, 2016.

[24] Y. Pan, W. Dou, Y. Wang et al., "Non-concomitant cortical structural and functional alterations in sensorimotor areas following incomplete spinal cord injury," *Neural Regeneration Research*, vol. 12, no. 12, pp. 2059–2066, 2017.

[25] S. Hétu, M. Grégoire, A. Saimpont et al., "The neural network of motor imagery: an ALE meta-analysis," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 5, pp. 930–949, 2013.

[26] M. Lotze and U. Halsband, "Motor imagery," *Journal of Physiology-Paris*, vol. 99, no. 4–6, pp. 386–395, 2006.

[27] S. Kraeutner, A. Gionfriddo, T. Bardouille, and S. Boe, "Motor imagery-based brain activity parallels that of motor execution: evidence from magnetic source imaging of cortical oscillations," *Brain Research*, vol. 1588, pp. 81–91, 2014.

[28] L. Xu, H. Zhang, M. Hui et al., "Motor execution and motor imagery: a comparison of functional connectivity patterns based on graph theory," *Neuroscience*, vol. 261, pp. 184–194, 2014.

[29] A. Guillot, C. Collet, V. A. Nguyen, F. Malouin, C. Richards, and J. Doyon, "Brain activity during visual versus kinesthetic imagery: an fMRI study," *Human Brain Mapping*, vol. 30, no. 7, pp. 2157–2172, 2009.

[30] N. Mizuguchi, M. Nakamura, and K. Kanosue, "Task-dependent engagements of the primary visual cortex during kinesthetic and visual motor imagery," *Neuroscience Letters*, vol. 636, pp. 108–112, 2017.

[31] J. Harris and A. Hebert, "Utilization of motor imagery in upper limb rehabilitation: a systematic scoping review," *Clinical Rehabilitation*, vol. 29, no. 11, pp. 1092–1107, 2015.

[32] L. Bunketorp Käll, R. J. Cooper, J. Wangdell, J. Fridén, and M. Björnsdotter, "Adaptive motor cortex plasticity following grip reconstruction in individuals with tetraplegia," *Restorative Neurology and Neuroscience*, vol. 36, no. 1, pp. 73–82, 2018.

[33] S. W. Tung, C. Guan, K. K. Ang et al., "Motor imagery BCI for upper limb stroke rehabilitation: an evaluation of the EEG recordings using coherence analysis," in *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 261–264, Osaka, Japan, 2013.

[34] A. R. C. Donati, S. Shokur, E. Morya et al., "Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients," *Scientific Reports*, vol. 6, no. 1, article 30383, 2016.

[35] V. Rajasekaran, E. López-Larraz, F. Trincado-Alonso et al., "Volition-adaptive control for gait training using wearable exoskeleton: preliminary tests with incomplete spinal cord injury individuals," *Journal of NeuroEngineering and Rehabilitation*, vol. 15, no. 1, p. 4, 2018.

[36] A. Athanasiou, I. Xygonakis, N. Pandria et al., "Towards rehabilitation robotics: off-the-shelf BCI control of anthropomorphic robotic arms," *BioMed Research International*, vol. 2017, Article ID 5708937, 17 pages, 2017.

[37] G. Arfaras, A. Athanasiou, P. Niki et al., "Visual versus kinesthetic motor imagery for BCI control of robotic arms (Mercury 2.0)," in *2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS)*, pp. 440–445, Thessaloniki, Greece, 2017.

[38] A. Athanasiou, G. Arfaras, I. Xygonakis et al., "Commercial BCI control and functional brain networks in spinal cord injury: a proof-of-concept," in *2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS)*, pp. 262–267, Thessaloniki, Greece, 2017.

[39] A. Athanasiou, G. Arfaras, N. Pandria et al., "Wireless brain-robot interface: user perception and performance assessment of spinal cord injury patients," *Wireless Communications and Mobile Computing*, vol. 2017, Article ID 2986423, 16 pages, 2017.

[40] "Brainwave control of a wearable robotic arm for rehabilitation and neurophysiological study in cervical spine injury (CSI:Brainwave)," https://clinicaltrials.gov/ct2/show/NCT02443558.

[41] D. F. Marks, "New directions in mental imagery research," *Journal of Mental Imagery*, vol. 19, no. 3-4, pp. 153–167, 1995.

[42] R. Oostenveld and P. Praamstra, "The five percent electrode system for high-resolution EEG and ERP measurements," *Clinical Neurophysiology*, vol. 112, no. 4, pp. 713–719, 2001.

[43] O. Christ and M. Reiner, "Perspectives and possible applications of the rubber hand and virtual hand illusion in non-invasive rehabilitation: technological improvements and their consequences," *Neuroscience & Biobehavioral Reviews*, vol. 44, pp. 33–44, 2014.

[44] A. Athanasiou, M. A. Klados, C. Styliadis, N. Foroglou, K. Polyzoidis, and P. D. Bamidis, "Investigating the role of alpha and beta rhythms in functional motor networks," *Neuroscience*, 2016, In press.

[45] L. Qin, L. Ding, and B. He, "Motor imagery classification by means of source analysis for brain–computer interface applications," *Journal of Neural Engineering*, vol. 1, no. 3, pp. 135–141, 2004.

[46] B. Kamousi, A. N. Amini, and B. He, "Classification of motor imagery by means of cortical current density estimation and Von Neumann entropy," *Journal of Neural Engineering*, vol. 4, no. 2, pp. 17–25, 2007.

[47] B. Kamousi, Z. Liu, and B. He, "Classification of motor imagery tasks for brain-computer interface applications by means of two equivalent dipoles analysis," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 13, no. 2, pp. 166–171, 2005.

[48] B. J. Edelman, B. Baxter, and B. He, "EEG source imaging enhances the decoding of complex right-hand motor imagery tasks," *IEEE Transactions on Biomedical Engineering*, vol. 63, no. 1, pp. 4–14, 2016.

[49] R. Oostenveld, P. Fries, E. Maris, and J.-M. Schoffelen, "FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data," *Computational Intelligence and Neuroscience*, vol. 2011, Article ID 156869, 9 pages, 2011.

[50] A. Belouchrani and A. Cichocki, "Robust whitening procedure in blind source separation context," *Electronics Letters*, vol. 36, no. 24, p. 2050, 2000.

[51] F. Perrin, J. Pernier, O. Bertrand, and J. F. Echallier, "Spherical splines for scalp potential and current density mapping," *Electroencephalography and Clinical Neurophysiology*, vol. 72, no. 2, pp. 184–187, 1989.

[52] M. Hamedi, S.-H. Salleh, and A. M. Noor, "Electroencephalographic motor imagery brain connectivity analysis for BCI: a

review," *Neural Computation*, vol. 28, no. 6, pp. 999–1041, 2016.

[53] J. Ginter Jr., K. J. Blinowska, M. Kamiński, P. J. Durka, G. Pfurtscheller, and C. Neuper, "Propagation of EEG activity in the beta and gamma band during movement imagery in humans," *Methods of Information in Medicine*, vol. 44, no. 1, pp. 106–113, 2005.

[54] P. Avanzini, M. Fabbri-Destro, R. Dalla Volta, E. Daprati, G. Rizzolatti, and G. Cantalupo, "The dynamics of sensorimotor cortical oscillations during the observation of hand movements: an EEG study," *PLoS One*, vol. 7, no. 5, article e37534, 2012.

[55] K. Sakihara and M. Inagaki, "Mu rhythm desynchronization by tongue thrust observation," *Frontiers in Human Neuroscience*, vol. 9, p. 501, 2015.

[56] R. Grech, T. Cassar, J. Muscat et al., "Review on solving the inverse problem in EEG source analysis," *Journal of NeuroEngineering and Rehabilitation*, vol. 5, no. 1, p. 25, 2008.

[57] B. He, Y. Dai, L. Astolfi, F. Babiloni, H. Yuan, and L. Yang, "*eConnectome*: a MATLAB toolbox for mapping and imaging of brain functional connectivity," *Journal of Neuroscience Methods*, vol. 195, no. 2, pp. 261–269, 2011.

[58] F. Babiloni, F. Cincotti, C. Babiloni et al., "Estimation of the cortical functional connectivity with the multimodal integration of high-resolution EEG and fMRI data by directed transfer function," *NeuroImage*, vol. 24, no. 1, pp. 118–131, 2005.

[59] A. C. Evans, D. L. Collins, S. R. Mills, E. D. Brown, R. L. Kelly, and T. M. Peters, "3D statistical neuroanatomical models from 305 MRI volumes," in *1993 IEEE Conference Record Nuclear Science Symposium and Medical Imaging Conference*, pp. 1813–1817, San Francisco, CA, USA, 1993.

[60] G. Buzsáki, C. A. Anastassiou, and C. Koch, "The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes," *Nature Reviews Neuroscience*, vol. 13, no. 6, pp. 407–420, 2012.

[61] H. Becker, L. Albera, P. Comon, R. Gribonval, F. Wendling, and I. Merlet, "Brain-source imaging: from sparse to tensor models," *IEEE Signal Processing Magazine*, vol. 32, no. 6, pp. 100–112, 2015.

[62] P. C. Hansen, T. K. Jensen, and G. Rodriguez, "An adaptive pruning algorithm for the discrete L-curve criterion," *Journal of Computational and Applied Mathematics*, vol. 198, no. 2, pp. 483–492, 2007.

[63] P. C. Hansen, "Regularization tools version 4.0 for Matlab 7.3," *Numerical Algorithms*, vol. 46, no. 2, pp. 189–194, 2007.

[64] C. Wilke, L. Ding, and B. He, "Estimation of time-varying connectivity patterns through the use of an adaptive directed transfer function," *IEEE Transactions on Biomedical Engineering*, vol. 55, no. 11, pp. 2557–2564, 2008.

[65] D. Kugiumtzis, "On the reliability of the surrogate data test for nonlinearity in the analysis of noisy time series," *International Journal of Bifurcation and Chaos*, vol. 11, no. 7, pp. 1881–1896, 2001.

[66] D. Kugiumtzis, "Surrogate data test on time series," in *Modelling and Forecasting Financial Data*, pp. 267–282, Springer, Boston, MA, USA, 2002.

[67] M. Kamiński, M. Ding, W. A. Truccolo, and S. L. Bressler, "Evaluating causal relations in neural systems: granger causality, directed transfer function and statistical assessment of significance," *Biological Cybernetics*, vol. 85, no. 2, pp. 145–157, 2001.

[68] C. W. J. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econometrica*, vol. 37, no. 3, p. 424, 1969.

[69] T. Schneider and A. Neumaier, "Algorithm 808: ARfit—a matlab package for the estimation of parameters and eigenmodes of multivariate autoregressive models," *ACM Transactions on Mathematical Software*, vol. 27, no. 1, pp. 58–65, 2001.

[70] A. Delorme, T. Mullen, C. Kothe et al., "EEGLAB, SIFT, NFT, BCILAB, and ERICA: new tools for advanced EEG processing," *Computational Intelligence and Neuroscience*, vol. 2011, Article ID 130714, 12 pages, 2011.

[71] B. H. Jansen, J. R. Bourne, and J. W. Ward, "Spectral decomposition of EEG intervals using Walsh and Fourier transforms," *IEEE Transactions on Biomedical Engineering*, vol. 28, no. 12, pp. 836–838, 1981.

[72] G. Florian and G. Pfurtscheller, "Dynamic spectral analysis of event-related EEG data," *Electroencephalography and Clinical Neurophysiology*, vol. 95, no. 5, pp. 393–396, 1995.

[73] M. Sabate, C. Llanos, E. Enriquez, B. Gonzalez, and M. Rodriguez, "Fast modulation of alpha activity during visual processing and motor control," *Neuroscience*, vol. 189, pp. 236–249, 2011.

[74] M. Rubinov and O. Sporns, "Complex network measures of brain connectivity: uses and interpretations," *NeuroImage*, vol. 52, no. 3, pp. 1059–1069, 2010.

[75] O. Sporns, "Graph theory methods for the analysis of neural connectivity patterns," in *Neuroscience Databases: a Practical Guide*, R. Kötter, Ed., pp. 171–185, Springer, Boston, MA, USA, 2003.

[76] O. Sporns and R. Kötter, "Motifs in brain networks," *PLoS Biology*, vol. 2, no. 11, article e369, 2004.

[77] R. W. Floyd, "Algorithm 97: shortest path," *Communications of the ACM*, vol. 5, no. 6, p. 345, 1962.

[78] J. Goni, M. P. van den Heuvel, A. Avena-Koenigsberger et al., "Resting-brain functional connectivity predicted by analytic measures of network communication," *Proceedings of the National Academy of Sciences*, vol. 111, no. 2, pp. 833–838, 2014.

[79] J.-P. Onnela, J. Saramäki, J. Kertész, and K. Kaski, "Intensity and coherence of motifs in weighted complex networks," *Physical Review E*, vol. 71, no. 6, article 065103, 2005.

[80] G. Fagiolo, "Clustering in complex directed networks," *Physical Review E*, vol. 76, no. 2, article 026107, 2007.

[81] D. J. Watts and S. H. Strogatz, "Collective dynamics of 'small-world' networks," *Nature*, vol. 393, no. 6684, pp. 440–442, 1998.

[82] S. Achard, R. Salvador, B. Whitcher, J. Suckling, and E. Bullmore, "A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs," *The Journal of Neuroscience*, vol. 26, no. 1, pp. 63–72, 2006.

[83] M. D. Humphries and K. Gurney, "Network 'small-worldness': a quantitative method for determining canonical network equivalence," *PLoS One*, vol. 3, no. 4, article e0002051, 2008.

[84] O. Sporns, C. J. Honey, and R. Kötter, "Identification and classification of hubs in brain networks," *PLoS One*, vol. 2, no. 10, article e1049, 2007.

[85] A. Zalesky, A. Fornito, and E. T. Bullmore, "Network-based statistic: identifying differences in brain networks," *NeuroImage*, vol. 53, no. 4, pp. 1197–1207, 2010.

[86] Y. Benjamini and Y. Hochberg, "Controlling the false discovery rate: a practical and powerful approach to multiple testing," *Journal of the Royal Statistical Society: Series B (Methodological)*, vol. 57, no. 1, pp. 289–300, 1995.

[87] M. Xia, J. Wang, and Y. He, "BrainNet Viewer: a network visualization tool for human brain connectomics," *PLoS One*, vol. 8, no. 7, article e68910, 2013.

[88] D. Cramer, *Fundamental Statistics for Social Research: Step-By-Step Calculations and Computer Techniques Using SPSS for Windows*, Routledge, New York, NY, USA, 1998.

[89] D. Cramer and D. Howitt, *The SAGE Dictionary of Statistics*, SAGE Publications Ltd, London, UK, 2004.

[90] D. P. Doane and L. E. Seward, "Measuring skewness : a forgotten statistic?," *Journal of Statistics Education*, vol. 19, no. 2, 2011.

[91] N. M. Razali, Y. B. Wah, and M. Sciences, "Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests," *Journal of Statistical Modeling and Analytics*, vol. 2, no. 1, pp. 21–33, 2011.

[92] S. S. Shapiro and M. B. Wilk, "An analysis of variance test for normality (complete samples)," *Biometrika*, vol. 52, no. 3-4, pp. 591–611, 1965.

[93] N. Kordjazi, A. Koravand, and H. Sveistrup, "Enhancing the representational similarity between execution and imagination of movement using network-based brain computer interfacing," *bioRxiv*, 2017, In press.

[94] N. Birbaumer and P. Sauseng, "Brain–computer interface in neurorehabilitation," in *Brain-Computer Interfaces*, pp. 155–169, Springer, Berlin, Heidelberg, 2009.

[95] F. De Vico Fallani, V. Latora, L. Astolfi et al., "Persistent patterns of interconnection in time-varying cortical networks estimated from high-resolution EEG recordings in humans during a simple motor act," *Journal of Physics A: Mathematical and Theoretical*, vol. 41, no. 22, article 224014, 2008.

[96] A. Athanasiou, C. Lithari, K. Kalogianni, M. A. Klados, and P. D. Bamidis, "Source detection and functional connectivity of the sensorimotor cortex during actual and imaginary limb movement: a preliminary study on the implementation of econnectome in motor imagery protocols," *Advances in Human-Computer Interaction*, vol. 2012, Article ID 127627, 10 pages, 2012.

[97] B. S. Baxter, B. J. Edelman, A. Sohrabpour, and B. He, "Anodal transcranial direct current stimulation increases bilateral directed brain connectivity during motor-imagery based brain-computer interface control," *Frontiers in Neuroscience*, vol. 11, p. 691, 2017.

[98] M. Grosse-wentrup, "Understanding brain connectivity patterns during motor imagery for brain-computer interfacing," in *Advances in Neural Information Processing Systems 21 (NIPS 2008)*, D. Koller, D. Schuurmans, Y. Bengio, and L. Bottou, Eds., pp. 561–568, Curran Associates, Inc., Red Hook, NY, USA, 2009.

[99] Y. K. Kim, E. Park, A. Lee, C.-H. Im, and Y.-H. Kim, "Changes in network connectivity during motor imagery and execution," *PLoS One*, vol. 13, no. 1, article e0190715, 2018.

[100] W. Yi, S. Qiu, K. Wang et al., "Evaluation of EEG oscillatory patterns and cognitive process during simple and compound limb motor imagery," *PLoS One*, vol. 9, no. 12, article e114853, 2014.

[101] M. Hamedi, S.-H. Salleh, S. B. Samdin, and A. M. Noor, "Motor imagery brain functional connectivity analysis via coherence," in *2015 IEEE International Conference on Signal and Image Processing Applications (ICSIPA)*, pp. 269–273, Kuala Lumpur, Malaysia, 2015.

[102] S. B. Samdin, C.-M. Ting, S.-H. Salleh, M. Hamedi, and A. B. M. Noor, "Estimating dynamic cortical connectivity from motor imagery EEG using KALMAN smoother & EM algorithm," in *2014 IEEE Workshop on Statistical Signal Processing (SSP)*, pp. 181–184, Gold Coast, VIC, Australia, 2014.

[103] B. K. Kang, J. S. Kim, S. Ryun, and C. K. Chung, "Prediction of movement intention using connectivity within motor-related network: an electrocorticography study," *PLoS One*, vol. 13, no. 1, article e0191480, 2018.

[104] A. Athanasiou, N. Foroglou, K. Polyzoidis, and P. D. Bamidis, "Graph analysis of sensorimotor cortex functional networks – comparison of alpha vs beta rhythm in motor imagery and execution," in *SAN/NIHC 2014 Meeting*, pp. 64-65, Utrecht, Netherlands, 2014.

[105] R. B. Willemse, J. C. de Munck, J. P. A. Verbunt et al., "Topographical organization of mu and beta band activity associated with hand and foot movements in patients with perirolandic lesions," *The Open Neuroimaging Journal*, vol. 4, pp. 93–99, 2010.

[106] F. De Vico Fallani, F. Pichiorri, G. Morone et al., "Multiscale topological properties of functional brain networks during motor imagery after stroke," *NeuroImage*, vol. 83, pp. 438–449, 2013.

[107] A. M. Bastos and J.-M. Schoffelen, "A tutorial review of functional connectivity analysis methods and their interpretational pitfalls," *Frontiers in Systems Neuroscience*, vol. 9, p. 175, 2016.

[108] B. He, Ed., *Modeling and Imaging of Bioelectrical Activity*, Springer, Boston, MA, USA, 2005.

[109] P. L. Nunez and R. Srinivasan, *Electric Fields of the Brain: the Neurophysics of EEG*, Oxford University Press, New York, NY, USA, 2006.

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Research Article

Change in Reciprocal Inhibition of the Forearm with Motor Imagery among Patients with Chronic Stroke

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We investigated cortically mediated changes in reciprocal inhibition (RI) following motor imagery (MI) in short- and long(er)-term periods. The goals of this study were (1) to describe RI during MI in patients with chronic stroke and (2) to examine the change in RI after MI-based brain-machine interface (BMI) training. Twenty-four chronic stroke patients participated in study 1. All patients imagined wrist extension on the affected side. RI from the extensor carpi radialis to the flexor carpi radialis (FCR) was assessed using a FCR H reflex conditioning-test paradigm. We calculated the "MI effect score on RI" (RI value during MI divided by that at rest) and compared that score according to lesion location. RI during MI showed a significant enhancement compared with RI at rest. The MI effect score on RI in the subcortical lesion group was significantly greater than that in the cortical lesion group. Eleven stroke patients participated in study 2. All patients performed BMI training for 10 days. The MI effect score on RI at a 20 ms interstimulus interval was significantly increased after BMI compared with baseline. In conclusion, mental practice with MI may induce plastic change in spinal reciprocal inhibitory circuits in patients with stroke.

1. Introduction

Motor imagery (MI) is the internal representation of an action without engaging in its actual physical execution. Neuroimaging findings indicated the activation of overlapping brain areas during MI and motor execution of the same task. [1–8]. Facilitation of the corticospinal descending volley during MI is nonetheless specific to the prime agonist muscles of the imagined task [9–12]. Reduced intracortical inhibition may cause corticospinal facilitation during MI [13, 14].

Mental practice (MP) has been popularized as a mental training intervention in which individuals imagine performing a given task. MP is a process in which an individual repeatedly mentally rehearses an action or a task (i.e., MI) without actually physically performing the action or task. MI has been used to specifically describe this mental task [15]. Several researchers have reported that MP combined with MI is a useful strategy for repetitive practice and skill learning, including for the paretic arm after stroke [16–20].

Despite its clinical promise, few studies have examined MP mechanisms. Some researchers reported that a rehabilitative program for the affected arm that incorporates MP appears to induce significant cortical reorganization as assessed with functional magnetic resonance imaging (MRI) [21, 22]. Few reports have described changes in spinal pathways after MP.

Reciprocal inhibition (RI) is a term that describes the inhibition of antagonist neuron pools immediately prior to or during activity within an agonist muscle [24, 25]. Voluntary muscle contraction is linked to proportional inhibition of its

antagonist [25, 26]. Patients with stroke show reduced or absent RI of the forearm from the extensor carpi radialis (ECR) to the flexor carpi radialis (FCR) on the affected side [27]. In the lower limb, supraspinal input from the motor cortex plays an important role in modulating RI [28–33]. The mechanisms of supraspinal modulation are thought to involve spinal Ia inhibitory interneurons that receive descending input from the motor cortex via corticospinal pathways [34].

We hypothesized that MI of wrist extension on the affected side is a potential new strategy for modulating RI of the forearm in patients with stroke. However, to the best of our knowledge, no reports have investigated changes in RI during MI or after MI training. The goals of this study were (1) to describe RI during MI in patients with chronic stroke and (2) to examine the change in RI after MP using a brain-machine interface (BMI) system. Thus, we investigated the "mechanisms," that is, cortically mediated changes in RI following MI in short- and long(er)-term periods.

2. Materials and Methods

2.1. Study 1: RI during MI in Stroke Patients

2.1.1. Participants. The experiments were carried out with 24 stroke patients (aged 22–68 years). Criteria for inclusion in the study were (1) the time since stroke onset was longer than 150 days; (2) no cognitive deficits; (3) no pain in the paretic upper extremity; (4) passive extension range of motion greater than 0 degrees of the affected wrist and −10 degrees of metacarpophalangeal joints; and (5) no severe proprioceptive deficits in the affected upper extremity.

The mean age of the study sample was 50.1 years, and the median time since stroke onset was 1099 days (range, 259 to 4467 days). Clinical details of the participants are shown in Table 1. The purpose and procedures of the study were explained to the participants, and informed consent was obtained. The study was approved by the institutional ethics review board and registered to the UMIN Clinical Trial Registry (UMIN000001986).

2.1.2. Assessment

(1) Clinical Evaluations. Stroke type (ischemic or hemorrhagic) and stroke location were confirmed with either MRI or computed tomography imaging.

The Stroke Impairment Assessment Set (SIAS) motor test and Fugl-Meyer Assessment (FMA) were used as measures of motor function in the affected upper extremity. The SIAS is a standardized measure of stroke impairment consisting of 22 subcategories [35, 36]. The paretic side motor functions of the upper extremity are tested with the knee-mouth test and the finger test. They are rated from 0 to 5, in which 0 indicates the most severe paralysis and 5 indicates no paresis. In addition, the score of 1 for the finger test is divided into three subscales: 1A (mass flexion), 1B (mass extension), and 1C (minimal individual movement). The FMA is a commonly used measure with excellent interrater reliability and construct validity [37–39]. The FMA consists of test A (shoulder/elbow/forearm: 36 points, A score), test B (wrist: 10 points, B score), test C (hand/finger: 14 points, C score), and test D (coordination: 6 points, D score).

The modified Ashworth scale (MAS) was used to assess spasticity in the affected upper extremity [40]. To determine sensory function, the SIAS sensory function was used [35, 36]. The paretic side position sense of the upper extremity was tested with the index finger or thumb movement. The score was graded in four grades from 0 to 3. When the patient detected no position change after the maximum possible passive motion of the index finger or thumb, a score of 0 was given. A score of 1 means that the patient could recognize movement of the digits but not the correct direction, even at maximal excursion. When the patient could correctly perceive the direction of a moderate excursion, the score was 2. A score of 3 means that the patient correctly identified the direction of a slight movement.

(2) H Reflex and RI. The participants were seated in a comfortable chair with their affected arms supported and relaxed on the armrests in pronation. The angle of their elbows was kept at 70–90 degrees. Percutaneous electrical pulses of 1 ms duration at a frequency of 0.3 Hz were delivered through surface electrodes. H reflexes were recorded from the FCR muscle in the paretic arm of patients with stroke following submaximal electrical stimulation of the median nerve at the antecubital fossa. The reflex responses were measured as the peak-to-peak amplitude of the H reflex recorded with a bipolar disc electrode placed over the FCR muscle [23].

RI was assessed using an FCR H reflex conditioning-test paradigm [23]. Ten conditioned and 10 test H reflexes were averaged at each time point. The test FCR H reflex amplitude was maintained at 15–20% of the maximal M wave amplitude for each block trial. Conditioning stimulation to the radial nerve was delivered at the spiral groove. Stimulus intensity of the conditioning stimulation was 1.0 motor threshold, which was defined as a 100 μV response of the ECR muscle. The conditioning test interstimulus interval (ISI) was set at two intervals of 0 and 20 ms based on previous reports [41–46]. The first phase, that is, ISI of 0 ms, is related to the Ia disynaptic pathway [23]. The second inhibitory phase, ISI of 20 ms, is thought to represent presynaptic inhibition [47]. The size of the conditioned H reflex was expressed as a percentage of the size of the unconditioned H reflex at each interval (e.g., RI 0 ms = conditioned H reflex amplitude of the ISI at 0 ms/test H reflex amplitude × 100).

In addition, participants were asked to imagine wrist extensions of their paretic wrist during assessment of RI as mentioned above. When the participant imagined wrist extensions of their paretic wrist, we checked the electromyographic activity of the ECR muscle. Thus, we assessed two patterns of RI. One was RI at rest, and the other was RI during MI. We calculated the "MI effect score on RI," which was the value of RI during MI divided by the value of RI at rest expressed as a percentage. That is, if MI led to a strong RI, the MI effect score was smaller and less than 100%.

2.1.3. Statistical Analyses. Comparison between the conditioned H reflex amplitude and test H reflex amplitude at each ISI was performed using the paired t-test. We compared RI at

Table 1: Clinical details of participants in study 1.

Age (years)	Diagnosis	Stroke location	Paretic side	TFO (days)	SIAS		MAS		
					Finger	Knee-mouth	Finger	Wrist	Elbow
65	CI	Medulla	Lt	516	1B	3	2	1+	1+
50	CI	Thalamus	Rt	584	1B	3	2	1+	1+
50	CI	MCA	Rt	4467	1C	3	1	1+	1+
43	CH	Putamen	Rt	829	1A	4	1	1	1+
39	CH	Putamen	Rt	358	1B	4	1	1	1+
63	CI	Insular cortex	Lt	863	1A	2	1+	2	1+
42	CH	Putamen	Rt	849	1A	4	2	1+	1+
49	CH	Putamen	Rt	343	1C	3	1	0	1
46	CH	Putamen	Lt	2109	1A	3	1	1	1
39	CI	MCA	Lt	687	1B	4	1	1	1
43	CI	Pons	Lt	668	1C	3	1+	2	1+
61	CI	Internal capsule	Rt	259	1B	3	1+	1	1+
33	CI	MCA	Rt	649	1A	3	1+	1+	1+
77	CH	Putamen	Rt	535	1C	3	1	0	1
46	CH	Putamen	Lt	1958	1A	3	1	1	1+
42	CH	Putamen	Lt	499	1A	3	2	2	1+
50	CI	MCA	Rt	1525	1A	3	1+	1+	1
55	CH	Thalamus	Lt	1922	1A	2	1+	0	0
37	CH	Putamen	Lt	1101	1A	2	2	1	1+
60	CH	Putamen	Rt	1146	1A	3	1	0	1
68	CI	Corona radiata	Lt	1386	1C	3	1	1+	1+
50	CH	Putamen	Rt	313	1A	2	1+	1	1+
51	CI	MCA	Lt	2160	1C	3	2	1+	2
43	CI	MCA	Lt	621	1A	2	1	1+	1

TFO: time from onset; SIAS: Stroke Impairment Assessment Set; MAS: modified Ashworth scale; CI: cervical infarction; CH: cervical hemorrhage; MCA: middle cerebral artery.

rest and during MI for each ISI group (ISI 0 ms, 20 ms) with the Wilcoxon signed-rank test and set the significance level at less than 0.05. Effect sizes were calculated using Cohen's d statistics, and the magnitude of the group difference was defined as small if $d = 0.2$, medium if $d = 0.5$, or large if $d = 0.8$, considering the clinical significance of the variables.

Patients were divided into two additional groups (cortical lesion group, subcortical lesion group) according to the stroke location. We compared the RI at rest and during MI for the two groups according to the stroke location using Welch's t-test and set the significance level at 0.05.

2.2. Study 2: The Change in RI during MI after MI Training Using the BMI in Stroke Patients with Severe Hemiparesis

2.2.1. Participants. Participants were recruited from an outpatient rehabilitation clinic of a university hospital. Patients were included in the study if they met the following criteria: (i) first unilateral subcortical stroke not involving the sensorimotor cortex as confirmed by brain MRI or computed tomography; (ii) time since stroke onset of more than 180 days; (iii) ability to raise the paretic hand to the height of the nipple; (iv) inability to extend the paretic fingers; (v) no motor improvement during the 30 days prior to starting the intervention as confirmed by both the patients and their physicians; (vi) ability to walk independently in their daily lives; (vii) no severe cognitive deficits as determined by a Mini Mental State Examination score > 25; (viii) no severe pain in the paretic upper extremity; (ix) no pacemaker or other implanted stimulator; and (x) no history of seizures within the past 2 years and no use of anticonvulsants 1 month before the intervention.

From January 2013 to March 2014, 11 patients were enrolled in the study. The study purpose and procedures were explained to the participants, and written informed consent was obtained from each.

The mean age of the study sample was 50.6 years (SD 10.9), and the median time since stroke onset was 30.5 months (range, 9 to 180 months). Clinical details of the participants are shown in Table 2.

This study was approved by the institutional ethics review board. This study was registered as a clinical trial with the University Hospital Medical Information Network in Japan (UMIN Critical Trial Registry UMIN000008468).

2.2.2. Intervention

(1) Electroencephalographic Recording. The participants wore a headset with two brush-type electrodes [48]. Electroencephalography was recorded with Ag-AgCl electrodes (1 cm

Table 2: Clinical details of participants in study 2.

Age (years)	Diagnosis	Stroke location	Paretic side	TFO (days)	SIAS		MAS		
					Finger	Knee-Mouth	Finger	Wrist	Elbow
46	CH	Putamen	Rt	1958	1A	3	1	1	1+
42	CH	Putamen	Rt	499	1A	3	2	2	1+
53	CH	Putamen	Rt	385	1A	3	2	1+	1+
50	CI	MCA	Lt	1525	1A	3	1+	1+	1
55	CH	Thalamus	Rt	1922	1A	2	1+	0	0
37	CH	Putamen	Rt	1101	1A	2	2	1	1+
47	CI	Putamen	Lt	410	1A	2	1	1+	1
60	CH	Putamen	Lt	1146	1A	3	1	0	1
65	CI	Corona radiata	Lt	695	1A	3	1	0	0
51	CH	Putamen	Lt	1522	1A	3	2	3	2
53	CI	MCA	Lt	983	1A	2	1	2	0

TFO: time from onset; SIAS: Stroke Impairment Assessment Set; MAS: modified Ashworth scale; MCA: middle cerebral artery.

in diameter), at C3 and the left ear in patients with right hemiparesis and at C4 and the right ear in patients with left hemiparesis, according to the international 10–20 system. An additional electrode was placed at a position 2.5 cm anterior to C3 or C4. A ground electrode was placed on the forehead, and the reference electrode was placed on either A1 or A2 (ipsilateral to the affected hemisphere). The experimenter monitored the electroencephalographic waveform on the computer at all times during BMI training.

(2) Event-Related Desynchronization (ERD) Quantification. As a feature to enhance the excitability of the ipsilesional sensorimotor cortex, ERD, which is a diminution of the alpha band (8–13 Hz) of the mu rhythm amplitude, was calculated as follows. ERD was used as a trigger signal for the feedback system in BMI training. ERD was expressed as the percentage of the power decrease related to the 1 s reference interval before the direction of intention. ERD at a certain frequency was calculated for each time and frequency according to the following equation:

$$\mathrm{ERD}\,(f,t) = \left\{\frac{(R(f) - A(f,t))}{R(f)}\right\} \times 100(\%), \qquad (1)$$

where $A(f,t)$ is the power spectrum density of electroencephalography at a certain frequency band f (Hz) and time t (s) since the imagery task was started, and $R(f)$ is the power spectrum at the same frequency f (Hz) of the baseline period.

(3) BMI Training. MI-based BMI training was performed for approximately 45 min a day, 5 times a week, for a total of 10 days. All participants underwent 40 min of standard occupational therapy per day, which consisted of gentle stretching exercises, active muscle reeducation exercises, and introduction to bimanual activities in their daily lives.

Because the details of the training protocol are explained elsewhere [48], a brief overview is described here. The participants were seated in a comfortable chair with their arms supported and relaxed on the armrest in pronation. The motor-driven orthosis was attached to the paretic hand to achieve finger extension movement at the metacarpophalangeal and proximal interphalangeal joints.

Participants faced a 15.4-inch computer monitor placed approximately 60 cm in front of their eyes, and pegs were set on the desk peg board next to the computer. Participants were asked to pick up a peg with the paretic hand with the orthosis.

A star-shaped cursor began to move at a fixed rate from left to right across the computer monitor over an 8 s period. Participants were instructed to rest for 5 s and then to imagine extending their paretic fingers for the next 3 s, depending on the task cue from the monitor. If the mu ERD was detected after the cue instruction of MI, the star-shaped cursor moved down on the screen as visual feedback, and then the motor-driven hand orthosis moved as the orthosis extended the paretic fingers. If the mu ERD was not detected after the cue, which meant that MI was not successfully performed, the orthosis did not move.

2.2.3. Assessment. We assessed the following items before and after BMI training: RI at rest, RI during MI, MI effect score on RI, and FMA.

2.2.4. Statistical Analyses. The Wilcoxon signed-rank test was used to compare the FMA score, RI at rest, and MI effect score on RI with a between-subject factor of time (pre- and post-BMI training). The significance level was set at 0.05.

3. Results

3.1. Study 1: RI during MI in Stroke Patients. The mean conditioned H reflex amplitude at the ISI of 0 ms was 1.06 ± 0.69 mV, which was significantly smaller than the test H reflex amplitude that was 1.49 ± 0.79 mV ($p < 0.001$). Similarly, the conditioned H reflex amplitude at the ISI of 20 ms was 1.33 ± 0.64 mV, which was significantly smaller than the test H reflex amplitude (1.43 ± 0.70 mV) ($p < 0.001$).

The Wilcoxon signed-rank test showed significant enhancement in RI during MI both at an ISI of 0 ms and 20 ms compared with RI at rest (71.20 ± 24.68 to 51.13

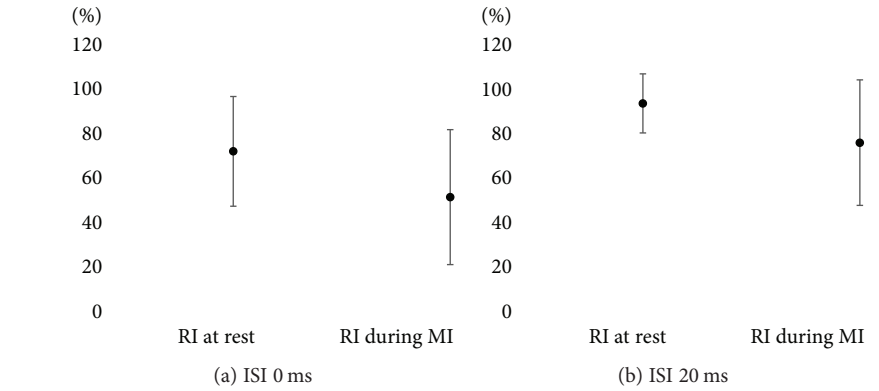

Figure 1: Comparison between reciprocal inhibition at rest and reciprocal inhibition during motor imagery. Significant changes were found in reciprocal inhibition (RI) during motor imagery (MI) at both an interstimulus interval (ISI) of 0 ms and 20 ms compared with RI at rest. Data are the mean ± standard deviation.

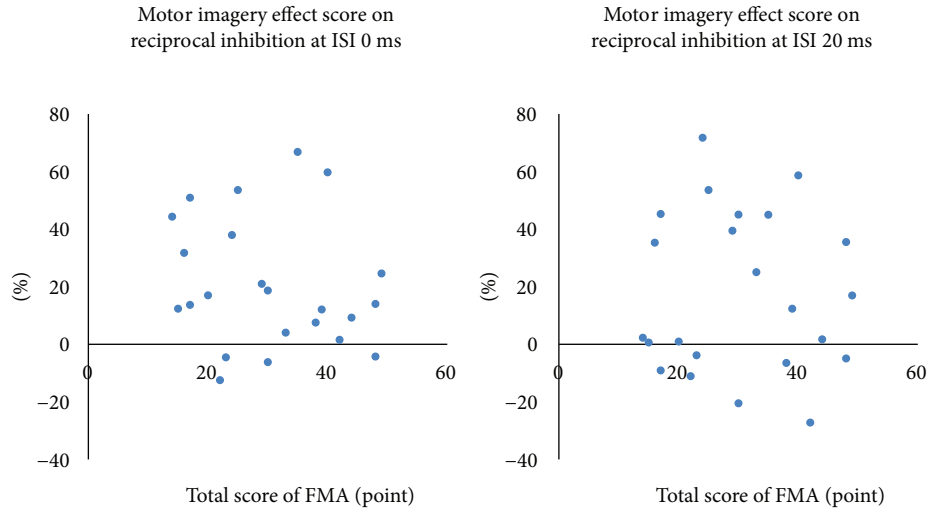

Figure 2: Correlation between the motor imagery effect score on reciprocal inhibition and motor function in the affected upper extremity. With a conditioning test interstimulus interval (ISI) of both 0 and 20 ms, no significant correlation was found between the motor imagery (MI) effect score on reciprocal inhibition (RI) or the motor function in the affected upper extremity as assessed with the Fugl-Meyer Assessment (FMA).

± 30.36 and 93.44 ± 13.28 to 75.79 ± 28.21, resp.) ($p < 0.01$) (Figure 1). Cohen's d statistics for the RI at an ISI of 0 ms and 20 ms were 0.74 and 0.80, respectively. No relationship was observed between the MI effect score on RI and FMA (Figure 2).

Regarding the stroke lesion, we observed no significant differences between the RI at rest and during MI for either ISI in the cortical lesion group. On the other hand, significant differences were observed between the RI at rest and during MI in the subcortical lesion group. In the subcortical lesion group, MI enhanced the RI for both ISIs (Table 3).

3.2. Study 2: The Change in RI during MI after MI Training Using BMI in Stroke Patients with Severe Hemiparesis. The Wilcoxon signed-rank test showed significant improvement in FMA after BMI training (21.4 ± 5.5 before versus 26.3 ± 4.9 after training, $p < 0.001$).

Table 3: Reciprocal inhibition at rest and during motor imagery in the two groups according to stroke location.

	RI at rest	RI during MI	
Cortical lesion ($N = 7$)			
ISI 0 ms	70.03 ± 31.07	62.71 ± 31.08	$p = 0.12$
ISI 20 ms	96.27 ± 8.58	95.90 ± 17.40	$p = 0.95$
Subcortical lesion ($N = 16$)			
ISI 0 ms	72.42 ± 21.24	46.07 ± 28.61	$p < 0.01$
ISI 20 ms	92.20 ± 14.70	66.99 ± 27.52	$p < 0.01$

RI: reciprocal inhibition; MI: motor imagery; ISI: interstimulus interval.

Although we found no differences in RI at rest between before and after BMI, the MI effect score on RI at an ISI of 20 ms was significantly increased after BMI

Table 4: Motor imagery effect on reciprocal inhibition after brain-machine interface training.

	Pre-BMI	After BMI	
RI at rest			
ISI 0 ms	70.06 ± 24.46	74.71 ± 31.65	$p = 0.47$
ISI 20 ms	84.64 ± 11.47	86.53 ± 16.90	$p = 0.73$
Motor imagery effect score on RI			
ISI 0 ms	92.83 ± 58.40	47.09 ± 22.16	$p = 0.08$
ISI 20 ms	83.69 ± 24.43	66.43 ± 19.65	$p = 0.04$

BMI: brain-machine interface training; RI: reciprocal inhibition; ISI: interstimulus interval.

(Table 4). MP using BMI was thought to enhance the modifying effect of MI on RI.

4. Discussion

This is the first study to show that RI of the antagonist muscle was increased during MI in patients with stroke. Moreover, this change was not found in patients whose lesion was in the cerebral cortex. In addition, we demonstrated that RI was reinforced by MI training using BMI technology. These results are helpful for understanding the effect of MI on spinal neural circuits.

A lot of electrophysiological research investigating the excitability of cortical and spinal pathways during MI has been performed. In previous research using transcranial magnetic stimulation, many researchers showed that the excitability of the corticospinal tract is increased during MI [9–12]. Therefore, MI-induced modulation is considered to occur at cortical levels. However, little is known about the effect of MI on spinal neural circuits, which has been measured with several methods (i.e., H reflex, F wave, cervicomedullary stimulation, and motor evoked potential). Cervicomedullary stimulation-evoked potentials, which provide a direct measurement of motoneuron excitability by eliciting a single volley in descending axons at the pyramidal decussation, are increased during MI [49]. Moreover, the frequency of F wave occurrence, in which F waves are produced by backfiring of alpha motor neurons, is also increased during MI [50, 51]. Thus, MI may generate a subliminal impulse that does not induce a discharge of alpha motor neurons. The result in this study indicated that not only alpha motor neurons but also interneurons at the spinal level were modulated during MI, because we observed an increase in disynaptic and presynaptic inhibition of agonist muscles during MI in patients with stroke. These modulations are similar to those seen in motor execution [52]. In previous studies, the authors thought that RI of the antagonist muscles may occur at the cortical and spinal levels when measurements were performed using indirect methods such as transcranial magnetic stimulation and H reflex during MI [53, 54]. In our study, we directly showed that RI of the antagonist muscle was increased at the spinal level using the FCR H reflex conditioning-test paradigm during MI in patients with stroke.

The amount of RI, especially presynaptic inhibition, was different depending on whether the lesion included the cerebral cortex. These results implied that patients who had brain lesions that included the cerebral cortex could not sufficiently modulate their spinal neural circuits during MI. Several hypotheses may explain this observation. The first hypothesis is that the exercise image is not performed well by patients with cortical lesions. The mechanisms of impairments in MI performance have not been clarified. MI is the internal representation of an action without any overt motor output. Therefore, its origin is an internal process at the level of the cortex. Indeed, parietal lobe damage impairs MI performance [55, 56]. In this study, most patients in the cortical lesion group had substantial damage to the parietal lobe because of cerebral infarction at the middle cerebral artery. Although we did not precisely investigate the damaged area, we speculate that patients in the cortical lesion group could not perform kinesthetic MI correctly. Therefore, the difference in the MI effect score on RI between the cortical lesion group and the subcortical lesion group may reflect the vividness of MI. This finding should be verified in a larger within-subgroup sample in a future study.

A second hypothesis is also possible. Previous studies have shown that presynaptic inhibition at the spinal level is cortically mediated [57–60]. Thus, lesions in cerebral sites may prevent cortically mediated changes in the inhibitory mechanisms that take place at the spinal level. This hypothesis is consistent with the results of our study 2. Presynaptic inhibition during MI was reinforced by MI training using BMI technology in patients with subcortical stroke in which the sensorimotor cortex was spared. Because presynaptic inhibition during the rest condition was not changed, we consider that plastic changes did not occur at lower nervous system levels that are intrinsically involved with RI. The MI-induced descending volley to the interneurons involved with presynaptic inhibition may have increased after BMI rehabilitation. In the BMI training, mu ERD was used as a biomarker of motor intention. In a previous study, Takemi et al. reported that the amount of ERD during MI is associated with corticospinal excitability and the potentiation of spinal motoneurons [14, 50]. ERD during MI is gradually increased in consecutive BMI rehabilitation sessions [61]. Thus, the MI-induced descending volley that is enhanced by the effect of BMI rehabilitation may increase presynaptic inhibition during MI. This result supports the hypothesis that presynaptic inhibition at the spinal level is cortically mediated.

Our study has some limitations. First, the small sample size is a limitation, and some variables may have shown no

significant differences between groups because of the small sample size. The unbalanced sample with regard to stroke severity is also a limitation. This study sample did not include patients who have fairly mild paresis. Third, the ability to perform MI and the quality of MI were not evaluated. In future studies, the ability to perform MI should be assessed with a questionnaire (e.g., the Kinesthetic and Visual Imagery Questionnaire). Despite these limitations, we believe that the present findings are helpful for understanding the effect of MI on spinal neural circuits and are also useful as supplementary evidence about the effectiveness of MI training in patients with stoke.

5. Conclusion

Our findings indicate that RI of the antagonist muscle was increased while imagining a contraction of the agonist muscle in patients with stroke and that RI was reinforced by MI training using BMI training.

Disclosure

The manuscript has been presented as an abstract in the following link "Society Proceedings/Clinical Neurophysiology 123 (2012)": http://www.clinph-journal.com/article/S1388-2457(12)00074-0/abstract.

Conflicts of Interest

The authors declare no competing financial interests.

Authors' Contributions

Dr. Michiyuki Kawakami and Dr. Toshiyuki Fujiwara contributed to the concept/idea/research design and project management. Dr. Michiyuki Kawakami, Mr. Kohei Okuyama, and Ms. Yoko Takahashi wrote the manuscript. Dr. Michiyuki Kawakami, Dr. Atsuko Nishimura, and Dr. Meigen Liu recruited participants and collected data. Dr. Michiyuki Kawakami, Ms. Miho Hiramoto, Dr. Atsuko Nishimura, and Dr. Toshiyuki Fujiwara performed data analysis. Dr. Michiyuki Kawakami and Dr. Meigen Liu provided facilities/equipment. Dr. Michiyuki Kawakami, Dr. Toshiyuki Fujiwara, and Dr. Meigen Liu procured funding. Dr. Michiyuki Kawakami, Mr. Kohei Okuyama, Ms. Yoko Takahashi, Ms. Miho Hiramoto, Dr. Toshiyuki Fujiwara, and Dr. Meigen Liu provided consultation (including review of the manuscript before submission).

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Supplementary Materials

Supplementary Table 1: the result of MI effect on RI in the two groups divided by the severity of position sense, spasticity, and stroke location. *(Supplementary Materials)*

References

[1] M. Jeannerod, "The hand and the object: the role of posterior parietal cortex in forming motor representations," *Canadian Journal of Physiology and Pharmacology*, vol. 72, no. 5, pp. 535–541, 1994.

[2] M. Jeannerod, "Neural simulation of action: a unifying mechanism for motor cognition," *NeuroImage*, vol. 14, no. 1, pp. S103–S109, 2001.

[3] P. S. Holmes and D. J. Collins, "The PETTLEP approach to motor imagery: a functional equivalence model for sport psychologists," *Journal of Applied Sport Psychology*, vol. 13, no. 1, pp. 60–83, 2001.

[4] M. Lotze and U. Halsband, "Motor imagery," *Journal of Physiology-Paris*, vol. 99, no. 4–6, pp. 386–395, 2006.

[5] J. Munzert and K. Zentgraf, "Motor imagery and its implications for understanding the motor system," *Progress in Brain Research*, vol. 174, pp. 219–229, 2009.

[6] J. Munzert, B. Lorey, and K. Zentgraf, "Cognitive motor processes: the role of motor imagery in the study of motor representations," *Brain Research Reviews*, vol. 60, no. 2, pp. 306–326, 2009.

[7] A. Guillot, F. Di Rienzo, T. MacIntyre, A. Moran, and C. Collet, "Imagining is not doing but involves specific motor commands: a review of experimental data related to motor inhibition," *Frontiers in Human Neuroscience*, vol. 6, p. 247, 2012.

[8] S. Hetu, M. Gregoire, A. Saimpont et al., "The neural network of motor imagery: an ALE meta-analysis," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 5, pp. 930–949, 2013.

[9] T. Kasai, S. Kawai, M. Kawanishi, and S. Yahagi, "Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery," *Brain Research*, vol. 744, no. 1, pp. 147–150, 1997.

[10] P. M. Rossini, S. Rossi, P. Pasqualetti, and F. Tecchio, "Corticospinal excitability modulation to hand muscles during movement imagery," *Cerebral Cortex*, vol. 9, no. 2, pp. 161–167, 1999.

[11] S. Facchini, W. Muellbacher, F. Battaglia, B. Boroojerdi, and M. Hallett, "Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study," *Acta Neurologica Scandinavica*, vol. 105, no. 3, pp. 146–151, 2002.

[12] C. M. Stinear and W. D. Byblow, "Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability," *Clinical Neurophysiology*, vol. 114, no. 5, pp. 909–914, 2003.

[13] C. M. Stinear, "Corticospinal facilitation during motor imagery," in *The Neurophysiological Foundations of Mental and Motor Imagery*, A. Guillot and C. Collet, Eds., Oxford University Press, New York, NY, USA, 2010.

[14] M. Takemi, Y. Masakado, M. Liu, and J. Ushiba, "Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex," *Journal of Neurophysiology*, vol. 110, no. 5, pp. 1158–1166, 2013.

[15] C. Schuster, R. Hilfiker, O. Amft et al., "Best practice for motor imagery: a systematic literature review on motor imagery training elements in five different disciplines," *BMC Medicine*, vol. 9, no. 1, p. 75, 2011.

[16] D. García Carrasco and J. Aboitiz Cantalapiedra, "Effectiveness of motor imagery or mental practice in functional recovery after stroke: a systematic review," *Neurología*, vol. 31, no. 1, pp. 43–52, 2016.

[17] A. Zimmermann-Schlatter, C. Schuster, M. A. Puhan, E. Siekierka, and J. Steurer, "Efficacy of motor imagery in post-stroke rehabilitation: a systematic review," *Journal of NeuroEngineering and Rehabilitation*, vol. 5, no. 1, p. 8, 2008.

[18] A. Y. Kho, K. P. Y. Liu, and R. C. K. Chung, "Meta-analysis on the effect of mental imagery on motor recovery of the hemiplegic upper extremity function," *Australian Occupational Therapy Journal*, vol. 61, no. 2, pp. 38–48, 2014.

[19] P. Langhorne, F. Coupar, and A. Pollock, "Motor recovery after stroke: a systematic review," *The Lancet Neurology*, vol. 8, no. 8, pp. 741–754, 2009.

[20] S. Braun, M. Kleynen, T. van Heel, N. Kruithof, D. Wade, and A. Beurskens, "The effects of mental practice in neurological rehabilitation; a systematic review and meta-analysis," *Frontiers in Human Neuroscience*, vol. 7, p. 390, 2013.

[21] S. J. Page, J. P. Szaflarski, J. C. Eliassen, H. Pan, and S. C. Cramer, "Cortical plasticity following motor skill learning during mental practice in stroke," *Neurorehabilitation and Neural Repair*, vol. 23, no. 4, pp. 382–388, 2009.

[22] H. Liu, L. Song, and T. Zhang, "Changes in brain activation in stroke patients after mental practice and physical exercise: a functional MRI study," *Neural Regeneration Research*, vol. 9, no. 15, pp. 1474–1484, 2014.

[23] B. L. Day, C. D. Marsden, J. A. Obeso, and J. C. Rothwell, "Reciprocal inhibition between the muscles of the human forearm," *Journal of Physiology*, vol. 349, no. 1, pp. 519–534, 1984.

[24] C. Aymard, L. Chia, R. Katz, C. Lafitte, and A. Pénicaud, "Reciprocal inhibition between wrist flexors and extensors in man: a new set of interneurones?," *Journal of Physiology*, vol. 487, no. 1, pp. 221–235, 1995.

[25] A. Lundberg, "The excitatory control of the Ia inhibitory pathway," in *Excitatory Synaptic Mechanisms*, P. Anderson and J. K. S. Jensen, Eds., pp. 333–340, The University Press, Oslo, Norway, 1970.

[26] I. Wargon, J. C. Lamy, M. Baret et al., "The disynaptic group I inhibition between wrist flexor and extensor muscles revisited in humans," *Experimental Brain Research*, vol. 168, no. 1-2, pp. 203–217, 2006.

[27] J. Artieda, P. Quesada, and J. A. Obeso, "Reciprocal inhibition between forearm muscles in spastic hemiplegia," *Neurology*, vol. 41, no. 2, Part 1, pp. 286–289, 1991.

[28] J. R. Wolpaw and A. M. Tennissen, "Activity-dependent spinal cord plasticity in health and disease," *Annual Review of Neuroscience*, vol. 24, no. 1, pp. 807–843, 2001.

[29] Y. Chen, X. Y. Chen, L. B. Jakeman, L. Chen, B. T. Stokes, and J. R. Wolpaw, "Operant conditioning of H-reflex can correct a locomotor abnormality after spinal cord injury in rats," *Journal of Neuroscience*, vol. 26, no. 48, pp. 12537–12543, 2006.

[30] T. Fujiwara, T. Tsuji, K. Honaga, K. Hase, J. Ushiba, and M. Liu, "Transcranial direct current stimulation modulates the spinal plasticity induced with patterned electrical stimulation," *Clinical Neurophysiology*, vol. 122, no. 9, pp. 1834–1837, 2011.

[31] T. Yamaguchi, T. Fujiwara, K. Saito et al., "The effect of active pedaling combined with electrical stimulation on spinal reciprocal inhibition," *Journal of Electromyography and Kinesiology*, vol. 23, no. 1, pp. 190–194, 2013.

[32] T. Yamaguchi, T. Fujiwara, Y. A. Tsai et al., "The effects of anodal transcranial direct current stimulation and patterned electrical stimulation on spinal inhibitory interneurons and motor function in patients with spinal cord injury," *Experimental Brain Research*, vol. 234, no. 6, pp. 1469–1478, 2016.

[33] Y. Takahashi, T. Fujiwara, T. Yamaguchi, M. Kawakami, K. Mizuno, and M. Liu, "The effects of patterned electrical stimulation combined with voluntary contraction on spinal reciprocal inhibition in healthy individuals," *Neuroreport*, vol. 28, no. 8, pp. 434–438, 2017.

[34] Y. Masakado, Y. Muraoka, Y. Tomita, and N. Chino, "The effect of transcranial magnetic stimulation on reciprocal inhibition in the human leg," *Electromyography and Clinical Neurophysiology*, vol. 41, no. 7, pp. 429–432, 2001.

[35] N. Chino, S. Sonoda, K. Domen, E. Saitoh, and A. Kimura, "Stroke Impairment Assessment Set (SIAS)," in *Functional Evaluation of Stroke Patients*, N. Chino and J. L. Melvin, Eds., pp. 19–31, Springer-Verlag, Tokyo, Japan, 1996.

[36] T. Tsuji, M. Liu, S. Sonoda, K. Domen, and N. Chino, "The stroke impairment assessment set: its internal consistency and predictive validity," *Archives of Physical Medicine and Rehabilitation*, vol. 81, no. 7, pp. 863–868, 2000.

[37] A. R. Fugl-Meyer, L. Jääskö, I. Leyman, S. Olsson, and S. Steglind, "The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance," *Scandinavian Journal of Rehabilitation Medicine*, vol. 7, no. 1, pp. 13–31, 1975.

[38] S. L. Wood-Dauphinee, J. I. Williams, and S. H. Shapiro, "Examining outcome measures in a clinical study of stroke," *Stroke*, vol. 21, no. 5, pp. 731–739, 1990.

[39] T. Platz, C. Pinkowski, F. van Wijck, I. H. Kim, P. di Bella, and G. Johnson, "Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study," *Clinical Rehabilitation*, vol. 19, no. 4, pp. 404–411, 2005.

[40] R. W. Bohannon and M. B. Smith, "Interrater reliability of a modified Ashworth scale of muscle spasticity," *Physical Therapy*, vol. 67, no. 2, pp. 206-207, 1987.

[41] G. Deuschl, C. Seifert, F. Heinen, M. Illert, and C. H. Lücking, "Reciprocal inhibition of forearm flexor muscles in spasmodic torticollis," *Journal of the Neurological Sciences*, vol. 113, no. 1, pp. 85–90, 1992.

[42] Y. -Z. Huang, I. Trender-Gerhard, M. J. Edwards, P. Mir, J. C. Rothwell, and K. P. Bhatia, "Motor system inhibition in dopa-responsive dystonia and its modulation by treatment," *Neurology*, vol. 66, no. 7, pp. 1088–1090, 2006.

[43] Y. Z. Huang, J. C. Rothwell, C. S. Lu et al., "The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord," *Clinical Neurophysiology*, vol. 120, no. 4, pp. 796–801, 2009.

[44] K. Nakashima, J. C. Rothwell, B. L. Day, P. D. Thompson, K. Shannon, and C. D. Marsden, "Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke," *Brain*, vol. 112, no. 3, pp. 681–697, 1989.

[45] C. H. Tsai, R. S. Chen, and C. S. Lu, "Reciprocal inhibition in Parkinson's disease," *Acta Neurologica Scandinavica*, vol. 95, no. 1, pp. 13–18, 1997.

[46] K. Okuyama, M. Kawakami, M. Hiramoto, K. Muraoka, T. Fujiwara, and M. Liu, "Relationship between spasticity and spinal neural circuits in patients with chronic hemiparetic stroke," *Experimental Brain Research*, vol. 236, no. 1, pp. 207–213, 2018.

[47] A. Berardelli, B. L. Day, C. D. Marsden, and J. C. Rothwell, "Evidence favouring presynaptic inhibition between antagonist muscle afferents in the human forearm," *The Journal of Physiology*, vol. 391, no. 1, pp. 71–83, 1987.

[48] A. Nishimoto, M. Kawakami, T. Fujiwara et al., "Feasibility of task-specific brain-machine interface training for upper-extremity paralysis in patients with chronic hemiparetic stroke," *Journal of Rehabilitation Medicine*, vol. 50, no. 1, pp. 52–58, 2017.

[49] S. Grosprêtre, F. Lebon, C. Papaxanthis, and A. Martin, "New evidence of corticospinal network modulation induced by motor imagery," *Journal of Neurophysiology*, vol. 115, no. 3, pp. 1279–1288, 2016.

[50] M. Takemi, Y. Masakado, M. Liu, and J. Ushiba, "Sensorimotor event-related desynchronization represents the excitability of human spinal motoneurons," *Neuroscience*, vol. 297, pp. 58–67, 2015.

[51] M. Naseri, P. Petramfar, and A. Ashraf, "Effect of motor imagery on the F-wave parameters in hemiparetic stroke survivors," *Annals of Rehabilitation Medicine*, vol. 39, no. 3, pp. 401–408, 2015.

[52] P. Cavallari, E. Fournier, R. Katz, E. Pierrot-Deseilligny, and M. Shindo, "Changes in reciprocal Ia inhibition from wrist extensors to wrist flexors during voluntary movement in man," *Experimental Brain Research*, vol. 56, no. 3, pp. 574–576, 1984.

[53] T. Ikai, T. W. Findley, S. Izumi et al., "Reciprocal inhibition in the forearm during voluntary contraction and thinking about movement," *Electroencephalography and Clinical Neurophysiology*, vol. 36, no. 5, pp. 295–304, 1996.

[54] H. D. Yang, Y. K. Minn, I. H. Son, and S. H. Suk, "Facilitation and reciprocal inhibition by imagining thumb abduction," *Journal of Clinical Neuroscience*, vol. 13, no. 2, pp. 245–248, 2006.

[55] J. Danckert, S. Ferber, T. Doherty, H. Steinmetz, D. Nicolle, and M. A. Goodale, "Selective, non-lateralized impairment of motor imagery following right parietal damage," *Neurocase*, vol. 8, no. 3, pp. 194–204, 2002.

[56] A. Sirigu, J. R. Duhamel, L. Cohen, B. Pillon, B. Dubois, and Y. Agid, "The mental representation of hand movements after parietal cortex damage," *Science*, vol. 273, no. 5281, pp. 1564–1568, 1996.

[57] H. Hultborn, S. Meunier, E. Pierrot-Deseilligny, and M. Shindo, "Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man," *The Journal of Physiology*, vol. 389, no. 1, pp. 757–772, 1987.

[58] J. F. Iles, "Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb," *The Journal of Physiology*, vol. 491, no. 1, pp. 197–207, 1996.

[59] S. Meunier and E. Pierrot-Deseilligny, "Cortical control of presynaptic inhibition of Ia afferents in humans," *Experimental Brain Research*, vol. 119, no. 4, pp. 415–426, 1998.

[60] R. Katz, S. Meunier, and E. Pierrot-Deseilligny, "Changes in presynaptic inhibition of Ia fibres in man while standing," *Brain*, vol. 111, no. 2, pp. 417–437, 1988.

[61] K. Shindo, K. Kawashima, J. Ushiba et al., "Effects of neurofeedback training with an electroencephalogram-based brain–computer interface for hand paralysis in patients with chronic stroke: a preliminary case series study," *Journal of Rehabilitation Medicine*, vol. 43, no. 10, pp. 951–957, 2011.

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Review Article

The Activation of the Mirror Neuron System during Action Observation and Action Execution with Mirror Visual Feedback in Stroke: A Systematic Review

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Objective. To evaluate the concurrent and training effects of action observation (AO) and action execution with mirror visual feedback (MVF) on the activation of the mirror neuron system (MNS) and its relationship with the activation of the motor cortex in stroke individuals. *Methods*. A literature search using CINAHL, PubMed, PsycINFO, Medline, Web of Science, and SCOPUS to find relevant studies was performed. *Results*. A total of 19 articles were included. Two functional magnetic resonance imaging (fMRI) studies reported that MVF could activate the ipsilesional primary motor cortex as well as the MNS in stroke individuals, whereas two other fMRI studies found that the MNS was not activated by MVF in stroke individuals. Two clinical trials reported that long-term action execution with MVF induced a shift of activation toward the ipsilesional hemisphere. Five fMRI studies showed that AO activated the MNS, of which, three found the activation of movement-related areas. Five electroencephalography (EEG) studies demonstrated that AO or MVF enhanced mu suppression over the sensorimotor cortex. *Conclusions*. MVF may contribute to stroke recovery by revising the interhemispheric imbalance caused by stroke due to the activation of the MNS. AO may also promote motor relearning in stroke individuals by activating the MNS and motor cortex.

1. Introduction

Stroke is one of the leading causes of adult disability. Patients commonly suffer lasting motor impairments and functional disability following a stroke [1]. A substantial number of advanced rehabilitation strategies have been applied in upper limb stroke rehabilitation, such as robot-assisted therapy [2], constraint-induced movement training (CIMT) [3], and virtual reality- (VR-) based rehabilitation [4], which are aimed at helping stroke survivors relearn motor skills through intensive training. These rehabilitation strategies have been reported to improve patients' motor functions by inducing experience-dependent neuroplasticity in their damaged hemispheres [5–7]. However, the neuroplasticity resulting from intensive-based interventions may be limited if the residual motor functions of the patients are also extremely limited. It is crucial to find an adjunct therapy, on top of limb training, to enhance the recovery of the ipsilesional motor cortex of patients with severe hemiplegia, in order to overcome the learned nonuse phenomenon in such patient populations [8].

There is evidence to support the theory that cortical areas involved in motor execution can be activated by observing actions performed by others, which is attributed to the function of the mirror neuron system (MNS). The MNS is a class of neural substrates that discharges during action observation (AO) and action execution [9, 10]. The MNS is also associated with various human functions, such as motor preparation [11], motion imitation [12, 13], language [14], and emotion recognition [15, 16]. In humans, the core MNS is understood to be located in the inferior frontal gyrus (IFG), including the ventral premotor cortex (PMv), the inferior parietal lobule (IPL), and the intraparietal sulcus (IPS) [9, 17]. An extended MNS involves additional brain regions,

such as the primary motor cortex, the primary somatosensory cortex, and the middle frontal cortex [18]. A bilaterally distributed parietofrontal network with mirror neuron (MN) properties (i.e., parietofrontal MNS) has been proposed, which serves as a neural substrate to achieve the transformation of visual information into cortical areas for motor execution (i.e., visuomotor transformation) [19].

Based on this theory, researchers believe that the motor cortex could be primed by activating the MNS, thus boosting the efficacy of standardized rehabilitation for patients after strokes [17, 20]. Subsequently, various rehabilitative strategies, aimed at facilitating the motor cortex through activating the MNS, have been applied in stroke rehabilitation, including action observation training (AOT) [21, 22] and action execution with MVF [23]. AOT usually consists of a session of AO followed by a session of imitating the observed action [22]. Some clinical trials have supported the efficacy of AO as a motor priming tool in stroke rehabilitation [24–28]. Previous neuroimaging studies have identified a bilateral AO network over the frontal, parietal, temporal, and occipital areas in the brain, which encompass the core MNS [29, 30]. Action execution with MVF, including mirror therapy (MT) [23], mirror box therapy [31], and VR-based MT [32], is already a commonly employed regimen in stroke rehabilitation. By virtue of MVF, patients receive a visual illusion showing that their hemiplegic upper limbs are moving normally when they move their nonparetic upper limbs simultaneously [23]. MVF could boost the effects of the conventional upper limb rehabilitation of stroke [33]. It has been proposed that the training-induced effects of MVF arise from the activation of the ipsilesional primary motor cortex by enriching the visual and proprioceptive inputs to the MNS [10, 19, 34], but this hypothesis has not been duly confirmed in human studies [35].

It is feasible nowadays for researchers to objectively measure the brain's activities before and after interventions using advanced functional neuroimaging and electrophysiological techniques [36]. An increasing number of studies regarding the effects of these two promising motor priming techniques (AO and MVF) on brain activation in stroke individuals have been published. However, there is a lack of focused reviews investigating the effects of AO or action execution with MVF on the activation of MNS and its subsequent effects on the activation of the motor cortex in patients who have had a stroke. We conducted this systematic review to evaluate the concurrent and training effects of AO and action execution with MVF on the activation of the MNS in stroke individuals, by reviewing available experimental studies as well as clinical trials with functional neuroimaging or electrophysiological examinations. In order to understand the role of the MNS in upper limb stroke rehabilitation, we have summarized the following information in this review: (1) MNS activation and (2) MNS activation and its relationship with the activation of the motor cortex.

2. Methods

2.1. Literature Search. A literature search for relevant studies was conducted using CINAHL (the Cumulative Index to Nursing and Allied Health Literature), PubMed, PsycINFO, Medline, SCIE (Science Citation Index Expanded), and SCOPUS. Two of the authors of this review independently identified the relevant studies. Keywords used during the search were "stroke" OR "hemiplegia"; "action observation" OR "action observation training" OR "mirror visual feedback" OR "mirror neuron" OR "mirror therapy" OR "mirror box therapy"; and "functional imaging" OR "functional magnetic resonance imaging" OR "fMRI" OR "electroencephalography" OR "EEG" OR "near-infrared spectrometry" OR "NIRS" OR "magnetoencephalography" OR "MEG" OR "positron emission tomography" OR "PET". The date of publication was limited to 10 years, from January 2007 to November 2017. The reference lists of the retrieved articles were manually searched to identify any further relevant articles.

2.2. Selection Criteria. We used the PICOS method to formulate our selection criteria. Studies that satisfied all the following criteria were considered for this review.

Population (P): studies recruiting adult patients diagnosed with having had strokes; *intervention (I)*: interventions or experimental paradigms using AO or MVF in regard to upper limb actions; *comparison (C)*: control conditions without AO or MVF or using sham AO or MVF; *outcomes (O)*: studies providing anatomical evidence of brain activation induced by AO or action execution with MVF, as represented by signal changes in PET, fMRI, or fNIRS; or using previously validated electrophysiological indices of MN activities, such as event-related desynchronization (ERD) of the mu band (i.e., mu suppression) [37] or the ERD of the beta band (i.e., beta suppression) [38]; or employing an advance analysis to explore the neural network related to AO or MVF, including but not limited to dynamic casual modelling (DCM) in regard to fMRI or a coherence analysis of EEG; and *study design (S)*: clinical trials investigating the training effects or experimental studies investigating the concurrent effects of the relevant experimental condition.

Studies were excluded if (1) they only recruited healthy subjects or patients with other primary diagnoses (e.g., Parkinson's disease); (2) they only focused on the lower limb or trunk actions; (3) the final analyzed sample size was less than five; (4) they were published as conference proceedings, dissertations, or in books; and (5) they were not published in English language.

2.3. Data Extraction. After identifying relevant studies, two authors independently extracted the following information from each article: (1) the characteristics of participants; (2) the protocol of the intervention or experiment; (3) the modalities of the functional neuroimaging or electrophysiological techniques used in the study; and (4) the main results of the studies. Any disagreement was settled by discussion with the third author.

2.4. Quality Assessment. We assessed the quality of the randomized controlled trials (RCTs) in regard to the training effects of AOT or action execution with MVF in patients who have had strokes, based on the Physiotherapy Evidence Database (PEDro) scale. Both independent reviewers evaluated

each article. The PEDro scale consists of 11 items. The first criterion, item eligibility, is not scored, as it is used as a component of external validity. The other criteria included random allocation, concealment of allocation, baseline equivalence, blinding procedure, intention to treat analysis, adequate follow-up, between-group statistical analysis, measurement of data variability, and point estimates. Any scoring discrepancies were resolved.

3. Results

3.1. Identification Process for the Selection of the Studies. The initial search yielded 332 results. After removing duplicates, a total of 191 records were screened, of which, 138 citations were excluded for the following reasons: the studies were reviews or meta-analyses ($n = 18$); the studies' protocols ($n = 6$); the studies focused on infants, children, or adolescents ($n = 4$); the studies enrolled only healthy participants or patients with neurological diseases other than strokes ($n = 58$); or the studies were irrelevant ($n = 52$). The remaining 53 articles were subjected to full-text reading, of which 34 articles were removed for the following reasons: the studies did not use functional neuroimaging or electrophysiological techniques for stroke participants ($n = 17$); the final analyzed sample sizes of the studies were less than five ($n = 8$); studies of motion observation with a brain-computer interface ($n = 2$); the visual feedback was based on the lower limbs or trunk actions, rather than upper limb actions ($n = 4$) [39–42]; or the studies used EEG spectrum analysis alone ($n = 1$) [43]. One study focused on the functional neuroplasticity induced by observing the skills of tool use, which was hard to compare with other protocols of AO. Another study enrolled both patients who have had strokes and brain tumors, and the data of stroke participants could not be separated; these studies were hence excluded [16, 44]. Finally, 19 articles satisfied our inclusion criteria and were included in the present review [13, 22, 28, 34, 45–59]. Figure 1 shows the identification process for the selection of studies.

3.2. Clinical Trials regarding the Training Effects of Long-Term Intervention. Among the included studies, six studies focused on the training effects of long-term therapeutic programs [22, 28, 45, 46, 52, 59]. Four of these were RCTs [22, 28, 45, 52], and the other two were interventional studies with pre-post comparisons [46, 59]. Three studies investigated the training effects of bimanual training with MVF (four- to eight-week interventions) [45, 46, 52]. Of these, two identified a shift of activation toward the ipsilesional hemisphere [46, 52], evidenced by fMRI. Cortical areas activated by MVF mainly included the primary motor cortex [46, 52] and the premotor cortex (PMC) [46]. A study with EEG reported that mu suppression over sensorimotor cortex (SMC) was higher in the group with MVF [45]. Sun et al., who also used mu suppression as an index, reported additional benefits of AO on the basis of motor imagery (MI) in regard to enhancing mu suppression over the ipsilesional SMC, compared with the control group (MI alone) [28]. A fNIRS study measured the difference in brain activity of participants before and after four weeks of MT in addition to conventional rehabilitation; however, the difference in the activation pattern over the primary motor cortex and the precuneus was insignificant over time [59].

An RCT investigating the training effects of AO found that the four-week AOT (AO followed by imitation) induced more evident activation over bilateral PMv, bilateral superior temporal gyrus (STG), supplementary motor area (SMA) over the contralesional hemisphere, and supramarginal gyrus (SMG) over the ipsilesional hemisphere, relative to the control group watching nonbiological videos followed by action execution [22]. Characteristics of these studies are summarized in Table 1.

3.3. Experimental Studies with fMRI Findings. Eight articles explored the concurrent effects of AO or action execution with MVF on brain activation, evidenced by fMRI [34, 47, 48, 50, 53, 55–57]. In studies regarding MVF, Michielsen et al. found that bimanual movement with MVF led to significant activation of the precuneus and the posterior cingulate cortex (PCC), rather than the MNS [53]. However, Saleh et al. [34, 55] reported that the ipsilesional primary motor cortex was activated by MVF, and connectivity between the ipsilesional primary somatosensory cortex and the primary motor cortex was stronger, relative to the control group without MVF [55]. The source of the ipsilesional primary motor cortex activation was further found by the DCM to be the contralesional intraparietal sulcus (IPS) [34]. Wang et al. reported that lateralized activation toward the affected hemisphere was in favor of virtual MVF, as reflected by the peak T value of the precuneus in the majority of their samples [57].

For studies concerning AO, Szameitat et al. found that AO of wrist movement activated the PMC and IPL; however, the pattern of neural activation in action execution more resembled MI, rather than AO [56]. Garrison et al. reported that left IFG, SMG, and bilateral precentral gyrus were activated during right-hand (paretic side) observation of reach and grasp actions. Lateralized activation toward the ipsilesional hemisphere was also noted [50]. During left-hand AO (nonparetic side), the bilateral activation was relatively symmetrical in stroke individuals. Brunner et al. [47] devised a protocol to observe bimanual action; they reported that stroke individuals (within one-to-two weeks after the stroke) showed activation in inferior and superior parietal lobes, IFG, and the primary motor cortex during AO. In the second fMRI exam (three months after the stroke), the neural response to AO was extended to more movement-related areas, including the PMC, primary motor cortex, and the SMA. The neural response to AO was increased from one or two weeks to three months after the individual suffered a stroke. Dettmers et al. compared the brain activities during AO and MI of patients with left or right subcortical strokes and reported that patients with left subcortical strokes presented higher levels of activity than those with right subcortical strokes [48]. The brain activation induced by AO or MVF shown by fMRI are summarized in Table 2.

3.4. Experimental Studies with EEG or MEG. Four experiments measured the concurrent effects of AO on mu rhythm

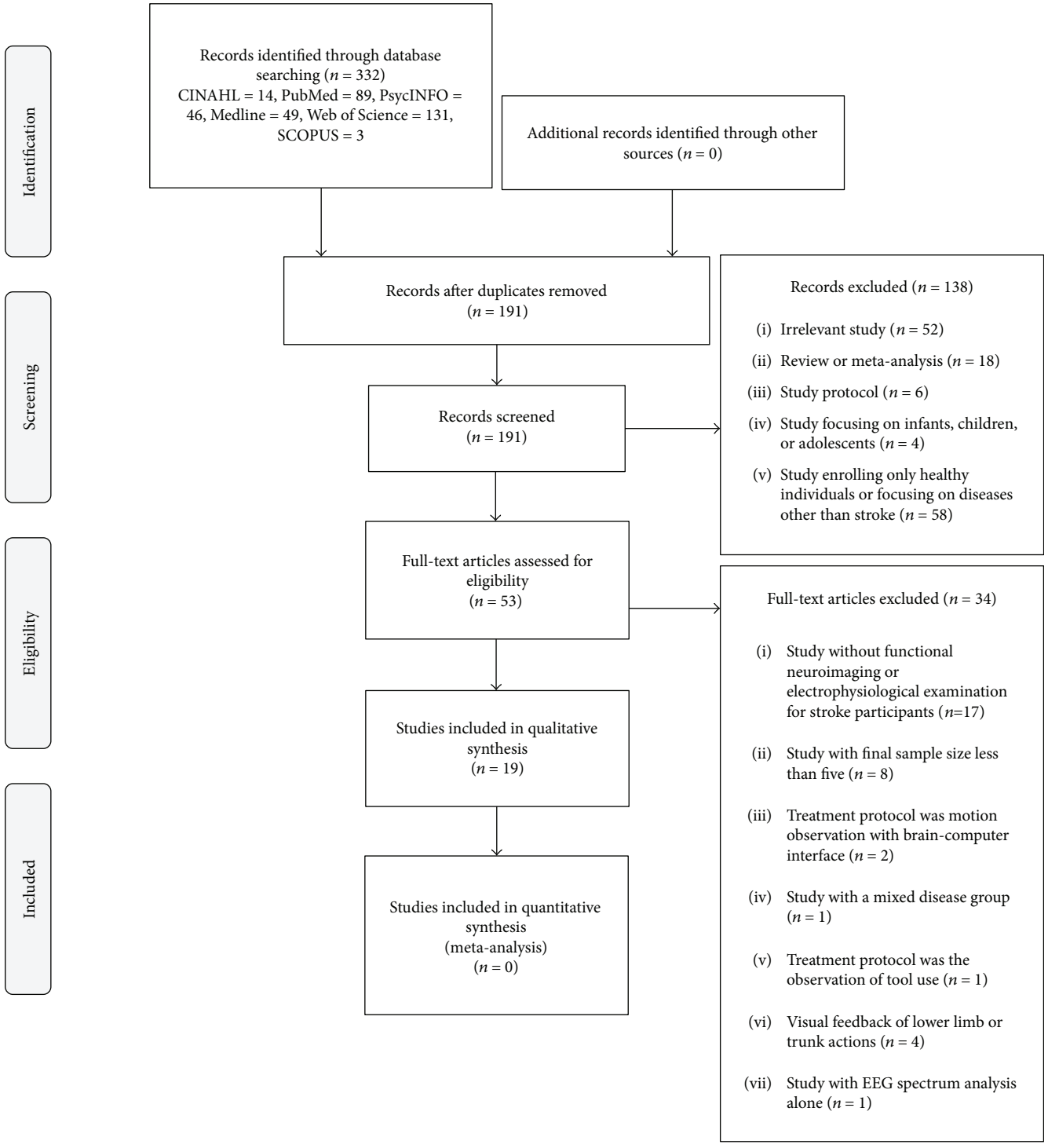

Figure 1: Flowchart of literature search.

using EEG [13, 49, 51, 58]. Another study used MEG to measure the difference in beta suppression during bimanual movement with and without MVF [54]. Kuk et al. reported the whole brain topography based on mu rhythm before and after AO and found that the middle frontal gyrus (MFG) was less active after a total of five sessions of AO [51]. Frenkel-Toledo et al. reported that observations of the reach-and-grasp hand action could induce mu suppression over the SMC, but the magnitude of mu suppression was significantly lower in the affected hemisphere, relative to the unaffected hemisphere. Mu suppression over the unaffected side was attenuated in patients with lesions over the right IPL [13, 49]. Tani et al. also showed that AO of the open-and-close action by the paretic hand induced stronger

Table 1: Characteristics of studies regarding the effects of long-term training on brain activation in stroke patients.

Study	Characteristics of stroke participants	Severity of hemiplegia	Intervention protocol	Intervention protocol	Imaging modality	Main results	
						Neuroimaging findings	Behavioral improvements
Ertelt et al. [22]	15 chronic stroke patients (>six months after stroke), aged 38–69.	Moderate arm paralysis (FAT: 0 to 5; WMFT (time): 2.41 to 41.29 seconds).	EG ($n = 7$): AOT (videos of upper limb actions followed by practice of observed actions, using the paretic upper limb); CG ($n = 8$): control (nonbiological videos followed by practice of the same actions, using the paretic upper limb).	Four-week intervention (90 minutes/session, 18 sessions in total).	fMRI (EG = 7 and CG = 6).	More evident activation of PMv, SMA, insula, and STG over the nonaffected hemisphere and PMv, SMG, and STG over the affected hemisphere in EG than CG.	FAT posttreatment (EG > CG) WMFT-posttreatment (–) SIS-posttreatment (EG > CG). No significant difference between posttreatment and follow-up in three assessments.
Michielsen et al. [52]	40 chronic stroke patients (>one year after stroke), aged 55.3 ± 12.0 (MT)/58.7 ± 13.5 (CG).	Brunnstrom stage for the upper extremity III-V.	MT ($n = 20$): bimanual exercise with MVF of the unaffected hand; CG ($n = 20$): bimanual exercise with direct view of both hands.	Six-week intervention (one hour/session, five sessions/week).	fMRI (MT = 9 and CG = 7).	A shift of activation toward the M1 over the affected hemisphere in MT.	FMA posttreatment (MT > CG); FMA 6-month follow-up (–) Jamar handheld dynamometer (–) Tardieu scale (–) ARAT (–) Stroke-ULAM (–) EQ-5D (–).
Bhasin et al. [46]	20 stroke patients (three 14 months after stroke), aged 45.45 ± 6.6.	Brunnstrom stage of the hand II-IV.	Bilateral hand exercise with virtual MVF of the nonparetic hand.	Eight-week intervention (five days/week, 60–90 minutes/session).	fMRI.	LI of BA 4 and BA 6 was increased at eight weeks.	FM scale (posttreatment and 24-week follow-up > pretreatment) MBI (posttreatment and 24-week follow-up > pretreatment) MRC grade scale (–) Brunnstrom stage (–).
Bae et al. [45]	20 stroke patients (<six months after stroke), aged 55.2 ± 8.5 (MT)/52.6 ± 11.2 (CG).	Brunnstrom stage of the hand II–IV.	MT ($n = 10$): bilateral upper limb exercise with MVF; CG ($n = 10$): paretic arm exercise only.	Four-week intervention (30 minutes/session, five times/week).	EEG.	Mu suppression at C3, Cz, and C4 was higher in MT than CG.	MFT posttreatment (MT > CG).
Sun et al. [28]	10 stroke patients (<two months after stroke), aged 59.4 ± 4.94.	Severe arm paralysis (FMA: 10 to 25).	On top of the CR, patients received the training: EG ($n = 5$): AO (paretic upper limb actions) with MI; CG ($n = 5$): MI alone.	Four-week intervention.	EEG.	AO with MI increased to higher mu suppression over C3 than MI at week 2, 3 and 4.	FMA week 2, 3 and 4; (EG > CG) PST week 3 and 4 (EG > CG).

Table 1: Continued.

Study	Characteristics of stroke participants	Severity of hemiplegia	Intervention protocol	Intervention protocol	Imaging modality	Main results	
						Neuroimaging findings	Behavioral improvements
Brunetti et al. [59]	11 stroke patients (15–92 days after stroke), aged 49–74.	Severe hand paralysis (a wrist extension of less than 20 degrees and metacarpophalangeal joint extension of less than 10 degrees).	On top of the CR, patients performed a bilateral exercise with MVF of nonparetic side.	Four-week intervention (30 minutes/session, five sessions/week).	fNIRS.	The activation pattern of M1 and precuneus was stable over time.	Six of eleven patients showed improvement (gain scores from one to eight) in FMA-finger.

FAT: Frenchay arm test; WMFT: Wolf motor function test; EG: experimental group; CG: control group; AOT: action observation training; fMRI: functional magnetic resonance image; PMv: ventral premotor cortex; SMA: supplementary motor area; STG: superior temporal gyrus; SMG: supramarginal gyrus; SIS: stroke impact scale; MVF: mirror visual feedback; MT: mirror therapy; M1: primary motor cortex; FMA: Fugl-Meyer assessment; ARAT: action research arm test; Stroke-ULAM: stroke upper limb activity monitor; EQ-5D: EuroQOL five-dimension questionnaire; LI: laterality index; BA: Broadman area; MBI: modified Barthel index; MRC: Medical Research Council; EEG: electroencephalography; BA: Broadman area; MFT: manual function test; PT: physical training; CR: conventional rehabilitation; AO: action observation; MI: motor imagery; ERD: event-related desynchronization; PST: pinch strength test; fNIRS: functional near-infrared spectroscopy.

Table 2: Brain activation or lateralization of brain activation measured by fMRI.

Brain areas	Concurrent effect of MVF versus the control without MVF during a motor task	Long-term rehabilitation with MVF versus the control without MVF	Concurrent effect of AO versus the control	Long-term rehabilitation with AO versus the control without AO
Frontal lobes				
Primary motor cortex	Ipsilesional activation [34, 55]	Ipsilesional lateralization [46, 52]	Bilateral activation [47]; ipsilesional lateralization [50]	
Premotor cortex		Ipsilesional lateralization [46]	Bilateral activation [47]; ipsilesional activation [56]	Bilateral activation [22]
Supplementary motor area			Bilateral activation [47]	Contralesional activation [22]
Superior frontal gyrus			Ipsilesional activation [48]	
Inferior frontal gyrus			Bilateral activation [47]; ipsilesional lateralization [48, 50]	
Prefrontal gyrus			Ipsilesional activation [48]	
Parietal lobes				
Primary somatosensory cortex	Bilateral activation [34, 55]			
Superior parietal gyrus			Bilateral activation [47]; ipsilesional activation [48]	
Precuneus	Bilateral activation [34, 53, 55]; ipsilesional lateralization [57]			
Inferior parietal gyrus			Ipsilesional activation [56]; bilateral activation [47]	
Supramarginal gyrus	Contralesional activation [34, 55]		Ipsilesional lateralization [50]	Ipsilesional activation [22]
Intraparietal sulcus	Contralesional activation [34, 55]			
Posterior cingular cortex	Contralesional activation [53]			
Temporal lobes				
Superior temporal gyrus				Bilateral activation [22]
Inferior temporal gyrus			Bilateral activation [47]	
Occipital lobes				
Occipital gyrus			Bilateral activation [47]	

Notes: MVF: mirror visual feedback; AO: action observation. Garrison et al. [50]: results of AO of the paretic hand movement were used; Bhasin et al [46]: the result of within-group difference was used, because the study did not have a control group.

mu suppression than the MI of the same action in stroke individuals [58]. Interhemispheric imbalance of movement-related beta suppression was noted in stroke participants in the study by Rossiter et al. when performing the bimanual open-and-close action. The initial asymmetricity was partially attenuated by MVF [54]. Characteristics of the experimental studies are summarized in Table 3, and brain activation induced by AO or MVF, measured by fMRI, is summarized in Table 2.

3.5. Methodological Quality of Included Randomized Controlled Trials. Four RCTs were included in this review [22, 28, 45, 52]. The results of the assessment of methodological quality are summarized in Table 4.

4. Discussion

The present study is aimed at systematically evaluating the evidence of MNS activation induced by AO or MVF and its potential effects on the activation of the motor cortex in patients who have had strokes. The main findings of the present review are (1) the ipsilesional primary motor cortex can be facilitated by MVF [46, 52], which may be achieved by recruiting the MNS [34, 55]; (2) long-term action execution

Table 3: Characteristics of studies regarding the concurrent effects of single-session or multiple-session experiments on brain activation in stroke patients.

Study	Characteristics of stroke participants	Severity of hemiplegia	Experiment conditions	Imaging modality	Main results
Garrison et al. [50]	12 chronic stroke patients (two to 17 years after stroke), aged 39 to 85.	Moderate to severe arm paresis (FMA-UE: 13 to 48).	AO (reach to grasp objects by the right or left hand) and fixation.	fMRI.	Right-hand (paretic side) AO resulted in lateralization toward the left hemisphere, including IFG pars opercularis, IFG pars triangularis, SMG, and precentral gyrus.
Michielsen et al. [53]	18 chronic stroke patients (>one year after stroke), aged 54.7 ± 9.9.	Brunnstrom stage for the upper extremity III-V.	Unimanual exercise (open-and-close action by the unaffected hand) with MVF; unimanual exercise without MVF; bimanual exercise (bilateral open-and-close actions) with MVF; bimanual exercise without MVF.	fMRI.	Bimanual exercise with MVF significantly increased the activity in precuneus and PCC, more than other conditions.
Szameitat et al. [56]	Five chronic right-hemispheric stroke patients (>one year after stroke), aged 57 to 67.	Unclear.	Action execution (left wrist flexion and extension), MI (MI of the same wrist movement), AO (watching a video showing the same action), passive movement and baseline.	fMRI.	AO activated right lateral medial anterior PMC and a small focus of right IPL than baseline result.
Wang et al. [57]	Five stroke patients (29 to 93 days after stroke), aged 53 to 72.	Severe arm paresis (a wrist extension ability of less than 20 degrees and metacarpophalangeal joint extension ability of less than 10 degrees).	Unilateral index finger-thumb opposition (by nonparetic hands) with virtual normal visual feedback or virtual MVF.	fMRI.	Four out of five patients displayed the lateralized activation toward the affected hemisphere (reflected by peak T values within the precuneus), evoked by virtual MVF.
Brunner et al. [47]	18 stroke patients, aged 41 to 79; first scan: 8.9 ± 4.1 days after stroke; second scan: 89.3 ± 8.3 days after stroke.	NHPT < 0.5 (pegs per second).	AO (a video of bimanual twisting of a cylindrical device) and its resting condition (a still image of the device being held); action execution (bimanual twisting of a cylindrical device) and its resting condition (hold the device without twisting).	fMRI.	AO (first scan): involvement of the occipital and temporal visual areas bilaterally with activation maxima in the MTG and ITG and occipital lobe. Patients also showed activation in the parietal and frontal areas and the IPL, SPL, IFG, and M1 were involved; AO (second scan): most activated clusters were observed in ITG and the ventral anterior of the thalamus, also in premotor areas, SMA and M1.
Dettmers et al. [48]	18 subcortical stroke patients (nine left stroke patients, aged 59.2 ± 7.1, 28.2 ± 40.9 months after stroke and nine right stroke patients aged 63 ± 10.3, 47.1 ± 89.5 months after stroke).	With the ability to grip a small object and release it by the paretic hand.	AO (static pictures) of object-related hand action by the paretic side, AO (movies) of object-related hand action by the paretic side, AO (same movies) with imagery (performing the shown action) and fixation.	fMRI.	AO (movies) elicited activation in visual cortex, SPL, prefrontal cortex, and superior and inferior frontal cortexes in both patient groups. AO (movies) with imagery revealed a very similar network as during AO (movies) alone.
Saleh et al. [55]	15 chronic stroke patients (>six months after stroke), aged 54 ± 12.	CMA: four to seven; CMH: three to seven.	Nonparetic hand action (finger flexion) with veridical feedback or MVF and the control (nonanthropomorphic objects).	fMRI (14 data).	MVF induced significant activation of the ipsilesional postcentral gyrus, M1, precuneus, contralesional postcentral gyrus, superior bank of the intraparietal

Table 3: Continued.

Study	Characteristics of stroke participants	Severity of hemiplegia	Experiment conditions	Imaging modality	Main results
					sulcus and precuneus, and SMG. Connectivity between BA 1 and M1 and between BA 1 and S1 was significantly stronger after MVF.
Saleh et al. [34]	15 chronic stroke patients (>six months after stroke), aged 54 ± 12.	CMA: four to seven; CMH: three to seven.	Nonparetic hand action (finger flexion) with veridical feedback or MVF and the control (nonanthropomorphic objects).	fMRI (12 data).	MVF-induced activation of the ipsilesional primary motor cortex arose from the contralesional parietal cortex, in a region along the IPS.
Frenkel-Toledo et al. [49]	33 stroke patients aged 24 to 76, 23 to 132 days after stroke.	FMA zero to 66.	AO (reach and grasp action by left or right hands), observation of nonbiological videos and the eye close condition.	EEG.	AO induced mu suppression over SMC rather than observation of nonbiological videos; mu suppression was significantly diminished in the ipsilesional SMC (C3 or C4), compared with the contralesional SMC (C3 or C4); right IPL damage lowered mu suppression over the unaffected hemisphere.
Rossiter et al. [54]	10 stroke patients aged 56 ± 12, one to 114 months after stroke.	ARAT zero to 57.	Bilateral open-and-close hand action with MVF of nonparetic hand and bilateral open-and-close hand movement while viewing the paretic hand.	MEG.	Movement-related beta desynchronization was greater in contralesional compared to ipsilesional hemisphere. The asymmetry in movement-related beta desynchronization was more symmetrical in the condition with MVF.
Frenkel-Toledo et al. [13]	36 stroke patients aged 24 to 81 years, 23 to 132 days after stroke.	FMA zero to 66.	AO (reach and grasp action by left or right hands), observation of nonbiological videos, and the eye close condition.	EEG.	Failure to imitate correlated with diminished mu suppression in patients with IPL or IFG pars opercularis damage.
Kuk et al. [51]	20 chronic stroke patients (>six months after stroke); EG ($n = 10$): stroke patients aged 60.0 ± 9.36; CG ($n = 10$): stroke patients aged 59.70 ± 6.58.	With the ability to grasp a small cube (2.5 cm^3) by the paretic hand.	EG: AO (watching videos of the actions of BBT performed by both hands), followed by performing the same task; CG: observation of nonbiological videos, followed by performing the same task.	EEG ($n = 10$, only for EG).	MTG was not activated after five sessions of AO, compared with pretraining.
Tani et al. [58]	11 stroke patients (18 to 1919 days after stroke), aged 64.1 ± 7.8.	Brunnstrom stage of the hand III–V.	AO (open-and-grasp action by the paretic hand), MI (the same actions by the paretic hand), and fixation.	EEG.	AO induced stronger mu suppression over the ipsilesional SMC (C3 or C4) than MI.

EG: experimental group; CG: control group; FMA-UE: Fugl-Meyer assessment upper extremity; AO: action observation; IFG: inferior frontal gyrus; SMG: supramarginal gyrus; fMRI: functional magnetic resonance imaging; MVF: mirror visual feedback; PCC: posterior cingular cortex; MI: motor imagery; PMC: premotor cortex; SMC: sensorimotor cortex; S1: primary somatosensory cortex; M1: primary motor cortex; NHPT: nine-hole peg test; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; SPL: superior parietal lobe; IPL: inferior parietal lobe; PMd: dorsal premotor cortex; SMC: sensorimotor cortex; CMA: Chedokee-McMaster motor assessment arm scale; CMH: Chedokee-McMaster motor assessment hand scale; BA: Broadman area; EEG: electroencephalography; IPS: intraparietal sulcus; ARAT: action research arm test; MEG: magnetoencephalography; BBT: box and block test; ERD: event-related desynchronization.

Table 4: Methodological assessment of included studies using the PEDro scale*.

Criterion	Ertelt et al. [22]	Michielsen et al. [52]	Bae et al. [45]	Sun et al. [28]
Eligibility criteria	Yes	Yes	No	Yes
Random allocation	1	1	1	1
Concealed allocation	0	1	0	0
Baseline comparability	1	1	1	1
Blind subjects	0	0	0	0
Blind therapists	0	0	0	0
Blind assessors	0	1	0	1
Adequate follow-up	1	1	0	1
Intention-to-treat analysis	0	1	0	1
Between group comparisons	1	1	1	1
Point estimates and variability	1	1	1	1
Total scores	5	8	4	7

*The PEDro scores were taken from the PEDro website, except Ertelt et al. [22] and Sun et al. [28], which were rated by our team.

with MVF resulted in a shifted activation toward the ipsilesional hemispheres in patients who have had strokes; hence, a more symmetrical state between the two hemispheres may be achieved [46, 52]; (3) AO induced broader brain activation in the frontal, parietal, temporal, and occipital areas in patients who have had strokes, which encompassed the MNS, as well as cortical areas of motor execution, including the primary motor cortex, PMC, and SMA [22, 47, 48, 50]; (4) mu suppression can be induced by AO in patients who have had strokes; however, mu suppression over the affected hemisphere is relatively diminished [13, 49, 58]; and (5) MVF [45] or AO [28] embedded in long-term rehabilitation could bring about additional neurophysiological effects in patients after they have had strokes, reflected by more evident mu suppression, which may indicate that MN activities can be increased by this training.

A classical pathological change following stroke involves the activities of the affected hemispheres being suppressed, while those of less affected hemispheres are heightened, due to interhemispheric competition rivalry [60]; hence, successful motor recovery in patients who have had strokes could be achieved by normalizing the interhemispheric asymmetricity and promoting the neuroplasticity of the ipsilesional motor cortex [61, 62]. As the present review has shown, long-term MVF can contribute to a shift in activation toward the affected hemisphere [46, 52]. Furthermore, MVF transiently attenuates the asymmetric activities of movement-related beta suppression [54]. These findings can partially explain the beneficial effects of MT, which induces more symmetrical activities between the two hemispheres in patients who have had strokes. This is in line with previous findings regarding the effects of MVF on the healthy brain [35]. However, evidence to support the way in which AO can induce a shift of activation toward the affected hemisphere is relatively limited [50].

The difference between the activation patterns of MVF and AO can be identified. MVF mainly activates the ipsilesional primary motor cortex [34, 40, 46, 52, 55], the PMC [46], the primary somatosensory cortex [34, 40, 55], and the IPL [34, 55]. Two articles (one study) using effective connectivity and DCM have proposed that MVF could increase the connectivity between the ipsilesional primary somatosensory and primary motor cortex [55]. This study also suggests that the activation of the ipsilesional primary motor cortex may arise from contralesional IPS [34], which is a part of the MNS. These results are in line with the assumed functions of the MNS: visuomotor transformation. However, this conclusion should be interpreted with caution, since some studies have not identified the MNS activation by MVF in either patients who have had strokes [53] or healthy subjects [35]. The studies by Saleh et al. did not choose another frontal MNS (e.g., PMC) as the node in the DCM [34, 55]. As the first fMRI study with DCM that supports the activation of the MNS induced by MVF and its subsequent effects on the activation of the primary motor cortex [34], it is worthwhile to further explore the neural network underlying the MVF, in order to explain the role of the MNS in the network.

For AO, the activated brain regions were much broader, including IFG [47, 50], the PMC [22, 47, 48], the IPL [47], the primary motor cortex [47, 50], and temporal and occipital structures, which encompass the parietofrontal MNS as well as the cortical areas for motor execution (e.g., the primary motor cortex, PMC, and SMA). Small et al. proposed a model of brain repair after a stroke, which hypothesized that the MNS activation induced by AO may promote the reorganization of the cortical motor loop (i.e., the primary motor cortex, PMC, and SMA), thereby improving the motor functions of stroke survivors [63]. Our findings provide anatomical evidence to support this model. Observations of the bimanual action elicited a similar activation pattern as the execution of the same action in one study [47], whereas another study showed that AO (of a simple wrist movement) activated a part of the PMC and IPL, which did not resemble the activation pattern of action execution to such a great extent [56]. This difference may be attributed to different experimental paradigms of AO. The AO network, which may be involved in the understanding of motor intention, may have a stronger response to an object-directed or goal-directed action [64, 65], relative to a single action without meaning, although this is still inconclusive [66]. All in all, the results are still consistent with previously defined bilateral AO networks in healthy human brains [29, 30]. The neural network underlying the AO remains unclear.

The activation patterns of MVF and AO are obviously different. AO elicited broader activation of the frontal, parietal, temporal, and occipital areas, while the activated regions of MVF mainly covered the frontal and parietal structures. The difference between these two regimens is that the participants were required to perform bilateral or unilateral movement themselves when observing the visual feedback in the

MVF experiments, while this was not required in the AO experiments. Previous studies have assumed that there are different neural networks in response to AO and MVF [35, 67], and this opinion was confirmed by the present review in the stroke cohorts. Even though the underlying neural network cannot be fully understood at this stage, MNS activation seems to play a key role in both AO- and MVF-induced functional plasticities. There have been several TMS studies that have provided indirect evidence of the activation of the primary motor cortex by AO or MVF [27, 68]. Therefore, these two modalities can be viewed as optional motor priming tools for stroke rehabilitation. However, there is still a lack of studies directly comparing the clinical improvements and the pattern of neuroplasticity induced by MVF and AO [69] and whether or not the activation pattern is congruent with the clinical improvements in patients with stroke.

Brain waveforms recorded by EEG are altered by AO, reflected by lower alpha power and higher beta power over the frontal, central, and occipital electrodes [41, 42]. Some studies have also shown that the electrophysiological responses to AO may decrease after repetitive stimulations [43, 51]. These changes may be related to the changes in cognitive activities related to the understanding of motor intention after receiving visual feedback [70]. However, pure spectrum analysis is less likely than detailed EEG analyses, for example, time-frequency analysis, to reflect MN activity and stroke recovery [71, 72]. A recent meta-analysis indicated that both AO and action execution could induce the suppression of mu rhythm with a significant effect size [73]. This property of dual activation makes the mu suppression a signature of human mirror neuron activity [37, 74]. Regarding the studies included in the present review, two articles investigated AO-induced mu suppression in stroke individuals and its relationship with brain lesions [13, 49]. They found that the magnitude of mu suppression was reduced in the affected hemisphere, relative to the unaffected hemisphere, which was also identified by another study [58]. Two RCTs demonstrated that AO- or MI-induced mu suppression can be enhanced after long-term AOT [28] or training with MVF [45], which implies enhanced MN activities after the AO or MI training. Lesion analysis also showed that the damage over IPL or IFG was correlated with the diminished mu suppression, which indicates that mu suppression may be a specific index of MN activities [13, 16, 49].

One study demonstrated that behavioral improvement is correlated with the neural response to AO (measured by fMRI) in stroke individuals, which indicates that the AO-induced neural response is likely to be an indicator that can evaluate the arm motor recovery of patients who have had strokes within the first three months [47]. As the MNS is correlated with motion imitation [75], its activation may be a neurobiomarker that can measure the potential of motor learning in patients who have had strokes [47], which could also be measured by mu suppression. The predictive value of mu suppression and its relationship with motor improvement remain speculative. Other frequency bands related to action execution and AO, such as the beta band, might also be suitable candidates in regard to measuring MN activities [38, 76], although evidence of this in the stroke population is fairly limited [54]. As EEG is a relatively low-cost technique, further studies are encouraged to longitudinally explore the role of the ERD of different frequency ranges over various brain regions in patients who have had strokes. This neurobiomarker may also serve as a useful reference of the patients' motor recovery trajectory and motor relearning potential, promoted by MNS activation in stroke individuals.

There are some limitations in the present review. First, the heterogeneous protocols of AO and MVF and different experimental designs in regard to implementing neuroimaging hindered us from giving a firm and precise conclusion. Second, potentially confounding factors cannot be fully explained, based on currently available evidence, such as the dominance of handedness [48] and the nature of stroke lesions [48], which may result in different responses to AO and MVF. Further studies are warranted to answer these questions. Finally, restricting our review to English publications may have resulted in language bias.

5. Conclusions

MVF may contribute to stroke recovery by revising the interhemispheric imbalance, and MNS recruitment may be one of the potential neural mechanisms in this process. AO is associated with the activation of the MNS and motor cortex, which may promote motor relearning in stroke individuals. More rigorous studies with functional neuroimaging or electrophysiological techniques should be performed to further explain the different functional neural networks underlying AO or MVF and to explore the relationship between MN activities and clinical recovery in patients who have had strokes.

Abbreviations

AO: Action observation
MVF: Mirror visual feedback
MNS: Mirror neuron system
fMRI: Functional magnetic resonance imaging
EEG: Electroencephalography
CIMT: Constraint-induced movement training
VR: Virtual reality
IFG: Inferior frontal gyrus
PMv: Ventral premotor cortex
IPL: Inferior parietal lobule
IPS: Intraparietal sulcus
MT: Mirror therapy
MEG: Magnetoencephalography
PET: Positron emission tomography
NIRS: Near-infrared spectrometry
ERD: Event-related desynchronization
DCM: Dynamic casual modelling
PMC: Premotor cortex
SMC: Sensorimotor cortex
MI: Motor imagery
STG: Superior temporal gyrus
SMA: Supplementary motor area
SMG: Supramarginal gyrus
PCC: Posterior cingulate cortex
MFG: Middle frontal gyrus.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] B. H. Dobkin, "Rehabilitation after stroke," *New England Journal of Medicine*, vol. 352, no. 16, pp. 1677–1684, 2005.

[2] A. C. Lo, P. D. Guarino, L. G. Richards et al., "Robot-assisted therapy for long-term upper-limb impairment after stroke," *New England Journal of Medicine*, vol. 362, no. 19, pp. 1772–1783, 2010.

[3] G. Kwakkel, J. M. Veerbeek, E. E. H. van Wegen, and S. L. Wolf, "Constraint-induced movement therapy after stroke," *The Lancet Neurology*, vol. 14, no. 2, pp. 224–234, 2015.

[4] K. E. Laver, S. George, S. Thomas, J. E. Deutsch, and M. Crotty, "Virtual reality for stroke rehabilitation," *Cochrane Database of Systematic Reviews*, no. 2, article CD008349, 2015.

[5] Y. T. Fan, K. C. Lin, H. L. Liu, C. Y. Wu, Y. Y. Wai, and T. H. Lee, "Neural correlates of motor recovery after robot-assisted stroke rehabilitation: a case series study," *Neurocase*, vol. 22, no. 5, pp. 416–425, 2016.

[6] J. Liepert, W. H. R. Miltner, H. Bauder et al., "Motor cortex plasticity during constraint-induced movement therapy in stroke patients," *Neuroscience Letters*, vol. 250, no. 1, pp. 5–8, 1998.

[7] S. Saleh, G. Fluet, Q. Qiu, A. Merians, S. V. Adamovich, and E. Tunik, "Neural patterns of reorganization after intensive robot-assisted virtual reality therapy and repetitive task practice in patients with chronic stroke," *Frontiers in Neurology*, vol. 8, no. 452, p. 452, 2017.

[8] V. Ramachandran, "Plasticity and functional recovery in neurology," *Clinical Medicine*, vol. 5, no. 4, pp. 368–373, 2005.

[9] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[10] G. Rizzolatti and G. Luppino, "The cortical motor system," *Neuron*, vol. 31, no. 6, pp. 889–901, 2001.

[11] L. Fadiga, L. Fogassi, G. Pavesi, and G. Rizzolatti, "Motor facilitation during action observation: a magnetic stimulation study," *Journal of Neurophysiology*, vol. 73, no. 6, pp. 2608–2611, 1995.

[12] G. Buccino, S. Vogt, A. Ritzl et al., "Neural circuits underlying imitation learning of hand actions: an event-related fMRI study," *Neuron*, vol. 42, no. 2, pp. 323–334, 2004.

[13] S. Frenkel-Toledo, D. G. Liebermann, S. Bentin, and N. Soroker, "Dysfunction of the human mirror neuron system in ideomotor apraxia: evidence from mu suppression," *Journal of Cognitive Neuroscience*, vol. 28, no. 6, pp. 775–791, 2016.

[14] W. Chen, Q. Ye, X. Ji et al., "Mirror neuron system based therapy for aphasia rehabilitation," *Frontiers in Psychology*, vol. 6, p. 1665, 2015.

[15] T. F. Yuan and R. Hoff, "Mirror neuron system based therapy for emotional disorders," *Medical Hypotheses*, vol. 71, no. 5, pp. 722–726, 2008.

[16] A. Perry, S. N. Saunders, J. Stiso et al., "Effects of prefrontal cortex damage on emotion understanding: EEG and behavioural evidence," *Brain*, vol. 140, no. 4, pp. 1086–1099, 2017.

[17] K. A. Garrison, C. J. Winstein, and L. Aziz-Zadeh, "The mirror neuron system: a neural substrate for methods in stroke rehabilitation," *Neurorehabilitation and Neural Repair*, vol. 24, no. 5, pp. 404–412, 2010.

[18] J. A. Pineda, "Sensorimotor cortex as a critical component of an 'extended' mirror neuron system: does it solve the development, correspondence, and control problems in mirroring?," *Behavioral and Brain Functions*, vol. 4, no. 1, p. 47, 2008.

[19] G. Rizzolatti and C. Sinigaglia, "The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations," *Nature Reviews Neuroscience*, vol. 11, no. 4, pp. 264–274, 2010.

[20] T. F. Yuan, W. Chen, C. Shan et al., "Activity-dependent neurorehabilitation beyond physical trainings: "mental exercise" through mirror neuron activation," *CNS & Neurological Disorders - Drug Targets*, vol. 14, no. 10, pp. 1267–1271, 2015.

[21] E. Sarasso, M. Gemma, F. Agosta, M. Filippi, and R. Gatti, "Action observation training to improve motor function recovery: a systematic review," *Archives of Physiotherapy*, vol. 5, no. 1, p. 14, 2015.

[22] D. Ertelt, S. Small, A. Solodkin et al., "Action observation has a positive impact on rehabilitation of motor deficits after stroke," *NeuroImage*, vol. 36, pp. T164–T173, 2007.

[23] E. L. Altschuler, S. B. Wisdom, L. Stone et al., "Rehabilitation of hemiparesis after stroke with a mirror," *The Lancet*, vol. 353, no. 9169, pp. 2035-2036, 1999.

[24] K. Sugg, S. Müller, C. Winstein, D. Hathorn, and A. Dempsey, "Does action observation training with immediate physical practice improve hemiparetic upper-limb function in chronic stroke?," *Neurorehabilitation and Neural Repair*, vol. 29, no. 9, pp. 807–817, 2015.

[25] M. Franceschini, M. G. Ceravolo, M. Agosti et al., "Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial," *Neurorehabilitation and Neural Repair*, vol. 26, no. 5, pp. 456–462, 2012.

[26] T. Cowles, A. Clark, K. Mares, G. Peryer, R. Stuck, and V. Pomeroy, "Observation-to-imitate plus practice could add little to physical therapy benefits within 31 days of stroke: translational randomized controlled trial," *Neurorehabilitation and Neural Repair*, vol. 27, no. 2, pp. 173–182, 2013.

[27] J. Fu, M. Zeng, F. Shen et al., "Effects of action observation therapy on upper extremity function, daily activities and motion evoked potential in cerebral infarction patients," *Medicine*, vol. 96, no. 42, article e8080, 2017.

[28] Y. Sun, W. Wei, Z. Luo, H. Gan, and X. Hu, "Improving motor imagery practice with synchronous action observation in stroke patients," *Topics in Stroke Rehabilitation*, vol. 23, no. 4, pp. 245–253, 2016.

[29] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[30] V. M. Pomeroy, C. A. Clark, J. S. G. Miller, J. C. Baron, H. S. Markus, and R. C. Tallis, "The potential for utilizing the "mirror neurone system" to enhance recovery of the severely

affected upper limb early after stroke: a review and hypothesis," *Neurorehabilitation and Neural Repair*, vol. 19, no. 1, pp. 4–13, 2005.

[31] V. S. Ramachandran and E. L. Altschuler, "The use of visual feedback, in particular mirror visual feedback, in restoring brain function," *Brain*, vol. 132, no. 7, pp. 1693–1710, 2009.

[32] K. Eng, E. Siekierka, P. Pyk et al., "Interactive visuo-motor therapy system for stroke rehabilitation," *Medical & Biological Engineering & Computing*, vol. 45, no. 9, pp. 901–907, 2007.

[33] S. F. M. Toh and K. N. K. Fong, "Systematic review on the effectiveness of mirror therapy in training upper limb hemiparesis after stroke," *Hong Kong Journal of Occupational Therapy*, vol. 22, no. 2, pp. 84–95, 2012.

[34] S. Saleh, M. Yarossi, T. Manuweera, S. Adamovich, and E. Tunik, "Network interactions underlying mirror feedback in stroke: a dynamic causal modeling study," *NeuroImage: Clinical*, vol. 13, pp. 46–54, 2017.

[35] F. J. A. Deconinck, A. R. P. Smorenburg, A. Benham, A. Ledebt, M. G. Feltham, and G. J. P. Savelsbergh, "Reflections on mirror therapy: a systematic review of the effect of mirror visual feedback on the brain," *Neurorehabilitation and Neural Repair*, vol. 29, no. 4, pp. 349–361, 2015.

[36] A. M. Auriat, J. L. Neva, S. Peters, J. K. Ferris, and L. A. Boyd, "A review of transcranial magnetic stimulation and multimodal neuroimaging to characterize post-stroke neuroplasticity," *Frontiers in Neurology*, vol. 6, p. 226, 2015.

[37] H. M. Hobson and D. V. M. Bishop, "Mu suppression – a good measure of the human mirror neuron system?," *Cortex*, vol. 82, pp. 290–310, 2016.

[38] S. D. Muthukumaraswamy and K. D. Singh, "Modulation of the human mirror neuron system during cognitive activity," *Psychophysiology*, vol. 45, no. 6, pp. 896–905, 2008.

[39] R. S. Calabrò, A. Naro, M. Russo et al., "The role of virtual reality in improving motor performance as revealed by EEG: a randomized clinical trial," *Journal of NeuroEngineering and Rehabilitation*, vol. 14, no. 1, p. 53, 2017.

[40] F. Guo, Q. Xu, H. M. Abo Salem, Y. Yao, J. Lou, and X. Huang, "The neuronal correlates of mirror therapy: a functional magnetic resonance imaging study on mirror-induced visual illusions of ankle movements," *Brain Research*, vol. 1639, pp. 186–193, 2016.

[41] J. Kim, B. Lee, H. S. Lee, K. H. Shin, M. J. Kim, and E. Son, "Differences in brain waves of normal persons and stroke patients during action observation and motor imagery," *Journal of Physical Therapy Science*, vol. 26, no. 2, pp. 215–218, 2014.

[42] J. H. Kim and B. H. Lee, "Action observation training for functional activities after stroke: a pilot randomized controlled trial," *NeuroRehabilitation*, vol. 33, no. 4, pp. 565–574, 2013.

[43] M. Y. Chang, H. H. Kim, K. M. Kim, J. S. Oh, C. Jang, and T. H. Yoon, "Effects of observation of hand movements reflected in a mirror on cortical activation in patients with stroke," *Journal of Physical Therapy Science*, vol. 29, no. 1, pp. 38–42, 2017.

[44] M. Martin, K. Nitschke, L. Beume et al., "Brain activity underlying tool-related and imitative skills after major left hemisphere stroke," *Brain*, vol. 139, no. 5, pp. 1497–1516, 2016.

[45] S. H. Bae, W. S. Jeong, and K. Y. Kim, "Effects of mirror therapy on subacute stroke patients' brain waves and upper extremity functions," *Journal of Physical Therapy Science*, vol. 24, no. 11, pp. 1119–1122, 2012.

[46] A. Bhasin, R. Bhatia, S. S. Kumaran, S. Mohanty, and M. V. Padma Srivastava, "Neural interface of mirror therapy in chronic stroke patients: a functional magnetic resonance imaging study," *Neurology India*, vol. 60, no. 6, pp. 570–576, 2012.

[47] I. C. Brunner, J. S. Skouen, L. Ersland, and R. Gruner, "Plasticity and response to action observation: a longitudinal fMRI study of potential mirror neurons in patients with subacute stroke," *Neurorehabilitation and Neural Repair*, vol. 28, no. 9, pp. 874–884, 2014.

[48] C. Dettmers, V. Nedelko, and M. Ariel Schoenfeld, "Impact of left versus right hemisphere subcortical stroke on the neural processing of action observation and imagery," *Restorative Neurology and Neuroscience*, vol. 33, no. 5, pp. 701–712, 2015.

[49] S. Frenkel-Toledo, S. Bentin, A. Perry, D. G. Liebermann, and N. Soroker, "Mirror-neuron system recruitment by action observation: effects of focal brain damage on mu suppression," *NeuroImage*, vol. 87, pp. 127–137, 2014.

[50] K. A. Garrison, L. Aziz-Zadeh, S. W. Wong, S. L. Liew, and C. J. Winstein, "Modulating the motor system by action observation after stroke," *Stroke*, vol. 44, no. 8, pp. 2247–2253, 2013.

[51] E. J. Kuk, J. M. Kim, D. W. Oh, and H. J. Hwang, "Effects of action observation therapy on hand dexterity and EEG-based cortical activation patterns in patients with post-stroke hemiparesis," *Topics in Stroke Rehabilitation*, vol. 23, no. 5, pp. 318–325, 2016.

[52] M. E. Michielsen, R. W. Selles, J. N. van der Geest et al., "Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial," *Neurorehabilitation and Neural Repair*, vol. 25, no. 3, pp. 223–233, 2011.

[53] M. E. Michielsen, M. Smits, G. M. Ribbers et al., "The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 82, no. 4, pp. 393–398, 2011.

[54] H. E. Rossiter, M. R. Borrelli, R. J. Borchert, D. Bradbury, and N. S. Ward, "Cortical mechanisms of mirror therapy after stroke," *Neurorehabilitation and Neural Repair*, vol. 29, no. 5, pp. 444–452, 2015.

[55] S. Saleh, S. V. Adamovich, and E. Tunik, "Mirrored feedback in chronic stroke: recruitment and effective connectivity of ipsilesional sensorimotor networks," *Neurorehabilitation and Neural Repair*, vol. 28, no. 4, pp. 344–354, 2014.

[56] A. J. Szameitat, S. Shen, A. Conforto, and A. Sterr, "Cortical activation during executed, imagined, observed, and passive wrist movements in healthy volunteers and stroke patients," *NeuroImage*, vol. 62, no. 1, pp. 266–280, 2012.

[57] J. Wang, C. Fritzsch, J. Bernarding et al., "Cerebral activation evoked by the mirror illusion of the hand in stroke patients compared to normal subjects," *NeuroRehabilitation*, vol. 33, no. 4, pp. 593–603, 2013.

[58] M. Tani, Y. Ono, M. Matsubara et al., "Action observation facilitates motor cortical activity in patients with stroke and hemiplegia," *Neuroscience Research*, 2017.

[59] M. Brunetti, N. Morkisch, C. Fritzsch et al., "Potential determinants of efficacy of mirror therapy in stroke patients – a pilot study," *Restorative Neurology and Neuroscience*, vol. 33, no. 4, pp. 421–434, 2015.

[60] P. Marque, D. Gasq, E. Castel-Lacanal, X. De Boissezon, and I. Loubinoux, "Post-stroke hemiplegia rehabilitation: evolution of the concepts," *Annals of Physical and Rehabilitation Medicine*, vol. 57, no. 8, pp. 520–529, 2014.

[61] T. Askim, B. Indredavik, T. Vangberg, and A. Haberg, "Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal functional magnetic resonance imaging study," *Neurorehabilitation and Neural Repair*, vol. 23, no. 3, pp. 295–304, 2009.

[62] D. A. Nowak, C. Grefkes, M. Ameli, and G. R. Fink, "Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand," *Neurorehabilitation and Neural Repair*, vol. 23, no. 7, pp. 641–656, 2009.

[63] S. L. Small, G. Buccino, and A. Solodkin, "Brain repair after stroke—a novel neurological model," *Nature Reviews Neurology*, vol. 9, no. 12, pp. 698–707, 2013.

[64] L. Koski, A. Wohlschläger, H. Bekkering et al., "Modulation of motor and premotor activity during imitation of target-directed actions," *Cerebral Cortex*, vol. 12, no. 8, pp. 847–855, 2002.

[65] S. L. Liew, K. A. Garrison, J. Werner, and L. Aziz-Zadeh, "The mirror neuron system: innovations and implications for occupational therapy," *OTJR: Occupation, Participation and Health*, vol. 32, no. 3, pp. 79–86, 2012.

[66] R. Newman-Norlund, H. T. van Schie, M. E. C. van Hoek, R. H. Cuijpers, and H. Bekkering, "The role of inferior frontal and parietal areas in differentiating meaningful and meaningless object-directed actions," *Brain Research*, vol. 1315, pp. 63–74, 2010.

[67] F. Hamzei, C. H. Lappchen, V. Glauche, I. Mader, M. Rijntjes, and C. Weiller, "Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere," *Neurorehabilitation and Neural Repair*, vol. 26, no. 5, pp. 484–496, 2012.

[68] Y. Kang, H. Park, H. Kim et al., "Upper extremity rehabilitation of stroke: facilitation of corticospinal excitability using virtual mirror paradigm," *Journal of NeuroEngineering and Rehabilitation*, vol. 9, no. 1, p. 71, 2012.

[69] T. Y. Shih, C. Y. Wu, K. C. Lin et al., "Effects of action observation therapy and mirror therapy after stroke on rehabilitation outcomes and neural mechanisms by MEG: study protocol for a randomized controlled trial," *Trials*, vol. 18, no. 1, p. 459, 2017.

[70] L. Fogassi, P. F. Ferrari, B. Gesierich, S. Rozzi, F. Chersi, and G. Rizzolatti, "Parietal lobe: from action organization to intention understanding," *Science*, vol. 308, no. 5722, pp. 662–667, 2005.

[71] S. Giaquinto, A. Cobianchi, F. Macera, and G. Nolfe, "EEG recordings in the course of recovery from stroke," *Stroke*, vol. 25, no. 11, pp. 2204–2209, 1994.

[72] C. Neuper, M. Wortz, and G. Pfurtscheller, "ERD/ERS patterns reflecting sensorimotor activation and deactivation," *Progress in Brain Research*, vol. 159, pp. 211–222, 2006.

[73] N. A. Fox, M. J. Bakermans-Kranenburg, K. H. Yoo et al., "Assessing human mirror activity with EEG mu rhythm: a meta-analysis," *Psychological Bulletin*, vol. 142, no. 3, pp. 291–313, 2016.

[74] H. M. Hobson and D. V. M. Bishop, "The interpretation of mu suppression as an index of mirror neuron activity: past, present and future," *Royal Society Open Science*, vol. 4, no. 3, article 160662, 2017.

[75] G. Rizzolatti, L. Cattaneo, M. Fabbri-Destro, and S. Rozzi, "Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding," *Physiological Reviews*, vol. 94, no. 2, pp. 655–706, 2014.

[76] C. Babiloni, C. del Percio, F. Vecchio et al., "Alpha, beta and gamma electrocorticographic rhythms in somatosensory, motor, premotor and prefrontal cortical areas differ in movement execution and observation in humans," *Clinical Neurophysiology*, vol. 127, no. 1, pp. 641–654, 2016.

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Research Article

Corticospinal and Spinal Excitabilities Are Modulated during Motor Imagery Associated with Somatosensory Electrical Nerve Stimulation

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Motor imagery (MI), the mental simulation of an action, influences the cortical, corticospinal, and spinal levels, despite the lack of somatosensory afferent feedbacks. The aim of this study was to analyze the effect of MI associated with somatosensory stimulation (SS) on the corticospinal and spinal excitabilities. We used transcranial magnetic stimulation and peripheral nerve stimulation to induce motor-evoked potentials (MEP) and H-reflexes, respectively, in soleus and medialis gastrocnemius (MG) muscles of the right leg. Twelve participants performed three tasks: (1) MI of submaximal plantar flexion, (2) SS at 65 Hz on the posterior tibial nerve with an intensity below the motor threshold, and (3) MI + SS. MEP and H-reflex amplitudes were recorded before, during, and after the tasks. Our results confirmed that MI increased corticospinal excitability in a time-specific manner. We found that MI + SS tended to potentiate MEP amplitude of the MG muscle compared to MI alone. We confirmed that SS decreased spinal excitability, and this decrease was partially compensated when combined with MI, especially for the MG muscle. The increase of CSE could be explained by a modulation of the spinal inhibitions induced by SS, depending on the amount of afferent feedbacks.

1. Introduction

Motor imagery (MI) is the mental simulation of a movement without muscular activities [1]. MI activates the motor cortical network, such as the primary motor cortex (M1), the premotor cortex, the supplementary motor area, and the parietal cortex [2], a network also involved when the movement is actually executed [3]. Most transcranial magnetic stimulation (TMS) studies have reported an increase of the corticospinal excitability (CSE) during MI in comparison to the rest, as evidenced by an increase of the motor-evoked potential (MEP) amplitude [4, 5]. Recently, the subliminal motor command evoked during MI has been evidenced to reach the spinal level and to modify the excitability of inhibitory interneurons [4].

Most of the previous cited results have been observed using kinesthetic imagery modality, which consists in imagining the actual movement feelings associated with its realization. Indeed, this MI modality has been reported to induce greater CSE increase in comparison to the visual modality [6, 7]. This difference is most likely due to the activation of the somatosensory cortex during kinesthetic MI [8], which interacts with M1 [3]. Interestingly, no somatosensory feedbacks related to the imagined movement are available as no movement is produced during MI. Therefore, the understanding of the interaction between MI and somatosensory feedbacks induced artificially could promote the use of MI for motor performance improvement [9].

Few studies analyzed the interaction between MI and external somatosensory inputs, such as those induced by somatosensory electrical nerve stimulation (SS). Saito et al. [10] measured CSE during an imagined opposition finger task combined with SS (10 Hz, 1 ms pulse width for 20 seconds). They observed an increase of CSE in the thumb muscle when SS intensity was set at the motor threshold. Similarly, Kaneko et al. [11] found an increase of CSE during an imagined index abduction combined with SS (50 Hz, 1 ms pulse width for 2–4 seconds) when the intensity was above the motor threshold in comparison to MI alone. These studies demonstrated the additional influence of SS during MI on

upper-limb CSE. However, the SS intensity was set at or above the motor threshold, inducing force development that can modulate MEP amplitude [12]. Indeed, the CSE increase, observed during the stimulation above the motor threshold, could be attributed to the direct activation of the alpha-motoneuron rather than the sole activation of the somatosensory afferent pathway. Indeed, peripheral somatosensory stimulation evoked near the motor threshold activates proprioceptive, sensory and cutaneous afferent fibers [13]. Repetitive activation of these fibers induces inhibitory and/or excitatory neurotransmitter release into the synaptic cleft that can modulate the excitability threshold, that is, the electrophysiological properties of the resting motor neuron membrane. Thus, when a cortical stimulation is induced, the motor neuron may not be in the same state and the MEP amplitude may be affected [14]. This phenomenon is accentuated as the stimulation intensity is high, due to the greater number of fibers activated. In summary, CSE change may be related to the modulation of cortical and/or spinal excitability when the peripheral somatosensory stimulation is near the motor threshold [15]. Therefore, to properly examine the neural impact of the solicitation of afferent fibers during MI, it appears necessary to analyze both corticospinal and spinal excitabilities with SS below the motor threshold that avoids the contamination of the efferent pathway.

In the current study, we conducted a couple of experiments aiming at determining whether the combination of MI and SS below the motor threshold exacerbated the effect of MI on corticospinal and spinal excitabilities. In the first experiment, the participants performed 3 tasks: (1) MI alone, (2) SS alone (65 Hz), and (3) MI combined with SS. We assessed corticospinal and spinal excitabilities at different time points to probe the effects and aftereffects of MI and SS. We hypothesized that MI associated with SS would potentiate to a greater extent corticospinal and spinal excitabilities. We investigated CSE by measuring MEP amplitude evoked by TMS over M1 and spinal excitability by measuring H-reflex amplitude evoked by peripheral electrical nerve stimulation (PNS) over the posterior tibial nerve. In our experimental setup, we applied several PNS with short interstimulus intervals (ranged between 5 s and 10 s) that can affect spinal excitability due to homonymous postactivation depression [16–18]. Therefore, we conducted a second experiment to quantify the effect of successive PNS on spinal excitability at rest and during MI for our specific setup.

2. Methods

2.1. Subjects. Twelve young healthy adults volunteered to participate in experiment 1 (10 males and 2 females; age 26 ± 8.6 years, height 175 ± 8.7 cm, and weight 72.3 ± 8.8 kg). Data analysis was performed on the data from 11 of the participants, as data from one participant were discarded due to data saving errors. Eight young healthy adults volunteered to participate in experiment 2 (7 males and 1 female; age 28 ± 10 years, height 175.5 ± 3.8 cm, and weight 72.3 ± 7.5 kg), three of them participating in both experiments. Participants had no history of neurological and musculoskeletal disorders. They were normally active and gave their written consent. They did not engage in any strenuous physical activity for at least 24 h before the experimental sessions. All protocols of the current investigation were approved by the University of Burgundy Committee on Human Research and were performed in accordance with the Declaration of Helsinki.

2.2. Experimental Setup

2.2.1. Mechanical Recording. Participants sat in a position with hip, knee, and ankle joints placed at a 90° angular position. Measurements were realized on the right calf muscles with the foot secured by two straps to the footplate of a dynamometer (Biodex, Shirley, NY, USA) with the motor axis aligned with the external malleolus of the ankle. Participants were securely stabilized by two crossover shoulder harnesses, and head movements were reduced by a cervical collar strapped to the headrest of the seat.

2.2.2. Electromyographic Recording. The electromyographic activity (EMG) was recorded from two muscles of the right sural triceps (soleus (SOL) and medialis gastrocnemius (MG)) using silver-chloride surface electrodes (8 mm diameter, Ag-AgCl, Mini KR, Contrôle-Graphique S.A., Brie-Comte-Robert, France). Bipolar surface electrodes (interelectrode center-to-center distance of 2 cm) were placed on the midmuscle belly for MG and along the mid-dorsal line of the leg, about 2 cm below the insertion of the gastrocnemius on the Achilles tendon for SOL. The reference electrode was placed between two gastrocnemius muscles of the right leg, below the stimulation site. Before electrode placement, the skin was shaved and cleaned with alcohol to obtain low impedance (<5 kΩ). EMG signals were amplified with a bandwidth frequency ranging from 15 Hz to 1 kHz (gain = 1000) and digitized online at a sampling frequency of 5 kHz using TIDA software (HEKA Elektronik, Lambrecht/Pfalz, Germany).

2.2.3. Transcranial Magnetic Stimulation. A TMS figure-of-eight-shaped conic coil (70 mm loop diameter) was positioned over the left M1 with anteroposterior-directed current orientation to elicit MEPs in SOL and MG muscles of the right leg (Magstim 200, Magstim Company Ltd., Great Britain). To find the optimal site, we stimulated the M1 area of the triceps surae muscle by starting from 1 cm posterior and 1 cm lateral to the vertex of the participant's head and using the lowest stimulation intensity that evoked the greatest amplitude in the SOL and MG muscles. Once the optimal site was found, a mark was placed on the scalp to ensure consistency between stimulations. The coil was then secured by using a homemade tripod with a lockable articulated arm (Otello Factory, T&O brand, France). Then, we realized a recruitment curve at rest to determine the optimal stimulation intensity. The stimulation intensity was increased by steps of 5% of the maximum stimulator output (MSO), and four consecutive stimulations were applied at the same intensity. The optimal intensity was defined when evoking the greatest and the less variable MEP amplitudes on the ascending part of the recruitment curve of both muscles (variation coefficient $< 5\%$). During exp. 1, mean TMS intensity was

72 ± 10% MSO (range: 60 to 98% MSO) corresponding to 131 ± 15% and 124 ± 16% of the rest motor threshold for SOL and MG, respectively. These stimulation intensities are in the range of those classically used in the literature when analyzing the CSE [19].

2.2.4. Peripheral Nerve Stimulation (PNS). To evoke M and H waves, a single 1 ms rectangular pulse was applied to the posterior tibial nerve using a Digitimer stimulator (model DS7, Hertfordshire, UK). We first placed the cathode electrode stylus in the popliteal fossa and the anode electrode (5 × 10 cm, Medicompex SA, Ecublens, Switzerland) over the patellar tendon, to find the optimal stimulation site, that is, the greatest H-reflex amplitude or M-wave amplitude for the SOL with the lowest stimulation intensity. Once the optimal site was found, we replaced the stylus with a surface electrode (8 mm diameter, Ag-AgCl), secured with a rubber band. Then, we realized a recruitment curve at rest to determine the three optimal stimulation intensities that evoked (1) the lowest EMG response (defined as the rest motor threshold (rMT)), (2) the most reproducible H-reflex, and (3) the maximal M-wave (M_{max}). For each participant, the stimulation intensity was progressively increased, with a 0.5 mA step, to the M_{max} amplitude.

In exp. 1, the mean PNS intensity inducing an H-reflex of about 10–15% of M_{max} was 9.1 ± 4.9 mA. The mean PNS intensity was 52.3 ± 20.6 mA corresponding to M_{max} wave amplitude of 8.0 ± 4.5 mV. For the somatosensory stimulation (SS), we applied 1 ms monophasic rectangular electrical pulses at 65 Hz for 9 seconds using a second Digitimer stimulator (model DS7, Hertfordshire, UK). The SS intensity was set at 80% of the participants' rMT (mean: 4.9 ± 3.1 mA) to induce afferent inputs without contaminating efferent activation. Due to the electrical noise induced by SS contaminating background EMG, the current was stopped 4 seconds after the beginning of SS for 200 ms to elicit H-reflex or MEP 100 ms after the last SS pulse.

In exp. 2, the PNS intensity to evoke H-reflexes was set at 15% of the M_{max} amplitude, to avoid antidromic collisions and to reduce intersubject variability (mean intensity: 10.3 ± 5.1 mA). The PNS intensity to evoke an M_{max} wave was set at 54.2 ± 18.1 mA corresponding to an M_{max} amplitude of 7.4 ± 4.2 mV.

2.3. Experimental Protocol. The duration of both experiments was about two hours. An overview of exp. 1 is depicted in Figure 1. The first experiment was designed to study the effects of MI associated with SS on corticospinal and spinal excitabilities. To determine maximal plantar flexion force, the participants first performed two maximal voluntary contractions (MVC). If the difference between the two exceeded 5%, an additional trial was performed. The maximal performance was considered for the continuation of the experiment. Then, PNS was applied 4 times at rest to record M_{max}. To memorize the sensations associated with actual contractions, the participants performed several trials at 50% MVC. A visual feedback helped the participants to match the level of force. Then, we assessed corticospinal and spinal excitabilities during the three tasks: MI only, SS only, and MI associated with SS (MI + SS). All tasks included 8 trials of 45-second duration, half with TMS to elicit MEPs and half with PNS to elicit H-reflexes. The low number of stimulations was chosen to limit the risk of discomfort. A preliminary experiment helped us in determining the number of trials: we found that for 20, 10, or 4 trials, the MEP variation was not significantly different for SOL and MG muscles with 20, 10, and 4 trials (41 ± 27% and 38 ± 16% with 20 trials; 35 ± 21% and 34.0 ± 18% with 10 trials; and 31 ± 28% and 31 ± 23% with 4 trials, resp.). The order of the tasks and of the stimulation type was counterbalanced across participants. TMS and PNS were evoked at 0 s (Pre), 9 s (Per), 16 s, 24 s, and 34 s (Post 1, 2, and 3, resp.). In SS and MI + SS tasks, SS was applied for 9 s (5 s after the first stimulation, i.e., Pre stimulation). In MI and MI + SS tasks, participants imagined a plantar-flexion contraction at 50% of MVC for 9 s. To start and stop imagining, the experimenter gave auditory go (5 s after the Pre stimulation) and stop signals (9 s after the go signal). Therefore, in the MI + SS task, MI and SS were performed at the same time. During MI, participants were instructed to feel the contraction normally generated during actual contractions (kinesthetic modality) and to stay relaxed to avoid muscular contractions.

SS, TMS, and PNS were triggered automatically by the TIDA patch-clamp software (HEKA Elektronik, Lambrecht/Pfalz, Germany) and synchronized with EMG recordings. During the experimental protocol, 60 TMS, 60 PNS, and 16 SS trains were applied.

Exp. 2 was designed to control the effects of successive PNS on H-reflex amplitude at rest and during MI. The experimental setup was similar to exp. 1, without application of SS. As in exp. 1, participants were instructed to stay at rest or to imagine a 50% MVC plantar-flexion contraction. In total, two tasks were performed: (1) PNS induced at 0 s, 9 s, and 16 s during MI (MI Pre-Per-Post) and (2) PNS induced at 0 s, 9 s, and 16 s at rest (Rest Pre-Per-Post). Eight trials were recorded for each task. During the experimental protocol, 48 PNS were applied (24 at rest and 24 during MI).

In both experiments, after each imagined trial, the subjects rated the vividness of their MI using a 7-point Likert scale (from 1 = "very hard to feel" to 7 = "very easy to feel," 2–6 being intermediate quotes).

2.4. Data Analysis. To ensure that the evoked responses were not contaminated by any muscle contraction, the normalized root mean square (RMS) EMG signal was measured 100 ms before each stimulation artefact. When the RMS/M_{max} ratio was different from the mean ± 2 SD of the RMS baseline, that is, observed at rest before the first stimulation, the trial was discarded from the general analysis (3% of all trials). Peak-to-peak MEP, M_{max}, and H-reflex amplitudes were measured during each task for SOL and MG muscles. The ratios MEP/M_{max} and H/M_{max} were calculated and analyzed.

2.5. Statistics Analysis. All data were normalized to M_{max} and expressed by their mean ± standard deviation (SD). Data distribution was tested using the Shapiro-Wilk test to ensure the use of the classical analysis of variance for parametric values when appropriate. In exp. 1, all variables were not normally

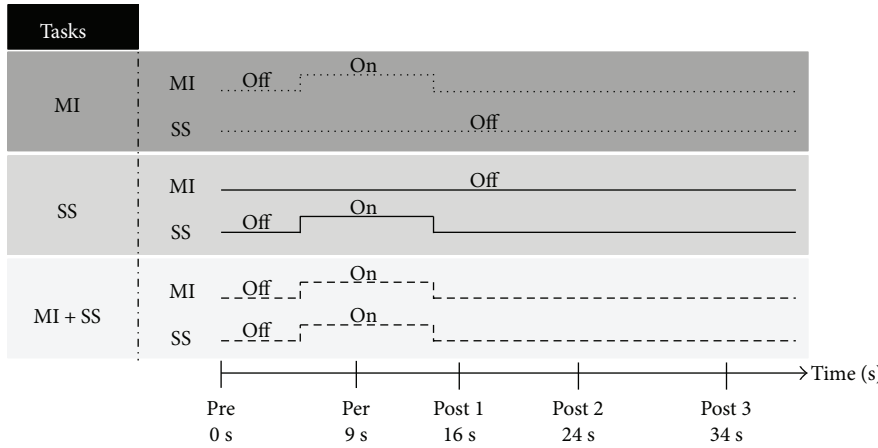

Figure 1: Experimental protocol of experiment 1. Transcranial magnetic stimulation and peripheral nerve stimulation were elicited at several stimulation times: 0, 9, 16, 24, and 34 seconds. Each trial lasted 45 seconds. During the motor imagery (MI) task, participants imagined a plantar-flexion contraction at 50% MVC for 9 s. During the somatosensory stimulation (SS) task, SS was applied for 9 s. During MI + SS, participants imagined the contraction when SS was applied.

distributed. The Likert scale score during MI and MI + SS was analyzed using a nonparametric Friedman ANOVA.

For both muscles, to ensure that muscles were relaxed, we used four nonparametric related samples Friedman's two-way ANOVAs by ranks with *stimulation* (Pre, Per, and Post 1) and *task* (MI, Rest) 100 ms before each stimulation artefact on EMG RMS/M_{max} ratios. We also analyzed MEP/M_{max} and H-reflex/M_{max} ratios with two nonparametric related samples Friedman's two-way ANOVAs by ranks with *stimulation* (Pre, Per, Post 1, Post 2, and Post 3) and *task* (MI, Rest). When appropriate, we used Wilcoxon's signed-rank tests for paired multiple comparisons applied with a Bonferroni correction.

For exp. 2, all variables were normally distributed for MG but not for SOL. We compared H-reflex ratios using nonparametric related samples Friedman's two-way ANOVAs by ranks for SOL. We used a two-way rmANOVA with *stimulation* (Pre, Per, and Post) and *task* (MI, Rest) for MG. When appropriate, we used Wilcoxon signed-rank tests or paired comparisons Bonferroni's tests, for SOL and MG muscles, respectively. Statistical analysis was performed with SPSS Statistics (2017 version, IBM). The level of significance was set at $p < 0.05$.

3. Results

3.1. Experiment 1. The vividness of MI, measured with a 7-point Likert scale, was not significantly different between all MI tasks ($\chi^2 = 6.94$, $p > 0.05$). The mean score was 5.3 ± 0.4 and 5.0 ± 0.2 for the MI and MI + SS tasks, respectively. This result ensured that modulations of MEP and H-reflex would not be attributed to the difficulty of task.

3.1.1. EMG Activity. The nonparametric related samples Friedman's two-way ANOVAs by ranks revealed an effect for SOL ($\chi^2 = 51.98$, $p < 0.01$ and $\chi^2 = 48.12$, $p < 0.01$ for TMS and PNS trials, resp.) and MG muscles ($\chi^2 = 35.88$, $p < 0.01$ and $\chi^2 = 33.27$, $p < 0.01$ for TMS and PNS trials, resp.). During SS and MI + SS tasks, SS increased background EMG at Per (for all, $p < 0.01$ compared to Pre and Post stimulations), without an extra increase when imagining ($p > 0.05$). During the MI task, EMG ratios were similar to those at rest (for all, $p > 0.05$). These results ensured that modulations of MEP and H-reflex amplitude would not be attributed to muscle activities (see Table 1).

3.1.2. Corticospinal Excitability. The first stimulation (Pre), induced at the beginning of each trial, was not significantly different between all tasks for both muscles (for all, $p > 0.05$). For MI, SS, and MI + SS, MEP amplitude for the first stimulation was $1.9 \pm 1.0\%$, $2.1 \pm 1.0\%$, and $1.9 \pm 0.8\%$ of M_{max}, respectively, for the SOL muscle and $2.9 \pm 1.5\%$, $3.5 \pm 2.0\%$, and $2.9 \pm 1.4\%$ of M_{max}, respectively, for the MG muscle.

For the SOL muscle, a typical trace of one participant was represented in Figure 2. The main results were illustrated in Figure 3(a). The nonparametric related samples Friedman's two-way ANOVA by ranks revealed an effect ($\chi^2 = 29.72$, $p = 0.008$). The Wilcoxon signed-rank tests demonstrated that MEPs increased when imagining with or without SS in comparison to the Pre test value, that is, baseline (at Per: $+106 \pm 140\%$, $p = 0.013$ and $+81 \pm 78\%$, $p = 0.026$, resp.). After imagining, MEPs returned to baseline from Post 1 for the MI task but not for the MI + SS task. Indeed, MEPs at Post 3 were still above baseline in this task. Note that MEP amplitude was not modulated during the SS task (all, $p > 0.05$).

For the MG muscle, a typical trace of one participant was represented in Figure 2. The main results were illustrated in Figure 3(c). The nonparametric related samples Friedman's two-way ANOVA by ranks revealed an effect ($\chi^2 = 30.82$, $p = 0.006$). The Wilcoxon signed-rank tests demonstrated that MEPs significantly increased when imagining in comparison to baseline (MI task, $+41 \pm 64\%$, $p = 0.041$; MI + SS task, $+84 \pm 66\%$, $p = 0.004$). Interestingly, MEP increase during MI + SS was marginally greater than that during MI alone ($p = 0.062$). After imagining, MEPs returned to

Table 1: Normalized EMG RMS (±SD) in experiment 1. RMS/M_{max} ratio is multiplied by 100 and recorded in SOL and MG muscles before (Pre), during (Per), and after (Post 1) motor imagery (MI), somatosensory stimulation (SS), and MI combined with SS (MI + SS) tasks. EMG RMS was measured 100 ms before each stimulation artefact. At Per, during SS and MI + SS (gray boxes), values significantly increased compared to that at Pre and Post 1 ($p < 0.05$).

		SOL			MG		
		Pre	Per	Post 1	Pre	Per	Post 1
MI	TMS	0.79 ± 0.31	0.84 ± 0.37	0.84 ± 0.38	1.6 ± 0.51	1.6 ± 0.47	1.6 ± 0.34
	PNS	0.84 ± 0.38	0.86 ± 0.39	0.84 ± 0.39	1.7 ± 0.56	1.6 ± 0.56	1.7 ± 0.60
SS	TMS	0.75 ± 0.31	5.4 ± 6.2	0.75 ± 0.28	1.6 ± 0.55	13.3 ± 21.9	1.5 ± 0.38
	PNS	0.94 ± 0.69	5.5 ± 6.2	0.95 ± 0.70	1.7 ± 0.56	14.0 ± 25.0	1.7 ± 0.60
MI + SS	TMS	0.79 ± 0.31	5.5 ± 6.2	0.80 ± 0.34	1.6 ± 0.60	13.9 ± 23.8	1.6 ± 0.57
	PNS	0.82 ± 0.33	5.6 ± 6.4	0.82 ± 0.36	1.6 ± 0.56	14.6 ± 26.1	1.6 ± 0.54

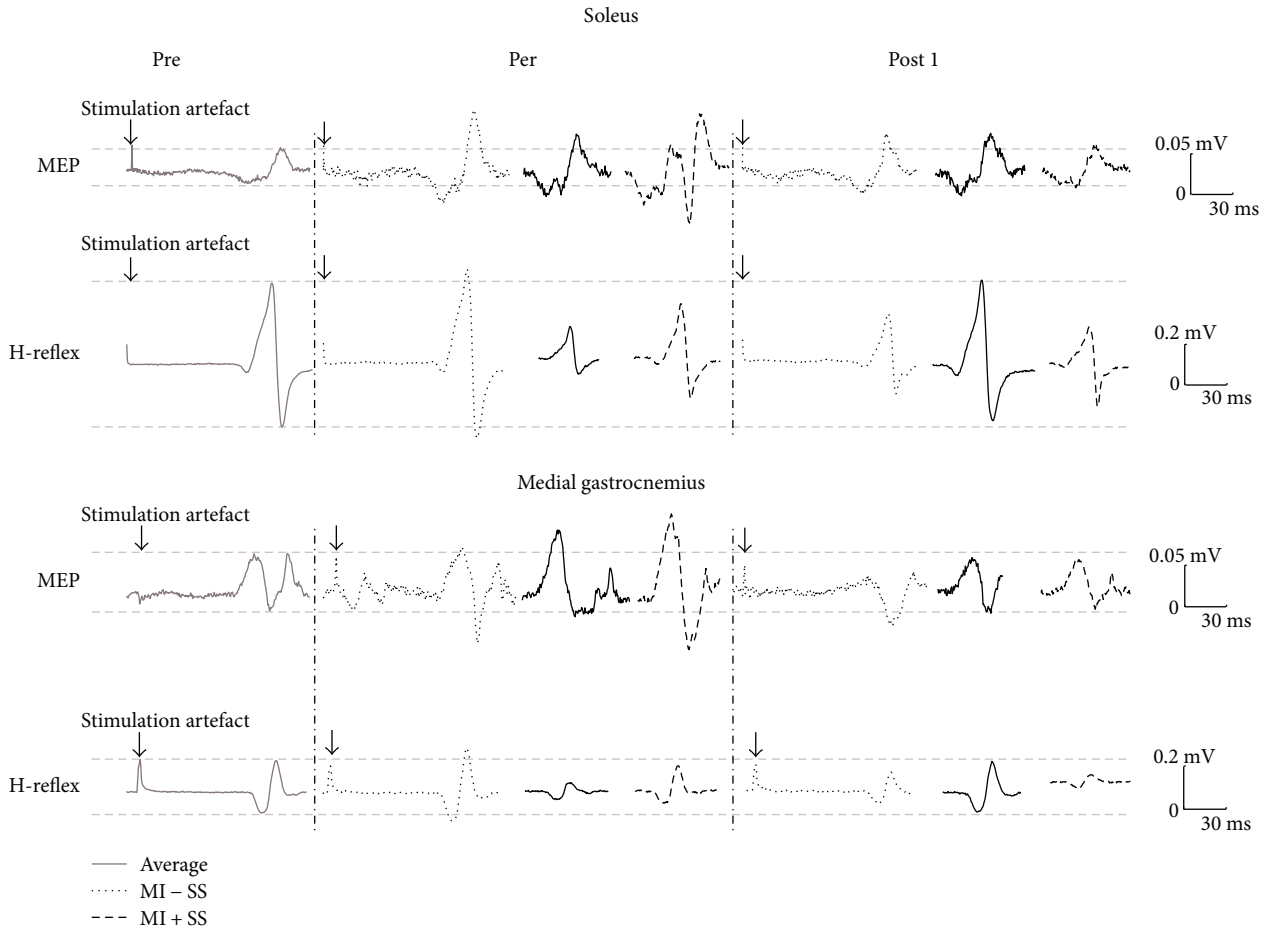

Figure 2: Typical subject. MEP and H-reflex mean responses at Pre, Per, and Post 1 stimulations during MI, SS, and MI + SS for SOL and MG muscles. For both muscles, MEP at Per, when imagining, were significantly greater in comparison to baseline. For MG muscle only, MEP amplitude tended to extra increase during MI + SS in comparison to MI alone. For both muscles, H-reflex at Per decreased during SS but not during the combination with MI.

baseline from Post 1 for the MI task (+15%±41%, $p > 0.05$) and at Post 3 for the MI + SS task (+13%±30%, $p > 0.05$). Note that MEP amplitude was not modulated during the SS task (all, $p > 0.05$).

3.1.3. Spinal Excitability. For both muscles, the first stimulation (Pre), applied at the beginning of each trial, did not differ between tasks (for all, $p > 0.05$). For MI, SS, and MI+SS tasks, H-reflex amplitude for the first stimulation was 12.7 ± 12.2%,

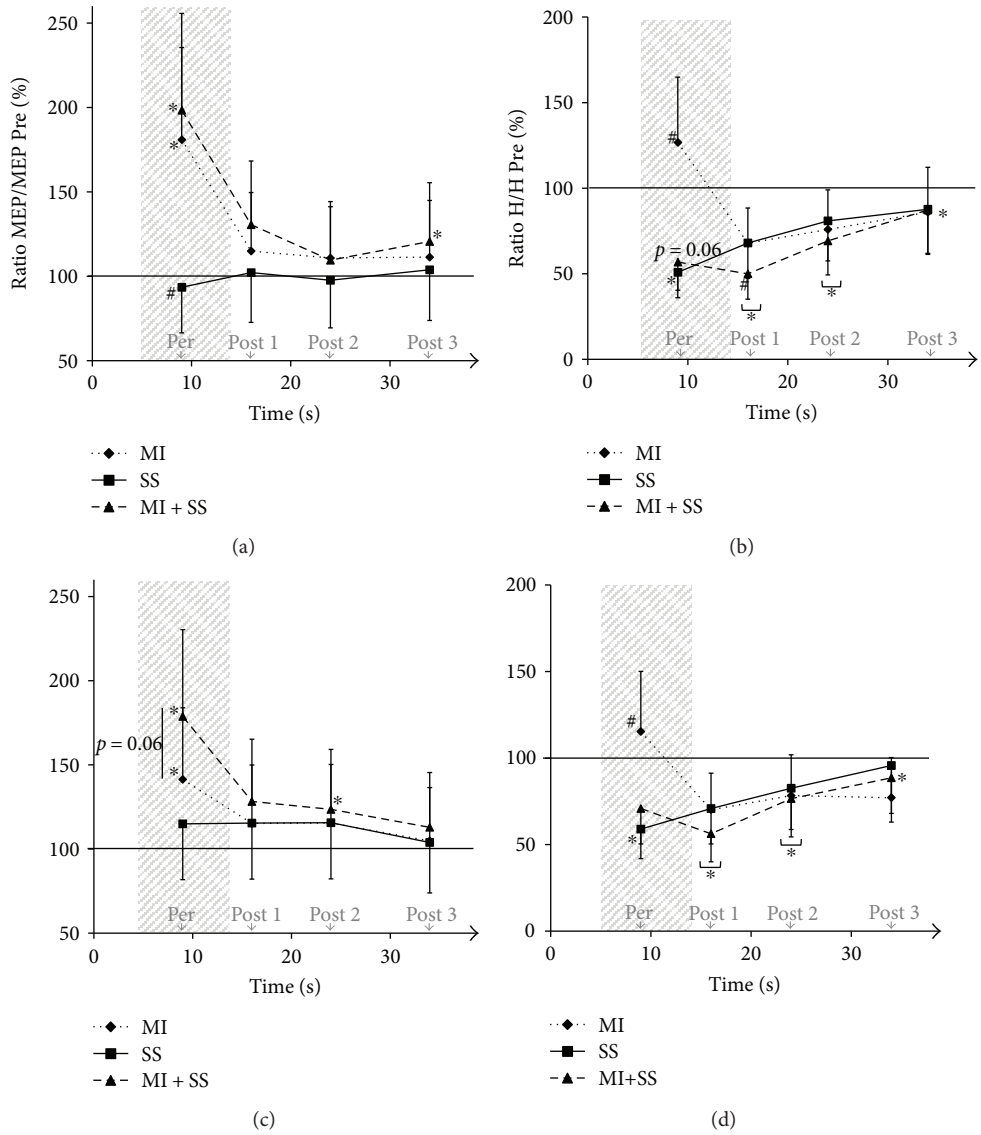

Figure 3: Normalized MEP and H-reflex amplitude. Values recorded in SOL (a and b) and MG (c and d) muscles. MEP amplitude increased when imagining (MI and MI + SS at Per). H-reflex amplitude decreased with SS (SS and MI + SS at Per) and progressively returned to baseline, except for MI + SS. *Significantly different from Pre test (baseline). #Significantly different from other conditions at the same stimulation time.

$14.4 \pm 10.0\%$, and $11.0 \pm 6.1\%$ of M_{max}, respectively, for the SOL muscle and $8.9 \pm 8.9\%$, $8.4 \pm 6.1\%$, and $6.9 \pm 5.4\%$ of M_{max}, respectively, for the MG muscle.

For the SOL muscle, a typical H-reflex trace of one participant was represented in Figure 2. The main results were illustrated in Figure 3(b). The nonparametric related samples Friedman's two-way ANOVA by ranks revealed an effect ($\chi^2 = 44.93$, $p < 0.001$). The Wilcoxon signed-rank tests demonstrated that H-reflex amplitude at Per was significantly depressed in comparison to baseline when SS was applied alone (SS task: $-52 \pm 54\%$, $p = 0.021$) and almost depressed when SS was combined with MI (MI + SS task: $-47 \pm 48\%$, $p = 0.062$). At Post 1 and 2, H-reflex was still depressed and returned to baseline at Post 3 for the SS task ($-12 \pm 27\%$, $p > 0.05$) but not for MI + SS ($-13\% \pm 20\%$, $p = 0.006$). Note that H-reflex amplitude was not modulated during MI ($p > 0.05$).

For the MG muscle, a typical H-reflex trace of one participant was represented in Figure 2. The main results were illustrated in Figure 3(d). The nonparametric related samples Friedman's two-way ANOVA by ranks revealed an effect ($\chi^2 = 32.67$, $p < 0.01$). The Wilcoxon signed-rank tests demonstrated that H-reflex amplitude at Per was depressed when SS was applied alone (SS task: $-41 \pm 42\%$, $p = 0.050$) but not when SS was combined with MI (MI + SS task: $-30 \pm 58\%$, $p > 0.05$). At Post 1 and 2, H-reflex was still depressed, but returned to baseline at Post 3 for SS ($-4\% \pm 19\%$, $p > 0.05$) but not for MI + SS ($-11\% \pm 26\%$, $p = 0.016$). Note that H-reflex amplitude was not modulated during MI ($p > 0.05$).

For both muscles, the results demonstrated a decrease of H-reflex amplitude at Post 1 in all conditions. For MI + SS and SS alone, this decrease may be due to the stimulation frequency, inducing homosynaptic post activation depression (HPAD) related to the repetitive stimulation of afferent fibers. However, after MI alone, this decrease may be related to a stimulation effect at Per and/or a condition effect. Experiment 2 was designed to examine the influence of successive PNS and condition effects on H-reflex amplitude.

3.2. Experiment 2. The main results of exp. 2 were illustrated in Figures 4(a) and 4(b), for the SOL and MG muscles, respectively.

For the SOL muscle, the nonparametric related samples Friedman's two-way ANOVA by ranks revealed an effect ($\chi^2 = 11.93$, $p < 0.05$). The Wilcoxon signed-rank tests showed that H-reflex amplitudes at Per and at Post were depressed in comparison to baseline when participants were at rest ($-11 \pm 10\%$, $p = 0.036$ and $-13 \pm 18\%$, $p = 0.017$, resp.). For the MI task, H-reflex at Per, that is, when imagining, almost increased compared to baseline ($+13 \pm 28\%$, $p = 0.069$) and was not different from baseline at Post ($-14\% \pm 19\%$, $p > 0.05$).

For the MG muscle, the rmANOVA revealed an interaction between *stimulation* and *task* ($F_{1,7} = 9.24$, $p = 0.003$). Bonferroni's post hoc test revealed that H-reflex amplitudes at Per, that is, when imagining, and at Post were not significantly modulated in comparison to baseline (MI task: $+12.8 \pm 13.9\%, p > 0.05; -8\% \pm 11\%, p > 0.05$, resp.). Note that H-reflex for the rest task was not modulated ($p > 0.05$).

4. Discussion

This study was designed to investigate how MI combined with SS modulated corticospinal and spinal excitabilities. The results confirmed that corticospinal excitability increased during MI and MI + SS but not during SS. During MI + SS, MEP amplitude was almost greater than that during MI alone, for MG muscle. On the contrary, spinal excitability was sensitive to SS, during which H-reflex was depressed. However, it was not modulated during MI associated or not with SS. Interestingly, the modulation of corticospinal and spinal excitabilities was muscle dependent.

4.1. Corticospinal Excitability. For both muscles, MEP amplitude only increased when participants imagined the plantar-flexion contractions, and not after imagining, which confirms that MI modulates CSE in a temporal-specific manner [20–23].

MEP amplitude during SS was similar to that at rest, showing that the excitatory afferent inputs induced by SS did not affect the corticomotoneuronal transmission efficacy. This result is in accordance with previous studies that applied a short SS duration below the motor threshold [24]. Other experiments using a longer SS duration showed an increase of MEP amplitude [25–28]. Therefore, it appears that the duration of SS seems to play a crucial role to modulate CSE.

MI associated with SS had a tendency to increase CSE to a greater extent in comparison to MI only for MG muscle. This finding may be due to an increase of afferent inputs into M1 at the time of the stimulation. Indeed, through afferent inputs, SS activates the somatosensory cortex (S1), which can mediate the primary motor cortex (M1) activity leading to increased CSE [13, 29]. However, CSE was not modulated by the SS alone, suggesting that SS must be combined with MI to facilitate the interactions between M1 and S1. An alternative explanation would involve the interaction of MI and SS at the spinal level. Grosprêtre et al. [4] recently showed that MI induces a subliminal motor command that modulates the influence of the afferent input to motoneurons at the spinal level, via primary afferent depolarizing interneurons. This interaction likely modulates CSE. The tendency for CSE to increase was not observed for the SOL muscle, suggesting that the difference with the MG muscle could be explained by the amount of afferent inputs recruited during SS at the spinal level.

4.2. Spinal Excitability. For both muscles, our results confirmed that spinal excitability was not modulated when imagining [4].

During SS, spinal excitability was depressed. It was demonstrated that the repetition of stimulations decreased the H-reflex amplitude [17] due to a smaller neurotransmitter amount available at the Ia afferent-alpha motoneuron synapse [16]. These inhibitions may originate from the homosynaptic post activation depression effect, the primary afferent depolarization effect, and/or the refractory period of Ia-afferent neurons [30].

When associating MI and SS, the spinal excitability of MG was no longer depressed from baseline. For the SOL muscle, the spinal excitability was less reduced in comparison to SS alone. It seems likely that MI may compensate the inhibitory effects induced by SS. The different behavior between the two muscles could be explained by the amount of afferent inputs recruited during SS. This hypothesis is supported by a lower quantity of neuromuscular spindles in the MG than in the SOL muscle [31, 32] inducing less presynaptic inhibition at the spinal level when SS is applied [33, 34]. Therefore, the subliminal motor command generated during MI that reaches the spinal level [4, 31] may compensate to a greater extent the transmission efficiency between Ia-afferents and motoneurons in the MG muscle. This was observed by a greater reduction of inhibition during MI + SS in this muscle, in comparison to the SOL muscle (Figures 3(b) and 3(d)).

Note that spinal excitability was depressed at posttest right after each task and progressively returned to baseline values. This reduction may be due to successive stimulations elicited to induce H-reflexes and especially to the interstimulation interval, that is, less than 10 seconds inducing presynaptic inhibitions at the spinal level [17]. Indeed, the results of experiment 2 demonstrated that, while participants stayed at rest, the spinal excitability was depressed at Per and Post stimulations in comparison to baseline, with an interstimulus interval of 9 seconds and 7 seconds, respectively. Interestingly, we observed, in experiment 1, a greater decrease of spinal excitability for the MI + SS task at Post 1, that is, right after the task. This greater reduction in the amplitude of

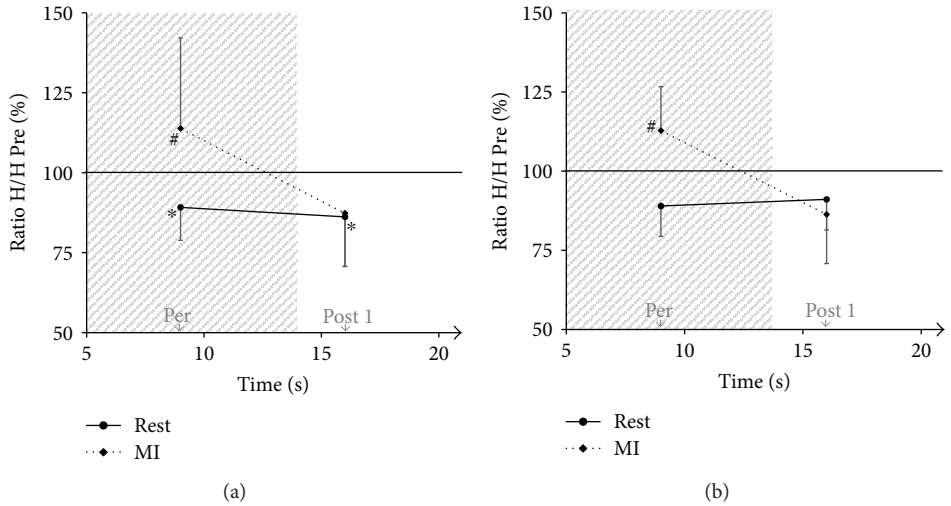

Figure 4: Normalized H-reflex amplitude. Values for SOL (a) and MG (b) muscles. At rest, H-reflex amplitude decreased at Per and Post 1 for the SOL but not for the MG. During the MI task, H-reflex amplitude was not modulated for both muscles. *Significantly different from Pre test (baseline). #Significantly different from other conditions at the same stimulation time.

the H-reflex after MI + SS may be related to the fact that MI compensates for SS-related inhibitions by reducing presynaptic inhibitions. This mechanism may induce a greater release of neurotransmitters, resulting in a reduction in the amount of neurotransmitters available to respond to Post 1 stimulation versus MI and SS tasks alone.

5. Conclusion

The combination of MI and SS exacerbated the effect of MI on corticospinal and spinal excitabilities depending on the afferent inputs elicited by SS at the spinal level. The results of this study were obtained during a single session when the participants were voluntarily engaged in the imagery task with or without SS. We know that MI training or repetitive somatosensory stimulation increases motor performance, specifically muscle strength. It would be of interest to test whether the repetition of the combination of MI and SS facilitates motor performance in comparison to MI and SS alone and to understand the underlying mechanisms.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] J. Decety, "The neurophysiological basis of motor imagery," *Behavioural Brain Research*, vol. 77, no. 1-2, pp. 45–52, 1996.

[2] E. Gerardin, A. Sirigu, S. Lehéricy et al., "Partially overlapping neural networks for real and imagined hand movements," *Cerebral Cortex*, vol. 10, no. 11, pp. 1093–1104, 2000.

[3] M. Lotze, P. Montoya, M. Erb et al., "Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study," *Journal of Cognitive Neuroscience*, vol. 11, no. 5, pp. 491–501, 1999.

[4] S. Grosprêtre, F. Lebon, C. Papaxanthis, and A. Martin, "New evidence of corticospinal network modulation induced by motor imagery," *Journal of Neurophysiology*, vol. 115, no. 3, pp. 1279–1288, 2016.

[5] C. Ruffino, C. Papaxanthis, and F. Lebon, "Neural plasticity during motor learning with motor imagery practice: review and perspectives," *Neuroscience*, vol. 341, pp. 61–78, 2017.

[6] A. D. Fourkas, V. Bonavolontà, A. Avenanti, and S. M. Aglioti, "Kinesthetic imagery and tool-specific modulation of corticospinal representations in expert tennis players," *Cerebral Cortex*, vol. 18, no. 10, pp. 2382–2390, 2008.

[7] C. M. Stinear, W. D. Byblow, M. Steyvers, O. Levin, and S. P. Swinnen, "Kinesthetic, but not visual, motor imagery modulates corticomotor excitability," *Experimental Brain Research*, vol. 168, no. 1-2, pp. 157–164, 2006.

[8] N. Mizuguchi, M. Sakamoto, T. Muraoka et al., "Influence of somatosensory input on corticospinal excitability during motor imagery," *Neuroscience Letters*, vol. 514, no. 1, pp. 127–130, 2012.

[9] M. Reiser, D. Büsch, and J. Munzert, "Strength gains by motor imagery with different ratios of physical to mental practice," *Frontiers in Psychology*, vol. 2, p. 194, 2011.

[10] K. Saito, T. Yamaguchi, N. Yoshida, S. Tanabe, K. Kondo, and K. Sugawara, "Combined effect of motor imagery and peripheral nerve electrical stimulation on the motor cortex," *Experimental Brain Research*, vol. 227, no. 3, pp. 333–342, 2013.

[11] F. Kaneko, T. Hayami, T. Aoyama, and T. Kizuka, "Motor imagery and electrical stimulation reproduce corticospinal excitability at levels similar to voluntary muscle contraction," *Journal of NeuroEngineering and Rehabilitation*, vol. 11, no. 1, p. 94, 2014.

[12] V. Di Lazzaro and U. Ziemann, "The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex," *Frontiers in Neural Circuits*, vol. 7, p. 18, 2013.

[13] M. P. Veldman, I. Zijdewind, S. Solnik et al., "Direct and crossed effects of somatosensory electrical stimulation on motor learning and neuronal plasticity in humans," *European Journal of Applied Physiology*, vol. 115, no. 12, pp. 2505–2519, 2015.

[14] D. F. Collins, D. Burke, and S. C. Gandevia, "Sustained contractions produced by plateau-like behaviour in human motoneurones," *The Journal of Physiology*, vol. 538, no. 1, pp. 289–301, 2002.

[15] J. Duclay, B. Pasquet, A. Martin, and J. Duchateau, "Specific modulation of corticospinal and spinal excitabilities during maximal voluntary isometric, shortening and lengthening contractions in synergist muscles," *The Journal of Physiology*, vol. 589, no. 11, pp. 2901–2916, 2011.

[16] C. Aymard, R. Katz, C. Lafitte et al., "Presynaptic inhibition and homosynaptic depression: a comparison between lower and upper limbs in normal human subjects and patients with hemiplegia," *Brain*, vol. 123, no. 8, pp. 1688–1702, 2000.

[17] E. P. Zehr, "Considerations for use of the Hoffmann reflex in exercise studies," *European Journal of Applied Physiology*, vol. 86, no. 6, pp. 455–468, 2002.

[18] J. Magladery and D. McDougal, "Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibres," *Bulletin of the Johns Hopkins Hospital*, vol. 86, no. 5, pp. 265–290, 1950.

[19] S. Bestmann and J. W. Krakauer, "The uses and interpretations of the motor-evoked potential for understanding behaviour," *Experimental Brain Research*, vol. 233, no. 3, pp. 679–689, 2015.

[20] S. Grosprêtre, C. Ruffino, and F. Lebon, "Motor imagery and cortico-spinal excitability: a review," *European Journal of Sport Science*, vol. 16, no. 3, pp. 317–324, 2015.

[21] L. Fadiga, G. Buccino, L. Craighero, L. Fogassi, V. Gallese, and G. Pavesi, "Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study," *Neuropsychologia*, vol. 37, no. 2, pp. 147–158, 1999.

[22] C. M. Stinear and W. D. Byblow, "Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability," *Clinical Neurophysiology*, vol. 114, no. 5, pp. 909–914, 2003.

[23] F. Lebon, W. D. Byblow, C. Collet, A. Guillot, and C. M. Stinear, "The modulation of motor cortex excitability during motor imagery depends on imagery quality," *The European Journal of Neuroscience*, vol. 35, no. 2, pp. 323–331, 2012.

[24] T. Hortobagyi, J. L. Taylor, N. T. Petersen, G. Russell, and S. C. Gandevia, "Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans," *Journal of Neurophysiology*, vol. 90, no. 4, pp. 2451–2459, 2003.

[25] L. S. Chipchase, S. M. Schabrun, and P. W. Hodges, "Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study," *Archives of Physical Medicine and Rehabilitation*, vol. 92, no. 9, pp. 1423–1430, 2011.

[26] M. C. Ridding, B. Brouwer, T. S. Miles, J. B. Pitcher, and P. D. Thompson, "Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects," *Experimental Brain Research*, vol. 131, no. 1, pp. 135–143, 2000.

[27] M. C. Ridding, D. R. McKay, P. D. Thompson, and T. S. Miles, "Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans," *Clinical Neurophysiology*, vol. 112, no. 8, pp. 1461–1469, 2001.

[28] D. McKay, R. Brooker, P. Giacomin, M. Ridding, and T. Miles, "Time course of induction of increased human motor cortex excitability by nerve stimulation," *Neuroreport*, vol. 13, no. 10, pp. 1271–1273, 2002.

[29] M. P. Veldman, N. A. Maffiuletti, M. Hallett, I. Zijdewind, and T. Hortobágyi, "Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans," *Neuroscience and Biobehavioral Reviews*, vol. 47, pp. 22–35, 2014.

[30] J. C. Dean, J. M. Clair-Auger, O. Lagerquist, and D. F. Collins, "Asynchronous recruitment of low-threshold motor units during repetitive, low-current stimulation of the human tibial nerve," *Frontiers in Human Neuroscience*, vol. 8, p. 1002, 2014.

[31] K. J. Tucker and K. S. Türker, "Muscle spindle feedback differs between the soleus and gastrocnemius in humans," *Somatosensory & Motor Research*, vol. 21, no. 3-4, pp. 189–197, 2004.

[32] K. J. Tucker, M. Tuncer, and K. S. Türker, "A review of the H-reflex and M-wave in the human triceps surae," *Human Movement Science*, vol. 24, no. 5-6, pp. 667–688, 2005.

[33] S. Grosprêtre and A. Martin, "H reflex and spinal excitability: methodological considerations," *Journal of Neurophysiology*, vol. 107, no. 6, pp. 1649–1654, 2012.

[34] J. Duclay and A. Martin, "Evoked H-reflex and V-wave responses during maximal isometric, concentric, and eccentric muscle contraction," *Journal of Neurophysiology*, vol. 94, no. 5, pp. 3555–3562, 2005.

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Research Article

Functional Role of Internal and External Visual Imagery: Preliminary Evidences from Pilates

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The present study investigates whether a functional difference between the visualization of a sequence of movements in the perspective of the first- (*internal* VMI-I) or third- (*external* VMI-E) person exists, which might be relevant to promote learning. By using a mental chronometry experimental paradigm, we have compared the time or execution, imagination in the VMI-I perspective, and imagination in the VMI-E perspective of two kinds of Pilates exercises. The analysis was carried out in individuals with different levels of competence (expert, novice, and no-practice individuals). Our results showed that in the Expert group, in the VMI-I perspective, the imagination time was similar to the execution time, while in the VMI-E perspective, the imagination time was significantly lower than the execution time. An opposite pattern was found in the Novice group, in which the time of imagination was similar to that of execution only in the VMI-E perspective, while in the VMI-I perspective, the time of imagination was significantly lower than the time of execution. In the control group, the times of both modalities of imagination were significantly lower than the execution time for each exercise. The present data suggest that, while the VMI-I serves to train an already internalised gesture, the VMI-E perspective could be useful to learn, and then improve, the recently acquired sequence of movements. Moreover, visual imagery is not useful for individuals that lack a specific motor experience. The present data offer new insights in the application of mental training techniques, especially in field of sports. However, further investigations are needed to better understand the functional role of internal and external visual imagery.

1. Introduction

Sport psychology has shown that in order to achieve a favorable outcome in sport, it is necessary to integrate physical and mental practice [1, 2]. In this line of thinking, motor imagery (MI) has been studied extensively since it represents a potentially effective mean to promote learning [3, 4]. MI is defined as the mental execution of a movement, motor act, or action, without any overt movement or muscle activation [5–8] and represents a cognitive tool strategically used by athletes for optimizing their specific motor skills [9]. To underline how the two processes, physical and mental, are related, several studies showed that changes in physiological parameters, such as vegetative indices, are similar during MI and during execution [10–12]. Furthermore, neuroimaging data have demonstrated that the imagined and actual movements are functionally equivalent in the sense they share the same neural circuitry

[13–15]. It could be hypothesized that such neural circuitry might underlie the improvements in movement efficiency induced by MI, allowing athletes to improve the level of performance [16, 17].

A modality of MI is represented by visuomotor imagery (VMI) that involves the visualization of a movement or a sequence of movements from the first- (*internal* VMI-I) or third- (*external* VMI-E) person perspective [18]. In the VMI-I perspective, the subjects imagine themselves from the same viewpoint experienced in the encoding phase [19, 20]. This perspective is greatly affected by the kinaesthetic features of the gesture and refers to the centredness of one's own multimodal experiential space upon one's own body, thus operating in an egocentric reference frame [21]. Conversely, the VMI-E perspective requires individuals to imagine themselves or others from an external point of view, observing the gesture as an onlooker [3, 19, 22]. In this modality, the subjects imagine the environment as well, the "background" of the scene, thus operating in an allocentric reference frame. The VMI-E perspective is considered to be a more complex mental process than the VMI-I perspective, because allocentric operations have to be integrated within the egocentric coordinates of the subject that is imagining, hence requiring an additional mental process [18].

In the last years, a much debated issue in sport psychology is whether internal or external VMI would be more efficient for athletes. Despite the multitude of studies present in the literature, this issue has not been investigated systematically. Namely, most of the research has focused either on specific types of sports, that is, open skill sport (such as karate, in which the participants fight in an environment that is changing rapidly) versus closed skill sport (such as gymnastics, in which the athletes perform in a relatively static environment) [23, 24], or on the level of competence of the athletes (i.e., experts versus novices) [25, 26]. Moreover, in the previous literature, the choice of the imagination perspective was based upon the athlete's preference (e.g., [27]).

From all these studies, several conflicting evidences can be drawn. With regard to the comparison between open skill sports and closed skill sports, it is shown that the VMI-E perspective is more used than VMI-I in open skill sports [18], while closed skill sport benefits from the VMI-I perspective [28, 29]. Such results are irrespective of the level of competence of the athletes. Moreover, the athletes specialized in open skill sport possess a high ability for mental processes and a better performance in the VMI-E perspective as compared to closed sport athletes [18]. These data could be explained by the notion that in open skill sports, the athletes move in environments that are rapidly changing and the VMI-E perspective includes such environments (e.g., opponents moving around). Other studies, based on the athlete's imagery preference, counteract these evidences. For example, it has been reported that athletes specialized in closed skill sport (e.g., golf) employed more imagery than those who participate in open sports (e.g., tennis and basketball) [30]. For what concerns the competence levels of the athletes, although imagery processes significantly help both novice and experienced athletes, the effects appear to be more pronounced for elite athletes [22, 25, 26], as demonstrated in studies with Olympic athletes [31–33]. To this regard, it has been highlighted that elite athletes, as compared to amateurs, had higher levels of imagery ability [27, 34, 35]. These data could be explained by the fact that elite athletes have had more opportunities to put into action imagery practice than lower level athletes [36, 37].

In the present study, we focused on the functional differences between internal and external perspectives, covering the issue from a different point of view. We set out to verify whether the two types of imagination improve different, yet integrated, cognitive-motor abilities in a closed skill discipline. This choice allows studying the VMI-E perspective in the contest of closed skill activities, differently from previous studies. Such an approach was chosen in order to study both perspectives separately, regardless of the specific kind of sport (closed or open skill).

In particular, we hypothesize that, while the VMI-I perspective revises a sequence of movements already internalised, the VMI-E perspective should be useful to learn, and improve, a recently acquired sequence of movements.

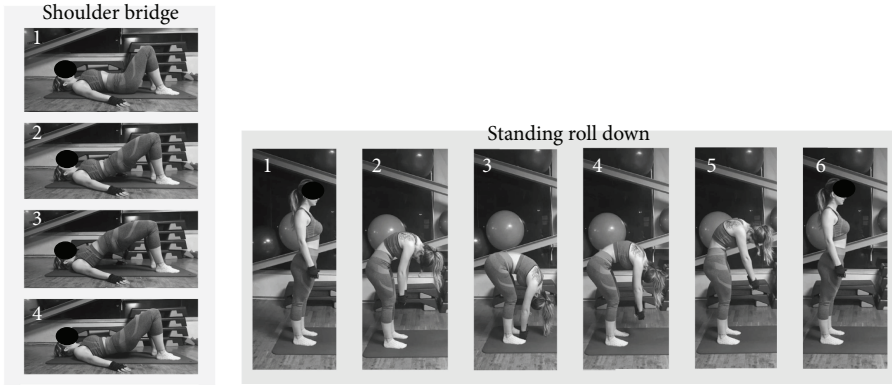
To address this issue, we used a mental chronometry paradigm in order to compare the time of execution of two Pilates exercises with the time of imagination of the same exercises in both VMI-I and VMI-E perspectives. Such experiment was carried out in individuals with different levels of competence (experts versus novices). As a control group, we analysed the execution and imagination time in individuals who had never practiced nor seen Pilates before.

We have chosen Pilates because it is a closed skill discipline, very much based on kinaesthetic features and practiced in stable and predictable conditions. Moreover, unlike other studies, we did not ask the participants to choose the modality of imagination they prefer, but we let them use both perspectives.

2. Materials and Methods

2.1. Participants. Forty-eight women (32 practicing Pilates, 16 not practicing Pilates) aged 24–58 years (mean age: 38.75 ± 11.25) participated in the study. According to their level of experience in the practice of Pilates, the participants were divided into 3 groups, each consisting of 16 women: *Expert group* (mean age: 39.25 ± 10.23), women who practiced Pilates regularly twice a week for the last twelve months at least; *Novice group* (mean age: 39.25 ± 12.82), women who started practicing Pilates no more than two months before the study; *no-Practice group* (mean age: 37.75 ± 11.2), women who have never practiced Pilates. We assessed through an informative questionnaire that women belonging to the *no-Practice group* had never seen a Pilates lesson or video or books showing Pilates. It is important to underline that, in order to perform Pilates correctly, it is essential to be aware of many aspects (motor control, breathing, etc.; see next paragraph) and that the knowledge of the sequence of movements to be performed is not enough. For this reason, the ones who have never practiced Pilates could not perform it correctly solely by imitation.

All participants did not have cardiovascular, neurological, or orthopaedic disorders and gave their written informed



(a) (b)

Figure 1: Sequences of the two Pilates exercises. (a) The shoulder bridge (SB) exercise: the individual lifts the pelvis whilst controlling breathing. Phase 1: start from the decubitus-supine position (1). Phase 2: the subject exhales. Then, the entire spine (vertebra by vertebra) is rolled up, until the weight is placed on the shoulder blades (2). Phase 3: the individual breathes in and holds still (3). Phase 4: while exhaling, the subject unrolls the spine (vertebra by vertebra) back to the starting position (4). (b) The standing roll down (SRD) exercise: the individual rolls down the spine, vertebra by vertebra, while controlling breathing. Phase 1: standing position with both legs extended at hip distance (1). Phase 2: the subject exhales and, starting from the cervical spine, rolls the whole spine (vertebra by vertebra), until the nose is at navel level (2). Phase 3: the individual inhales, relaxes, and abduces the shoulder blades, then exhales and moves the pelvis slightly forward, continuing to roll the vertebrae until the fingers touch the ground (3). Phase 4: the individual exhales and starts to unroll the spine vertebra by vertebra, beginning from the lumbar spine (4). Phase 5: the individual continues to unroll the spine, concentrating on the dorsal spine, keeping the arms relaxed (5). Phase 6: the individual returns to the starting position (6).

consent. They were recruited in sporting centres located in South Italy.

The study was conducted according to the 1964 Declaration of Helsinki.

2.2. Pilates Method and Exercises Chosen. Before considering the chosen exercises, it is appropriate to explain what Pilates is, designed by Joseph Pilates (1883–1967). Pilates is a type of discipline that pays great attention to self-awareness and to the pursuit of both physical and mental balance. It can be considered as a closed skill activity because the subjects perform the movements under a static and predictable environment. In particular, Pilates aimed at getting to know one's body and achieve its full acceptance. Through the improvement of concentration, breathing, balance, control, precision, and fluidity of movement, the individuals earn greater awareness of themselves, of their body, and of every single motor gesture.

For all these characteristics, Pilates is useful for studying the two types of perspectives of imagination. To this aim, we have chosen two classical Pilates exercises of different difficulty: shoulder bridge (SB) and standing roll down (SRD) (Figure 1).

Although both exercises require concentration, breathing, balance, control, precision, and fluidity of movement during execution, SRD is considered more difficult than SB [38]. In particular, SRD is performed standing and starts by flexing the neck down followed by rolling down of the spine, vertebra by vertebra, preventing flexion of the trunk forward, and back to the initial position rolling out the column gradually. Instead, SB is performed in the supine position with the knees bent and arms along the body, starting with the retroversion of the pelvis and its upwards climb, vertebra by vertebra, and return to the starting position (Figure 1). Moreover, SRD necessitates good flexibility by the performer, and therefore, a physical impediment, such as visceral fat, can mechanically limit the movements.

2.3. Experimental Procedure. After the demonstration offered by the instructor, the experimental procedure consisted of 3 phases (VMI-I, VMI-E, and execution) repeated for both Pilates exercises (SB and SRD) in all the 3 groups of participants. The imagination phases (VMI-I and VMI-E) were performed in random order in the same day and separated by at least thirty minutes. However, the execution phase was performed 3 days after the imagination phases, so as not to create influences between imagination and execution. The entire experiment was completed in two consecutive weeks. The procedure is summarized in Table 1, while Figure 1 shows an example of the two different exercises.

In the demonstration, the instructor showed the randomly chosen exercise (SRD or SB) individually to each participant. Subsequently (first and second phases), the participants had to image in VMI-I or in VMI-E the exercise that had been previously shown by the instructor. The order of the two modalities of imagination was randomized within subjects. In both conditions, the participants were asked to close their eyes from the beginning to the end of the imagined exercise to guarantee the highest possible correspondence to physical exercise.

Finally, after 3 days, in the execution phase (third phase), the participants performed the exercise.

The following week, all participants repeated the entire procedure for the other exercise.

All participants did a single repetition in order not to create further learning of the exercise during the imagination phase.

Table 1: Experimental procedure. Each participant started randomly with either shoulder bridge or standing roll down.

Demonstration	Pause	Phase 1	Pause	Phase 2	Interval	Phase 3
Shoulder bridge (SB)						
The instructor shows the SB exercise.	30 min	VMI-I perspective: imagine performing SB with closed eyes and with the body in the starting position (supine position)	30 min	VMI-E perspective with closed eyes: imagine the instructor performing SB starting from the initial position (supine position)	3 days	Execution: all participants performed the SB exercise
Standing roll down (SRD)						
The instructor shows the SRD exercise.	30 min	VMI-I perspective: imagine performing SRD with closed eyes and with the body in the starting position (standing position)	30 min	VMI-E perspective with closed eyes: imagine the instructor performing SRD starting from the initial position (standing position)	3 days	Execution: all participants performed the SRD exercise

The times of imagination (in seconds) were compared with those of execution.

2.4. Chronometer Features. Imagination and execution times were measured using a commercial digital stopwatch (Samsung Galaxy S4). The participants received instructions for the use of the stopwatch before the imagination task, in which they had to start and stop the clock on their own. In particular, they pointed the finger on the display, closed the eyes, said "go," and, at the same time, activated the stopwatch. To control that the registration was done correctly, even the experimenter recorded the times. In the execution task, the stopwatch was used only by the experimenter.

The times recorded have been measured in seconds.

2.5. Statistical Analysis. The recorded data were first tested for normality (Shapiro–Wilk's test) and homoscedasticity (Levene's test) and then analysed by a three-way mixed-model analysis of variance (ANOVA): group (Expert, Novice, and no-Practice) × condition (VMI-I perspective, VMI-E perspective, and execution) × exercise (SRD, SB); post hoc analysis for multiple comparisons (Duncan's test) have been calculated when appropriate. Differences were considered significant at the $P < 0.05$ level. Time in seconds has been used as a dependent variable.

3. Results and Discussion

As shown in Figures 2(a) and 2(b) and in Table 2, in the VMI-I, the Expert group needed the same time to imagine and perform both the Pilates exercises, while in the VMI-E, it took them less time to imagine than to perform both exercises. An opposite pattern was found in the Novice group, in which a significant time difference was present between VMI-I imagination and execution, in both exercises. In particular, it took them less time to imagine than to perform both exercises in VMI-I, while the same time was needed for imagination and for the execution in VMI-E. In the no-Practice group, both modalities of imagination for each exercise required a significantly lower time than the execution.

The present data evidenced that each modality of imagination is related to a different level of motor experience.

More specifically, the ANOVA revealed a statistically significant main effect for group ($F_{(2,45)} = 5.08$; $P = 0.01$). Post hoc comparisons showed that the Expert group differed significantly from the other two groups, while the Novice and no-Practice groups were similar (Expert versus Novice: $P = 0.009$; Expert versus no-Practice: $P = 0.01$; Novice versus no-Practice: $P = 0.94$). Also, the condition factor showed a significant main effect ($F_{(2,90)} = 54.94$; $P = 0.00001$). Post hoc comparisons showed that each condition was significantly different from the others (VMI-I versus VMI-E perspective: $P = 0.02$; VMI-I perspective versus execution: $P = 0.01$; VMI-E perspective versus execution: $P = 0.0001$). Finally, the types of exercise were statistically different ($F_{(1,45)} = 25.71$; $P = 0.00001$), with SRD requiring more time (10.71 ± 2.12) than SB (9.02 ± 0.83). The second-order interaction was also significant ($F_{(4,90)} = 5.68$; $P = 0.0004$), and the relative post hoc comparisons are shown in Figure 2. Furthermore, the interactions group × condition ($F_{(4,90)} = 23.81$, $P = 0.00001$) and exercise × condition ($F_{(2,90)} = 5.19$, $P = 0.007$) resulted to be statistically significant.

From these results, different conclusions can be drawn, in line with our hypothesis. In fact, we asked ourselves whether the two types of visuomotor imagery could have a different role in promoting learning and could have different applications in sport.

The similar times of VMI-I and execution and the dissimilar times of VMI-E and execution in experts (Figure 2 and Table 2) suggest that the level of motor competence induces a mental representation of the gesture. Such evidence is in line with Jeannerod [15] who underlined that to successfully employ VMI-I, it is necessary to have well-developed motor representations. It was then proposed that VMI-I might better suited for high-competence athletes [32]. Furthermore, VMI-I could be considered as a sort of "readiness for action" [39]. To this regard, it has been reported that VMI-I produces an increased electrical activity in muscles involved in the imagined activity with respect to VMI-E [40]. Conversely, the similar times of VMI-E and execution and the dissimilar times of VMI-I perspective and execution

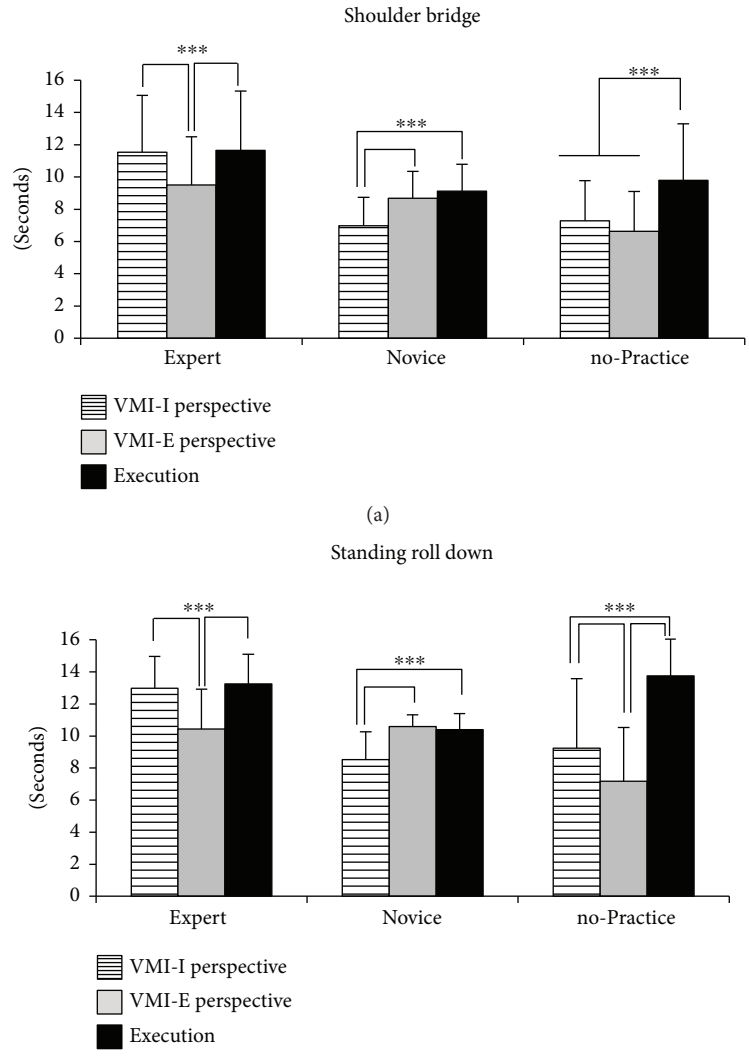


Figure 2: Execution and imagination times of the three experimental groups in both Pilates exercises: (a) VMI-I, VMI-E, and execution times in the shoulder bridge exercise; (b) times of both imagination perspectives and execution in the standing roll down exercise. Data are expressed as average ± SD. The asterisks indicate the significance level of the post hoc comparisons among groups ($^{***}P < 0.0001$).

Table 2: Mean time and standard deviation of the three experimental groups in the shoulder bridge (SB) and the standing roll down (SRD) Pilates exercises.

Group	SB			SRD		
	VMI-I	VMI-E	Execution	VMI-I	VMI-E	Execution
Expert	11.54 ± 3.52	9.50 ± 2.99	11.65 ± 3.67	12.99 ± 1.97	10.44 ± 2.49	13.25 ± 1.84
Novice	6.98 ± 1.75	8.68 ± 1.67	9.12 ± 1.67	8.53 ± 1.74	10.59 ± 0.73	10.40 ± 1.01
no-Practice	7.29 ± 2.49	6.63 ± 2.47	9.79 ± 3.52	9.24 ± 4.33	7.18 ± 3.35	13.76 ± 7.59

in the Novice group (Figure 2 and Table 2) suggest that VMI-E is facilitated by the allocentric reference frame. Probably, the novice, having to improve the gesture, uses the VMI-E perspective mainly to promote motor learning and to acquire behavioural skills. According to our interpretation, the VMI-E perspective represents a mental way to improve the execution of a sequence of movements [41] through a sort of "mental observation" of the background of the scene that induces skill acquisition.

Functional studies have correlated the brain activation to the competence levels. Olsson and coworkers [32] have evidenced that experts activate mainly motor areas and the cerebellum during the imagination of a sequence of movements (as long as such sequence belonged to their motor

repertoire), while novices mainly activated the visual areas, thus suggesting functional differences in mental imagination related to experience. Cerebellar activation during imagery supports the internal model theory [42]. According to this concept, the cerebellum forms (through a learning process) an internal model that reproduces the dynamics of a body part [43]. In this line, VMI-I could be related to an internal model that allows neural circuits to precisely put the movement into action, without the need to refer the feedback from the moving body part [43].

The interpretation about a functional role of the two imagination perspectives is supported also by other functional imaging, neuropsychology, and lesion data that show that different cerebral areas are activated during these two modalities of imagination [21]. In particular, medial cortical structures (comprising anterior medial prefrontal, medial parietal, and posterior cingulate cortices) and the inferior lateral parietal cortex have been identified as the basic neural mechanisms involved in VMI-I, while the superior parietal lobe bilaterally (predominantly on the right side) and the right premotor cortex are associated with VMI-E [21].

The significant difference between both imagination conditions and execution times in the no-Practice group (Figure 2 and Table 2) suggests that imagery is not particularly helpful in the first phases of motor learning. As shown in Figure 2, regardless of the difficulty of the exercises, in both perspectives, the no-Practice group imagines the sequences of movements much faster than the actual execution, suggesting a reduced and limited knowledge and awareness of the exercise itself.

Another point to consider is the difficulty to imagine such exercises. As specified in Materials and Methods, SRD is more difficult than SB. Despite this difference, experts and novices obtained similar imagination and execution times even in the more difficult exercise in using the VMI-I for experts and the VMI-E for novices. Instead, for the SRD Pilates exercise, the no-Practice group obtained lower time imagination in VMI-E as compared to VMI-I probably since as the difficulty increases, the VMI-E imagination becomes faster because some movement or environment elements are omitted.

As a potential limitation of the study, we have to highlight that the entire sample was composed exclusively by women. This choice was not wanted but dictated by recruitment availability, since women practice Pilates more than men [44]. Although gender differences in motor imagery are not found frequently [45], some studies reported that females use less VMI-I perspective and more VMI-E perspective than males [19].

Another limitation of the study could be the fact that in the present paradigm, the subjects performed a single trial of each condition. Although we retain that this is a way to prevent the learning of the exercise during the imagination phases, further studies will be necessary to investigate VMI perspectives with more repetitions of the exercises.

Our experiment evidenced that the type of imagery is correlated to motor experience and independent from the type of sport or discipline, open or closed skill. Further studies are needed to clarify whether gender differences in the VMI perspectives really exist and what is their effective magnitude.

4. Conclusions

The present study allows us to draw different conclusions.

Firstly, visuomotor imagery is not a unique process. In fact, we propose that the internal view perspective serves to train or to revise a gesture already internalised. However, to reach such scope, a previous high motor competence level is needed. Indeed, the external view perspective, characterizing novices' abilities, serves to improve the learning of the gesture throughout "mental observation." Finally, the visuomotor imagery in this context is not useful for individuals that lack the specific motor experience.

Although the present preliminary data offer insights on the application of mental training techniques, further studies are needed to analyse this topic in males.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] C. Frank and T. Schack, "The representation of motor (inter)-action, states of action, and learning: three perspectives on motor learning by way of imagery and execution," *Frontiers in Psychology*, vol. 8, p. 678, 2017.

[2] T. V. B. Gomes, H. Ugrinowitsch, N. Marinho, J. B. Shea, L. D. Raisbeck, and R. N. Benda, "Effects of mental practice in novice learners in a serial positioning skill acquisition," *Perceptual and Motor Skills*, vol. 119, no. 2, pp. 397–414, 2014.

[3] R. S. Weinberg and D. Gould, *Foundations of Sport and Exercise Psychology*, Human Kinetics, Champaign, IL, USA, 6th edition, 2015.

[4] T. Kim, C. Frank, and T. Schack, "A systematic investigation of the effect of action observation training and motor imagery training on the development of mental representation structure and skill performance," *Frontiers in Human Neuroscience*, vol. 11, p. 499, 2017.

[5] J. Decety, "The neurophysiological basis of motor imagery," *Behavioural Brain Research*, vol. 77, no. 1-2, pp. 45–52, 1996.

[6] A. Guillot, F. Di Rienzo, T. MacIntyre, A. Moran, and C. Collet, "Imagining is not doing but involves specific motor commands: a review of experimental data related to motor inhibition," *Frontiers in Human Neuroscience*, vol. 6, p. 247, 2012.

[7] M. Jeannerod, *Motor Cognition: What Actions Tell the Self*, Oxford University Press, Oxford, 2006.

[8] M. Lotze and U. Halsband, "Motor imagery," *Journal of Physiology-Paris*, vol. 99, no. 4–6, pp. 386–395, 2006.

[9] T. Schack, K. Essig, C. Frank, and D. Koester, "Mental representation and motor imagery training," *Frontiers in Human Neuroscience*, vol. 8, p. 328, 2014.

[10] L. Adams, A. Guz, J. A. Innes, and K. Murphy, "The early circulatory and ventilatory response to voluntary and electrically induced exercise in man," *The Journal of Physiology*, vol. 383, no. 1, pp. 19–30, 1987.

[11] C. Collet, A. Guillot, F. Lebon, T. MacIntyre, and A. Moran, "Measuring motor imagery using psychometric, behavioral, and psychophysiological tools," *Exercise and Sport Sciences Reviews*, vol. 39, no. 2, pp. 85–92, 2011.

[12] J. Decety, M. Jeannerod, M. Germain, and J. Pastene, "Vegetative response during imagined movement is proportional to mental effort," *Behavioural Brain Research*, vol. 42, no. 1, pp. 1–5, 1991.

[13] J. Grèzes and J. Decety, "Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis," *Human Brain Mapping*, vol. 12, no. 1, pp. 1–19, 2001.

[14] H. Burianová, L. Marstaller, P. Sowman et al., "Multimodal functional imaging of motor imagery using a novel paradigm," *NeuroImage*, vol. 71, pp. 50–58, 2013.

[15] M. Jeannerod, "Mental imagery in the motor context," *Neuropsychologia*, vol. 33, no. 11, pp. 1419–1432, 1995.

[16] A. Dana and E. Gozalzadeh, "Internal and external imagery effects on tennis skills among novices," *Perceptual and Motor Skills*, vol. 124, no. 5, pp. 1022–1043, 2017.

[17] C. Ruffino, C. Papaxanthis, and F. Lebon, "The influence of imagery capacity in motor performance improvement," *Experimental Brain Research*, vol. 235, no. 10, pp. 3049–3057, 2017.

[18] Q. H. Yu, A. S. N. Fu, A. Kho, J. Li, X. A. Sun, and C. C. H. Chan, "Imagery perspective among young athletes: differentiation between external and internal visual imagery," *Journal of Sport and Health Science*, vol. 5, no. 2, pp. 211–218, 2016.

[19] H. J. Rice and D. C. Rubin, "I can see it both ways: first- and third-person visual perspectives at retrieval," *Consciousness and Cognition*, vol. 18, no. 4, pp. 877–890, 2009.

[20] G. Nigro and U. Neisser, "Point of view in personal memories," *Cognitive Psychology*, vol. 15, no. 4, pp. 467–482, 1983.

[21] K. Vogeley and G. R. Fink, "Neural correlates of the first-person-perspective," *Trends in Cognitive Sciences*, vol. 7, no. 1, pp. 38–42, 2003.

[22] C. R. HallR. Singer and H. Hausenblas, "Imagery in sport and exercise," in *Handbook of Sport Psychology*, C. Janelle, Ed., pp. 529–549, Wiley, New York, NY, USA, 2001.

[23] M. Glisky, G. Williams, and J. Kihlstrom, "Internal and external mental imagery perspectives and performance on two tasks," *Journal Sport Behavior*, vol. 19, pp. 3–18, 1996.

[24] A. White and L. Hardy, "An in-depth analysis of the uses of imagery by high-level slalom canoeists and artistic gymnasts," *The Sport Psychologist*, vol. 12, no. 4, pp. 387–403, 1998.

[25] M. Arvinen-Barrow, D. A. Weigand, S. Thomas, B. Hemmings, and M. Walley, "Elite and novice athletes' imagery use in open and closed sports," *Journal of Applied Sport Psychology*, vol. 19, no. 1, pp. 93–104, 2007.

[26] A. P. Watt, M. Spittle, T. Jaakkola, and T. Morris, "Adopting Paivio's general analytic framework to examine imagery use in sport," *Journal of Imagery Research in Sport and Physical Activity*, vol. 3, pp. 121–129, 2008.

[27] S. E. Williams and J. Cumming, "Measuring athlete imagery ability: the sport imagery ability questionnaire," *Journal of Sport & Exercise Psychology*, vol. 33, no. 3, pp. 416–440, 2011.

[28] M. Spittle and T. Morris, "Internal and external imagery perspective measurement and use in imagining open and closed sports skills: an exploratory study," *Perceptual and Motor Skills*, vol. 104, no. 2, pp. 387–404, 2007.

[29] K. Munroe-Chandler and T. Morris, "Imagery," in *The New Sport and Exercise Psychology Companion*, T. Morris and P. C. Terry, Eds., pp. 275–308, Fitness Information Technology, Morgantown, WV, USA, 2011.

[30] R. Weinberg, J. Butt, B. Knight, K. L. Burke, and A. Jackson, "The relationship between the use and effectiveness of imagery: an exploratory investigation," *Journal of Applied Sport Psychology*, vol. 15, no. 1, pp. 26–40, 2003.

[31] A. Guillot, E. Nadrowska, and C. Collet, "Using motor imagery to learn tactical movements in basketball," *Journal of Sport Behavior*, vol. 32, no. 2, pp. 189–206, 2009.

[32] C. J. Olsson, B. Jonsson, and L. Nyberg, "Internal imagery training in active high jumpers," *Scandinavian Journal of Psychology*, vol. 49, no. 2, pp. 133–140, 2008.

[33] C. Schuster, R. Hilfiker, O. Amft et al., "Best practice for motor imagery: a systematic literature review on motor imagery training elements in five different disciplines," *BMC Medicine*, vol. 9, no. 1, p. 75, 2011.

[34] S. E. Williams, A. Guillot, F. Di Rienzo, and J. Cumming, "Comparing self-report and mental chronometry measures of motor imagery ability," *European Journal of Sport Science*, vol. 15, no. 8, pp. 703–711, 2015.

[35] R. Roberts, N. Callow, L. Hardy, D. Markland, and J. Bringer, "Movement imagery ability: development and assessment of a revised version of the vividness of movement imagery questionnaire," *Journal of Sport and Exercise Psychology*, vol. 30, no. 2, pp. 200–221, 2008.

[36] N. Callow and L. Hardy, "Types of imagery associated with sport confidence in netball players of varying skill levels," *Journal of Applied Sport Psychology*, vol. 13, no. 1, pp. 1–7, 2001.

[37] J. Cumming and C. Hall, "Athletes' use of imagery in the off-season," *The Sport Psychologist*, vol. 16, no. 2, pp. 160–172, 2002.

[38] D. Lawrence, *Pilates Method: An Integrative Approach to Teaching (Fitness Professionals)*, A & C Black Publishers Ltd, UK, 2008.

[39] H. Kockler, L. Scheef, R. Tepest et al., "Visuospatial perspective taking in a dynamic environment: perceiving moving objects from a first-person-perspective induces a disposition to act," *Consciousness and Cognition*, vol. 19, no. 3, pp. 690–701, 2010.

[40] D. B. Hale, "Imagery perspectives and learning in sports performance," in *Imagery in Sports and Physical Performance*, A. Sheikh and E. Korn, Eds., pp. 75–96, Baywood, Farmingdale, NY, USA, 1994.

[41] D. M. Ste-Marie, B. Law, A. M. Rymal, O. Jenny, C. Hall, and P. McCullagh, "Observation interventions for motor skill learning and performance: an applied model for the use of observation," *International Review of Sport and Exercise Psychology*, vol. 5, no. 2, pp. 145–176, 2012.

[42] D. M. Wolpert, R. C. Miall, and M. Kawato, "Internal models in the cerebellum," *Trends in Cognitive Science*, vol. 2, no. 9, pp. 338–347, 1998.

[43] M. Ito, "Control of mental activities by internal models in the cerebellum," *Nature Reviews Neuroscience*, vol. 9, no. 4, pp. 304–313, 2008.

[44] M. von Sperling de Souza and C. Brum Vieira, "Who are the people looking for the Pilates method?," *Journal of Bodywork and Movement Therapies*, vol. 10, no. 4, pp. 328–334, 2006.

[45] A. Campos, "Gender differences in imagery," *Personality and Individual Differences*, vol. 59, pp. 107–111, 2014.

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Research Article

Boosting the Motor Outcome of the Untrained Hand by Action Observation: Mirror Visual Feedback, Video Therapy, or Both Combined—What Is More Effective?

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Action observation (AO) allows access to a network that processes visuomotor and sensorimotor inputs and is believed to be involved in observational learning of motor skills. We conducted three consecutive experiments to examine the boosting effect of AO on the motor outcome of the untrained hand by either mirror visual feedback (MVF), video therapy (VT), or a combination of both. In the *first* experiment, healthy participants trained either with MVF or without mirror feedback while in the *second* experiment, participants either trained with VT or observed animal videos. In the *third* experiment, participants first observed video clips that were followed by either training with MVF or training without mirror feedback. The outcomes for the untrained hand were quantified by scores from five motor tasks. The results demonstrated that MVF and VT significantly increase the motor performance of the untrained hand by the use of AO. We found that MVF was the most effective approach to increase the performance of the target effector. On the contrary, the combination of MVF and VT turns out to be less effective looking from clinical perspective. The gathered results suggest that action-related motor competence with the untrained hand is acquired by both mirror-based and video-based AO.

1. Introduction

Research of the past years clearly demonstrated that action observation (AO) is an effective method to boost motor skill learning (see [1–4] for reviews on observational learning). In fact, the leading advantage of the AO concept is the boosting effect on motor performance before the actual execution takes place. This is because a video-depicted action conveys a visuomotor and sensorimotor information to the observer that contains on the one hand the goal of the action and on the other hand how this action is being performed accurately [5–7]. AO is therefore a promising method in the field of neurorehabilitation to improve the motor and the functional outcome of stroke patients (see [8] for a review).

However, basic concepts of the applied AO interventions in neurorehabilitation stem from findings of neurophysiological studies on *mirror neurons* which explained the promoting effect of AO on action execution for the first time [9–11]. Furthermore, execution and observation of a goal-directed motor act excite the same mirror neuron population [12]. The main hypothesis about the *mirror neuron mechanism* postulates that the goal of an action links the performing actor with the observer by stimulating a reenactment of similar embodied action representations that are already stored in the motor repertoire of the observer [13, 14]. Further studies demonstrate that the mirror neuron mechanism is multimodal and not only triggered by a visual stimulus. Instead, it can be triggered when merely an action is presented acoustically [15], when some events of an action

remain hidden [16], and when different actions were required to reach the same goal [17]. Mirror neurons were found in several brain areas of nonhuman primates: the premotor cortex (PMC), the inferior parietal lobule (IPL), and the superior temporal sulcus (STS). These aforementioned subareas are component units of what is functionally summarized as the *mirror neuron system* (MNS) [18]. Recent functional magnetic resonance imaging (fMRI) studies suggested that a comparable network also exists in humans which is being termed *action observation network* (AON) [19–22]. In this regard, a large-scale brain fMRI study and two meta-analyses reported a robust overlapping network that comprises areas of IPL and the inferior frontal gyrus (IFG) including the Broca's area that was also activated during AO and an immediate execution of observed actions [21–23]. Further studies supposed that the AON is primarily involved in observational learning of new motor skills [24, 25] and facilitates skill acquisition after stroke [26]. Accordingly, Fadiga et al. demonstrated that AO facilitates the primary motor cortex (M1), which in turn excites the same muscles in the same dynamics responsible for the execution of the observed action [27]. For example, Calvo-Merino et al. found increased fMRI activation in the AON when highly experienced dancers observed their characteristic embodied dance movements compared to unfamiliar movements of another dance style [28]. Additionally, Stefan et al. showed that AO facilitates learning of unfamiliar thumb movements by driving the formation of new motor memories inside M1, which are comparable to those acquired by physical practice [29]. From a clinical point of view, it is particularly interesting that a comparable effect of AO on motor learning was also demonstrable on older adults [30], and on stroke patients [31]. In a pilot study, employing the newly introduced *video therapy* (VT), Ertelt et al. showed that AO improves motor recovery after stroke. The combination of video observation and immediate execution of the observed movements with the paretic hand resulted in a highly significant improvement of motor performance compared to the execution after observing geometric symbols [26]. AO thus opens the opportunity to boost functional recovery without necessarily moving the paretic hand. Interestingly, exactly this basic concept has already been successfully applied in stroke rehabilitation using the so-called *mirror visual feedback* (MVF) [32]. Here, patients sit in front of a mirror placed along the midsagittal plane between both arms. While looking continually into the mirror, patients perform a motor task with their nonaffected arm. This creates the optical illusion that the paretic arm is performing the task. Remarkably, clinical studies using MVF reported improved motor performance on the untrained paretic hand [33–35]. Therefore, further studies assume that the MVF effect on the untrained hand is directly related to the activation of the AON as a result of inputs received via the mirror while observing one's own actions [32, 36–42].

MVF and VT provide inputs of an action (mirrored or displayed) that are matching the actual execution with the untrained hand. It is likely that these inputs are processed via the AON to build up a task-related motor schema for the target effector. Therefore, our primary aim was to examine the boosting effect of action observation (AO) on the motor outcome of the untrained hand by means of mirror visual feedback (MVF), video therapy (VT), or a combination of both. Our main motivation for this study was the evaluation of the effectiveness of the deployed methods with the prospect of application in stroke therapy on patient with a severe paresis. Thus, two questions arise which may be crucial for an application of MVT and VT. The first question examines what boosting effect AO has on the motor result of the untrained hand in both conditions (MVF and VT). To clarify this question, we conducted two experiments. The *first* experiment scrutinized the effect of AO after training with MVF compared to training without mirror feedback as already demonstrated in a previous study [37]. We suggested that motor outcome of MVF is superior due to the AO during the training. By using the same tasks, in the *second* experiment, we examined the effect of AO after observing action-related video clips (VT) compared to non-action-related animal video clips. In this regard, we expected that the outcome for VT is superior because of the AO during the training. The second question then investigates the possibility of an increased training effectiveness by combining MVF and VT. Therefore, in the *third* experiment, we examined the effect of additional AO on motor outcome of the untrained hand. Participants first observed action-related video clips (VT) followed by either training with MVF or training without mirror feedback. In consequence, we presumed that the combination of training with VT and MVF is more effective due to the additional AO.

2. Materials and Methods

2.1. Participants. A total of 60 right-handed (according to the Edinburgh handedness inventory [43]) healthy volunteers (29 females; age 21–27 years, $M = 23.38 \pm 1.58$ years) participated in this study. No one had a history of brain trauma or other disease that alters the brain. Exclusion criteria were drug use and musculoskeletal or neurological diseases. Volunteers gave informed consent before participating in this study, which was approved by the Ethics Committee of the Friedrich Schiller University Jena and conformed to the standards set by the Declaration of Helsinki (1964).

2.2. Experimental Protocol. At baseline (*pre*), all participants initially performed a standardized motor skill test including five tasks [37, 38, 44]. Each participant performed the respective tasks with the left (test) hand for exactly two minutes, which amounts to a total testing time of 10 minutes. The five tasks were performed as follows: (i) *Marbles*: participants used a teaspoon to move marbles from one bowl to another. Marbles successfully moved into the new bowl were counted. (ii) *Nine-hole peg test (NHPT)*: participants were asked to remove a peg out of the board and place it onto a predefined position on a desk before they return the previously removed peg into the board. Returned pegs were then counted. (iii) *Cards*: participants were asked to draw cards from a stack and turn them before they stacked them one above another onto a predefined position on a desk. The

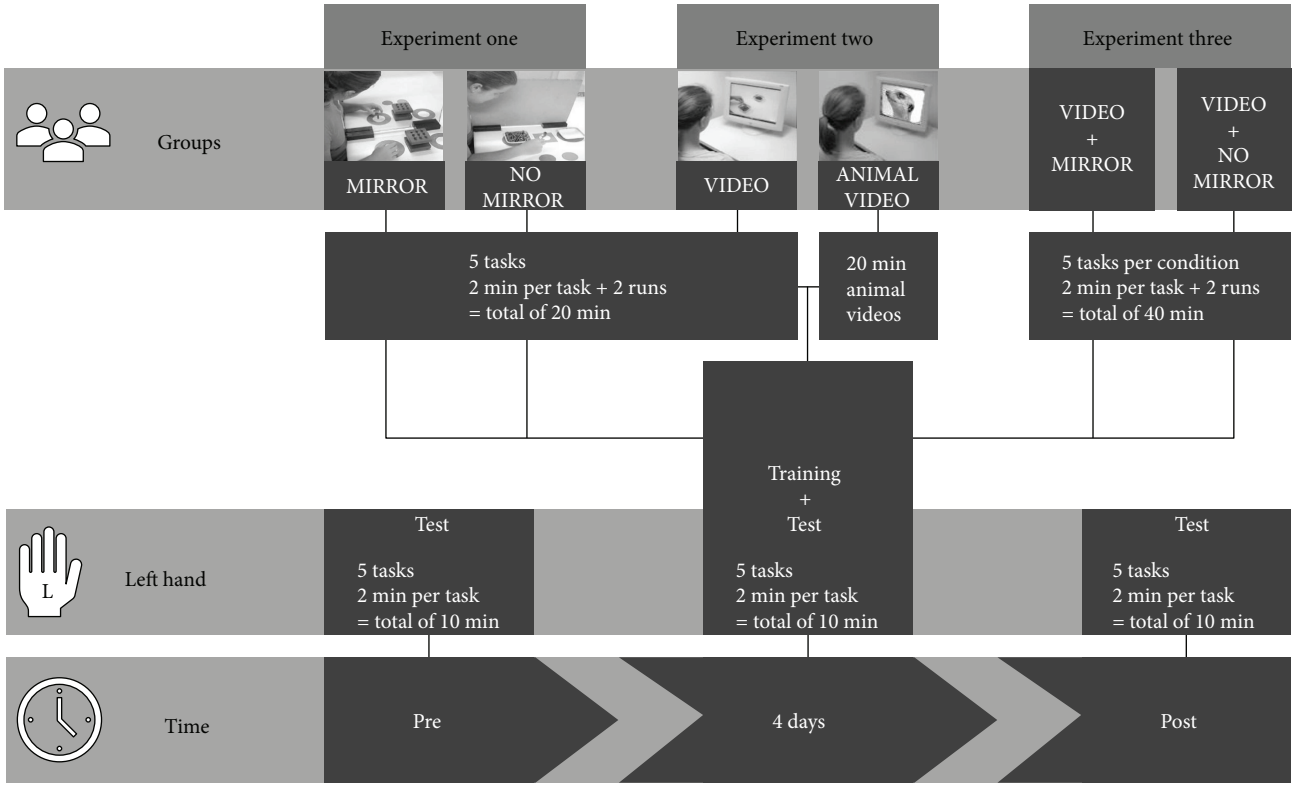

Figure 1: Schedule of the study. On the bottom, from left to right: timeframe from *pre* (baseline) to *post*. Thereover, from left to right: scope of the content at the points in time. Uppermost: group conditions within the three experiments and their training protocol.

cards of the new stack were then counted. (iv) *Pick-a-stick*: a number of sticks were positioned one after another in front of the participant parallel to the edge of a desk on a predefined position. At first, participants were asked to take the nearest stick in front of them. With the help of the tip of this stick, they were required to lightly move the following stick into their direction before they are to take it, too. Without putting away the supporting stick, participants were asked to place the other stick into a drinking glass located atop the positioned sticks on the desk. Again, sticks successfully placed into the drinking glass were then counted. (v) *Rubber band*: participants were asked to take a rubber band from a stack and to unroll it along the outside of a drinking glass. The successfully unrolled rubber bands were then counted. Furthermore, participants were encouraged to execute the given tasks quickly and to remain focused on their task while an instructor sat next to them.

Following the initial baseline (*pre*), participants started a training session where they trained each task for two minutes in two runs with a three-minute break between both runs (the total training time for the five tasks was 20 min). At the end of each training session, the left hand was tested again. The purpose of the daily testing was to assess possible learning and ceiling effects. After four days of training (*post*), all participants performed the same standardized test with the left hand (tasks and conditions were the same as on the first day of the study; see Figure 1).

2.3. Experiments

2.3.1. First Experiment: Effect of AO by Training with MVF Compared to Training without Mirror Feedback. In the *first* experiment, 20 participants were randomly assigned to two groups. Participants from the mirror training group MIRROR ($n = 10$, six females) trained while they were continually looking into a mirror placed along the midsagittal plane between their arms. In contrast, participants from the NO MIRROR group ($n = 10$, five females) trained while they were looking continually at their training hand. For this purpose, a board with the same dimensions as the mirror was placed along the midsagittal plane between their arms. Participants from both groups could not see their test hand and were instructed to refrain from any movements with this hand.

2.3.2. Second Experiment: Effect of AO by Training with Action-Related Video Clips (VT) Compared to Non-Action-Related Animal Video Clips. In the second experiment, 20 participants were randomly assigned into two groups. Participants from the video training group VIDEO ($n = 10$, four females) observed prerecorded video tapes that contain the respective tasks of daily training sessions performed with the test hand. Video tapes showed the actor from the first-person perspective. The number of videos displayed during training sessions corresponded to the mean amount of action executions per task of the group NO MIRROR from the first experiment. The number of videos was then accordingly

adjusted to each training session. Participants from the animal video group ANIMAL VIDEO ($n = 10$, five females) observed non-action-related animal video tapes in their training sessions (in the same amount of time as in the VIDEO group). Video training sessions in both groups had been conducted in the same period of time scheduled for the training sessions in the groups of the *first* experiment.

2.3.3. Third Experiment: Effect of Additional AO on Motor Outcome of the Untrained Hand. In the *third* experiment, 20 participants were randomly assigned into two groups. Participants from the mirror training group with additional video training, that is, VIDEO + MIRROR ($n = 10$, four females) first underwent the VIDEO procedure (as described in the *second* experiment) and then the MIRROR procedure (as described in the first experiment). Participants of the no mirror training group with additional video training, that is, VIDEO + NO MIRROR ($n = 10$, five females) first carried out the VIDEO procedure (as described in the *second* experiment) and secondly the NO MIRROR procedure (as described in the first experiment). Thus, these training sessions lasted twice as long as in the *first* and *second* experiment.

2.4. Data Analysis. The result of the untrained hand in each of the five respective tasks (i.e., marbles, nine-hole peg test, cards, pick-a-stick, and rubber band) of each participant was summed up and then divided by the number of tests. This average sum was then defined as the mean score of the overall test result of the untrained hand (M). The calculated mean scores of pre- and post-measurements (M_{pre}, M_{post}) were compared to compute the score difference (ΔM) for each participant ($\Delta M = M_{post} - M_{pre}$). Statistical calculations were carried out using IBM SPSS Statistics 23 (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software, La Jolla, California, USA). Normal distribution was determined by D'Agostino & Pearson omnibus normality test. Levene's test was applied to assess the equality of variances between the groups for each experiment. In order to test the differences between the groups in each experiment, a two-way analysis of covariance (ANCOVA; between-subjects factor *group*, within-subjects factor ΔM, and covariate M_{pre}) was performed as proposed by Atkinson and Batterham [45]. We considered values of $p < 0.05$ to be statistically significant. Additionally, we calculated the effect size Glass' delta (Δ) of each experimental condition (MIRROR, NO MIRROR, VIDEO, VIDEO + MIRROR, and VIDEO + NO MIRROR) on the left test hand compared to the control condition (ANIMAL VIDEO) from the *second* experiment as proposed by Hedges and Olkin [46]. Cohen defined that $\Delta \leq 0.2$ indicates a small effect, $\Delta \leq 0.5$ indicates a medium effect, and $\Delta \leq 0.8$ indicates a large effect [47].

3. Results

3.1. First Experiment. Analyzing the mean score of the overall test result of the untrained hand (M) of the groups MIRROR ($M = 24.4$, 95% CI 20.48–28.31) and NO MIRROR ($M = 18.82$, 95% CI 15.39–22.24) after four days of training, ANCOVA with the factors group, mean score difference (ΔM), and the covariate mean score at baseline (M_{pre}) revealed a significant main effect for the factor group ($F_{1,17} = 10.08$, $p = 0.006$, $\eta^2 = 0.372$). This main effect resulted from the overall higher mean score of the group MIRROR compared to the group NO MIRROR (see Figures 2 and 3).

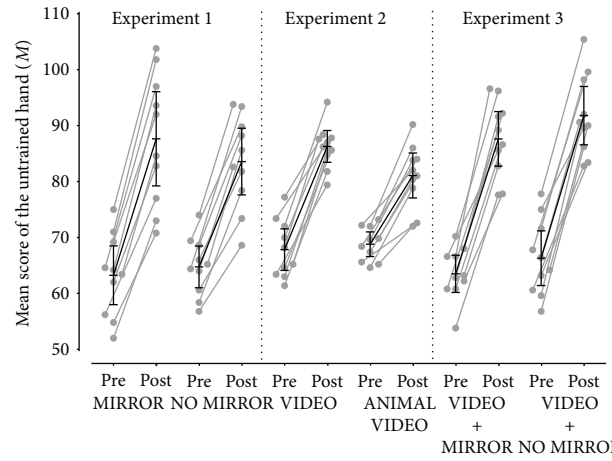

FIGURE 2: Mean score of the overall test result of the untrained hand (M) to each point of measurement (pre, post; individual values, mean, and 95% CI) of each experimental condition (MIRROR, NO MIRROR, VIDEO, TEST, VIDEO + MIRROR, and VIDEO + NO MIRROR) assigned to the corresponding experiment which are separated from each other by the dotted line. Mean score of the overall test result of the untrained hand (M) was calculated as follows. The test result of the untrained hand in each of the five respective tasks (i.e., marbles, nine-hole peg test, cards, pick-a-stick, and rubber band) was summed up for each participant and then divided by the number of tests.

3.2. Second Experiment. Analyzing the mean score of the overall test result of the untrained hand (M) of the groups VIDEO ($M = 18.44$, SD = 4.14) and ANIMAL VIDEO ($M = 12.28$, SD = 3.69) after four days of training, ANCOVA with the factors group, mean score difference (ΔM), and the covariate mean score at baseline (M_{pre}) revealed a significant main effect for the factor group ($F_{1,17} = 11.57$, $p = 0.003$, $\eta^2 = 0.405$). This main effect resulted from the overall higher mean score of the group VIDEO compared to the group ANIMAL VIDEO (see Figures 2 and 3).

3.3. Third Experiment. No significant differences were found between the mean score of the overall test result of the untrained hand (M) of the groups VIDEO + MIRROR ($M = 24.12$, SD = 4.79) and VIDEO + NO MIRROR ($M = 25.48$, SD = 5.45) after four days of training. ANCOVA with the factors group and mean score difference (ΔM) including the covariate mean score at baseline (M_{pre}) revealed no significant main effect ($F_{1,17} = 5.61$, $p = 0.464$, $\eta^2 = 0.032$) (see Figures 2 and 3).

3.4. Effect Sizes. Calculation of the effect size Glass' delta (Δ) of the experimental conditions after four days of training revealed the largest effect of the untrained hand for

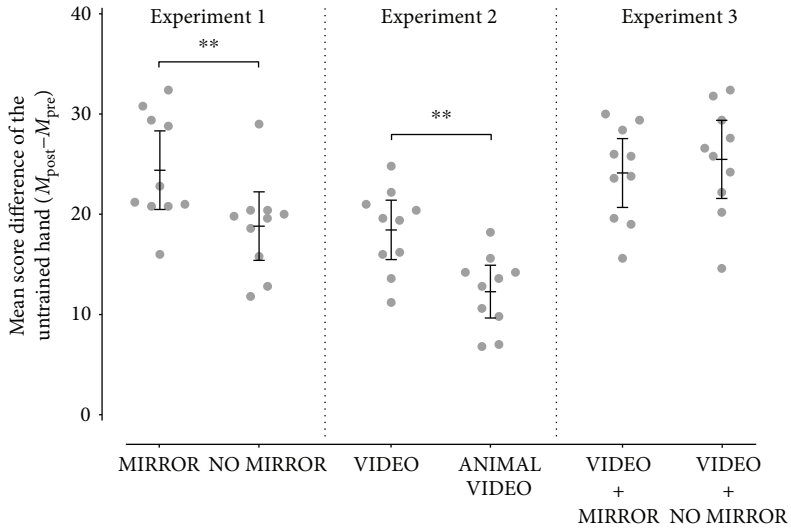

Figure 3: Mean score difference of the overall test result of the untrained hand to each point of measurement (ΔM ($M_{post} - M_{pre}$); individual values, mean, and 95% CI) of each experimental condition (MIRROR, NO MIRROR, VIDEO, TEST, VIDEO + MIRROR, and VIDEO + NO MIRROR) assigned to the corresponding experiment which are separated from each other by the dotted line. Asterisks (**) indicate the significant main effect of the factor group of $p < 0.01$.

VIDEO + NO MIRROR ($\Delta = 3.58$, 95% CI 2.17–4.99), followed by MIRROR ($\Delta = 3.29$, 95% CI 1.94–4.63), VIDEO + MIRROR ($\Delta = 3.21$, 95% CI 1.89–4.54), and NO MIRROR ($\Delta = 1.77$, 95% CI 0.74–2.81). The smallest effect was found for the condition VIDEO ($\Delta = 1.67$, 95% CI 0.65–2.69) (see Figure 4).

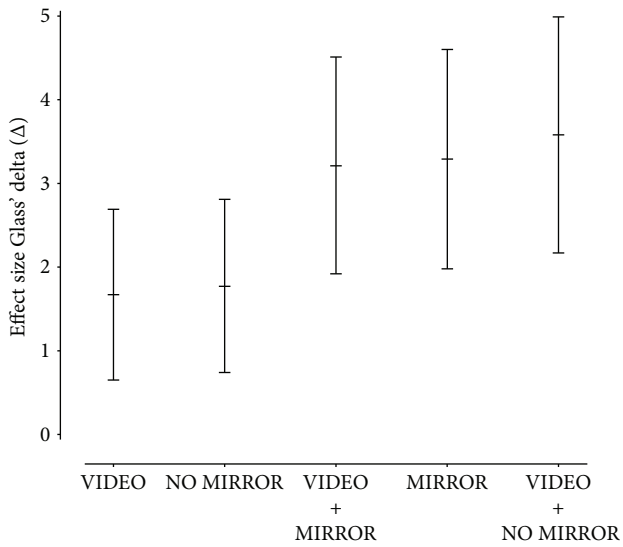

Figure 4: Effect size Glass' delta (Δ and 95% CI) of the experimental conditions VIDEO, NO MIRROR, VIDEO + MIRROR, MIRROR, and VIDEO + NO MIRROR of the untrained hand after four days of training.

4. Discussion

The primary aim of the present study was to examine the boosting effect of action observation (AO) on the motor outcome of the untrained hand by means of mirror visual feedback (MVF), video therapy (VT), or a combination of both. In our *first* experiment, we confirmed the boosting effect of AO during MVF by means of previously evaluated tasks [22, 40, 48]. Motor outcome of the untrained hand was greater after training with MVF compared to training without mirror feedback. With our findings from the *second* experiment, we extend the spectrum of application for the tasks to the possibility of using them in a video training protocol (VT). Here, we demonstrated a boosting effect on motor outcome of the untrained hand by mere AO in comparison to watching non-action-related animal video clips. Eventually, in our *third* experiment, we combined MVF and VT for the first time and demonstrated that doubling AO has no additional boosting effect.

4.1. The Boosting Effect of Action Observation on the Motor Outcome of the Untrained Hand during Both Mirror Visual Feedback and Video Therapy. The reported positive effect by MVF on the performance of the untrained hand from our *first* experiment is well established and already demonstrated on healthy adults using the same motor tasks [37], and on patients suffering from stroke [33–35]. Several studies thus infer that this effect is based on inputs received by AO during the observation of one's own action in the mirror [32, 36, 37, 39, 40]. This notion is supported by findings that show human premotor and parietal regions of the AON becoming active during both execution and observation of similar motor acts [21, 22, 49]. The same regions also exhibit a strong homology to MNS-associated regions in nonhuman primates [50]. However, activation of these regions within the AON increases as a function of motor competence linked to the observed action [28, 51–54]. By means of an optical illusion, the received mirror-based inputs of AO may feed a motor schema with visuomotor information that is consistent with the execution of the resting target effector during

MVF training (MIRROR). In order to benefit from AO during MVF, control signals for the muscles within the motor schema are possibly transformed by the received corresponding visuomotor information [5, 27, 29]. This constitutes a sharp difference to training without a mirror (NO MIRROR), since here, visuomotor information of the actual training hand is being processed. We therefore evaluate this information to be rather "inconsistent" with respect to the passive test hand because there is no transfer to the muscles of the target effector. We assume that the lack of control signals for the muscles of the target effector during training without a mirror may be a possible explanation for the significant difference to training with MVF, since these signals are processed by AO.

Accordingly, results from our *second* experiment clearly indicate the positive effect of mere AO on the motor outcome of the untrained hand when participants watch video clips that show the target effector performing the assigned tasks (VIDEO; see Figure 3). In contrast to non-action-related animal videos (ANIMAL VIDEO), action-related video clips provide visuomotor inputs that contain consistent information about the actual execution of the tested motor tasks with the target effector. Our results correspond with previous findings on AO, demonstrating that even mere short-term observational practice mediates visuomotor information of the observed action that immediately improves the motor outcome of both hands, regardless of which hand was observed [5, 6]. However, it remains unclear how the visual information about an action is linked to the brain of the observer [55]. One idea is that the sensorimotor system is activated during AO [56]. Current studies further support this idea by demonstrating substantial anatomical projections from the primary and secondary somatosensory cortices (S1, S2) to the intraparietal area (AIP) [57–59] as well as projections from parietal areas to M1 and the PMC via S1 [60]. A recent study postulates that the sensorimotor system, and more specifically S1, is indeed involved in motor learning by AO [7]. We therefore support the assumption that the positive effect of both MVF and VT on the untrained hand is based on visuomotor inputs and sensorimotor inputs received by AO. This is further supported by results indicating that regions of visual attention and the integration of visual and somatosensory information, such as the secondary visual cortex (V2) and the anterior intraparietal sulcus (aIPS), are active during both MVF and VT [22, 40, 48]. Observed more closely, the aIPS, as the human homologue of the AIP in nonhuman primates, is part of the AON and links V2 and the PMC during the visuomotor processing [18, 61–63]. The PMC is densely connected to the hand representation area of M1 [64] and thus crucial for the combination of both external sensory signals and learned motor behavior in order to interact with the hands in the peripersonal space [65, 66]. Consequently, the involvement of the PMC during AO results in a cortical formation of new motor memory traces in M1 [29–31] that is consistent with studies on AO which demonstrated the vital importance of the AON in observational learning of new guitar chords [24, 25] and motor skills after stroke [26]. Taken together, the *first* and *second* experiments provide evidence that the increased motor outcome of the untrained hand is a result of the received visuomotor and sensorimotor inputs by AO, which are mediated via both a mirror and action-related video clips.

Considering the effectiveness of MVF (MIRROR) and VT (VIDEO) with respect to the untrained hand, there is an obvious difference in favor of MVF (see Figure 4). Hence, visuomotor and sensorimotor inputs by AO alone are not a sufficient explanation for the positive effect during training with MVF. Indeed, performance improvements of the untrained hand after unilateral skill training without mirror feedback (NO MIRROR) are due to the intermanual transfer, which is accompanied by changes in interhemispheric interactions between left and right motor cortices via the corpus callosum [65, 67, 68]. A complete section of the corpus callosum stops or greatly decelerates the intermanual transfer [69]. However, studies using MVF found that more interregional than interhemispheric interactions between primary motor cortices are crucial for the performance improvements [37, 38]. These results were confirmed by a case study that reported MVF-induced performance improvements in patients despite a callosal section [42]. Moreover, excitability in motor-related areas contralateral to the untrained hand is facilitated by training with MVF [41, 70, 71]. It is likely that during MVF training, received inputs via AO are combined with parallel-mediated sensorimotor inputs by the actual execution with the training hand (see Figure 5) that is different to VT where only information is received via the observed video clips. Therefore, concerning the effectiveness of MVF, we suggest that MVF provides a more holistic training due to the combination of parallel received inputs via the AON and sensorimotor inputs by the actual execution.

4.2. The Possibility of an Increased Training Effectiveness by Combining Mirror Visual Feedback and Video Therapy. In our *third* experiment, we combined VT and MVF (VIDEO + MIRROR) to further boost the effectiveness of MVF by AO. To our knowledge, there is no study that has already attended this issue. We found that effectiveness of VT in addition to MVF is not substantially greater than VT in addition to training without mirror feedback (VIDEO + NO MIRROR) nor MVF alone (MIRROR) (see Figures 3 and 4). This result clearly supports the idea that both VT and MVF rest upon the AO concept mediating information about an action via the same pathways of the AON. Therefore, we argue that there is a striking resemblance between received video-based and mirror-based inputs (see Figure 5). This resemblance of received information is reflected by the similar effectiveness of VT in combination with MVF in contrast to MVF alone (see Figure 4). However, the controlling condition of the *third* experiment, which was a combination of VT and immediate execution without mirror feedback (VIDEO + NO MIRROR), showed a greater effectiveness in comparison to the sole training without mirror feedback (NO MIRROR) and a comparable effectiveness to MVF alone (see Figure 4). It is likely that the received inputs during the observation of action-related video clips are complemented by sensorimotor experience during the immediate execution with the training hand.

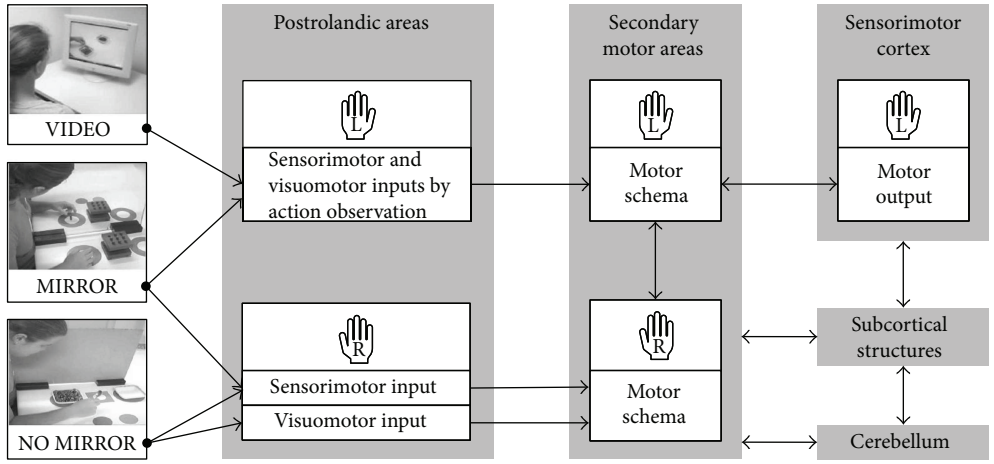

Figure 5: Proposed conceptual framework for acquired motor competence of the untrained (left) hand as a result of different network inputs.

Therefore, the motor schema is fed by visuomotor and sensorimotor inputs of the untrained hand during VT and sensorimotor inputs during the immediate action execution with the training hand (see Figure 5). These inputs are also processed during MVF. Thus, we suggest that motor competence of the untrained hand can be acquired both by parallel as well as directly consecutive visuomotor and sensorimotor inputs. However, combined methods in the third experiment, although their trainings sessions lasted twice as long as training sessions in all previous experiments, did not substantially increase effectiveness in comparison to MVF. Thus, the combination of MVF and VT turns out to be less effective looking from a clinical perspective.

To sum up the present study, we offer a conceptual framework (see Figure 5) that highlights our suggestions regarding acquired motor competence of the untrained hand as a result of different network inputs. Video clips that show a task-specific motor performance with the target effector (VIDEO) convey visuomotor and sensorimotor information to the observer. This information is processed in postrolandic areas, which in turn trigger secondary motor areas to build up a motor schema consistent with the observed action of the target effector. By training with action-related video clips, the schema is refined before it is retrieved by the sensorimotor cortex during actual execution with the target effector. Subcortical structures such as the basal ganglia and the cerebellum have a determining influence on these processes [65]. During the execution in front of a mirror (MIRROR), visuomotor and sensorimotor inputs are mediated by mere observation of one's own action via a mirror. Due to the optical illusion during observation, the AON is fed by information that is consistent with the execution of the resting target effector. At the same time, sensorimotor inputs are conveyed via a further network as a consequence of the actual execution with the performing nontarget effector. As a result, a more holistic schema than by mere observational training (VIDEO) is built up, which in turn is reflected by a greater motor performance of the untrained hand after training with MVF. Consequently, the combination of action-related video clips and training in front of a mirror (VIDEO + MIRROR) has no additional effect on the motor outcome of the untrained hand since the same information is processed twice via the pathways of the AON. Therefore, an expanded training program including similar inputs is not effective means to introduce a new training stimulus over the course of four days. In contrast, during training without mirror feedback (NO MIRROR), a motor schema is built up by sensorimotor and visuomotor inputs of the nontarget effector. Both sensorimotor and visuomotor inputs contain information that is inconsistent with the execution of the resting target effector. Thus, the training effect for the untrained hand is smaller than by training with MVF. It is more probable that the acquired motor competence of the untrained hand is mediated via the intermanual transfer [65, 67, 68]. However, by combination of observational training with action-related video clips and training without mirror feedback (VIDEO + NO MIRROR), corresponding visuomotor and sensorimotor inputs of the target effector are processed additionally by AO. Therefore, by this combination, a comparable training effect to MVF is attainable, although the training lasts twice as long.

5. Limitations and Clinical Implications

One limitation of this study is that it demonstrates results from healthy volunteers. Considering this, clinical implications addressing patients that suffer from motor deficits can only be drawn with reservation. Furthermore, the motor outcome of the untrained hand was only measured by means of a behavioral parameter. We did not present any neuronal correlates that could possibly elucidate the causal background of the training-induced increase of motor performance on the untrained hand. Any functional mechanisms, that is, underlying networks, and training-induced changes or modulations could only be presumed and argued with reference to comparable studies. We did not conduct a kinematic examination of muscle activity or trajectory. Therefore, implications regarding the quality of the observed performance

increase are not thoroughly conclusive. However, we mainly focused on the practicability of the deployed methods.

Considering that our results from the *third* experiment provide a clear indication that the combination of VT and MVF under the defined conditions is not beneficial, we conclude that the application is not suitable in a clinical context. Future studies therefore should focus on a training that provides a further input to the motor control network besides AO. Thus, an additional increase in the effectiveness of the motor outcome could be achieved.

6. Conclusion

The results at hand demonstrate that AO induces a boosting effect on the motor outcome of the untrained hand during training with both MVF and VT. We therefore support that in both approaches, the pathways of the AON are employed to process visuomotor and sensorimotor inputs. Concerning MVF, our results suggest that additional sensorimotor inputs are processed in parallel by means of action execution with the nontarget effector. This is shown by the overall greater effectiveness of MVF training compared to VT alone. Our results indicate that the boosting effect by AO alone is limited. The doubling of AO during the training sessions by means of action-related video clips in combination with MVF did not substantially increase effectiveness of the training in comparison to MVF. It is more probable that the additional sensorimotor inputs of the nontarget effector are necessary to introduce a more effective training stimulus. In this context, our results also indicate that motor competence of the target effector benefits from additional AO when VT is combined with physical training of the nontarget effector in close succession. Therefore, from a methodological point of view, mere AO training is probably the method of choice to build up a precise schema of a target action within the initial stage of motor learning. On the contrary, MVF is the more effective approach to increase the motor performance of the untrained hand in the further process of motor learning because of the combination of AO and physically received sensorimotor inputs.

Abbreviations

AIP: Anterior intraparietal area
aIPS: Anterior intraparietal sulcus
AO: Action observation
AON: Action observation network
fMRI: Functional magnetic resonance imaging
IPL: Inferior parietal lobule
IFG: Inferior frontal gyrus
M1: Primary motor cortex
MNS: Mirror neuron system
MVF: Mirror visual feedback
PMC: Premotor cortex
S1: Primary somatosensory cortex
S2: Secondary somatosensory cortex
STS: Superior temporal sulcus
V2: Secondary visual cortex
VT: Video therapy.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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References

[1] S. Vogt and R. Thomaschke, "From visuo-motor interactions to imitation learning: behavioural and brain imaging studies," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 497–517, 2007.

[2] G. Wulf, C. Shea, and R. Lewthwaite, "Motor skill learning and performance: a review of influential factors," *Medical Education*, vol. 44, no. 1, pp. 75–84, 2010.

[3] N. J. Hodges, A. M. Williams, S. J. Hayes, and G. Breslin, "What is modelled during observational learning?," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 531–545, 2007.

[4] D. M. Ste-Marie, B. Law, A. M. Rymal, O. Jenny, C. Hall, and P. McCullagh, "Observation interventions for motor skill learning and performance: an applied model for the use of observation," *International Review of Sport and Exercise Psychology*, vol. 5, no. 2, pp. 145–176, 2012.

[5] A. A. G. Mattar and P. L. Gribble, "Motor learning by observing," *Neuron*, vol. 46, no. 1, pp. 153–160, 2005.

[6] A. Williams and P. L. Gribble, "Observed effector-independent motor learning by observing," *Journal of Neurophysiology*, vol. 107, no. 6, pp. 1564–1570, 2012.

[7] H. R. McGregor, J. G. A. Cashaback, and P. L. Gribble, "Functional plasticity in somatosensory cortex supports motor learning by observing," *Current Biology*, vol. 26, no. 7, pp. 921–927, 2016.

[8] D. Ertelt and F. Binkofski, "Action observation as a tool for neurorehabilitation to moderate motor deficits and aphasia following stroke," *Neural Regeneration Research*, vol. 7, no. 26, pp. 2063–2074, 2012.

[9] G. di Pellegrino, L. Fadiga, L. Fogassi, V. Gallese, and G. Rizzolatti, "Understanding motor events: a neurophysiological study," *Experimental Brain Research*, vol. 91, no. 1, pp. 176–180, 1992.

[10] V. Gallese, L. Fadiga, L. Fogassi, and G. Rizzolatti, "Action recognition in the premotor cortex," *Brain*, vol. 119, no. 2, pp. 593–609, 1996.

[11] G. Rizzolatti, L. Fadiga, V. Gallese, and L. Fogassi, "Premotor cortex and the recognition of motor actions," *Brain Research. Cognitive Brain Research*, vol. 3, no. 2, pp. 131–141, 1996.

[12] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[13] V. Gallese, "The 'shared manifold' hypothesis - from mirror neurons to empathy," *Journal of Consciousness Studies*, vol. 8, no. 5–7, pp. 33–50, 2001.

[14] G. Rizzolatti, L. Fogassi, and V. Gallese, "Neurophysiological mechanisms underlying the understanding and imitation of action," *Nature Reviews Neuroscience*, vol. 2, no. 9, pp. 661–670, 2001.

[15] E. Kohler, C. Keysers, M. A. Umilta, L. Fogassi, V. Gallese, and G. Rizzolatti, "Hearing sounds, understanding actions: action representation in mirror neurons," *Science*, vol. 297, no. 5582, pp. 846–848, 2002.

[16] M. A. Umilta, E. Kohler, V. Gallese et al., "I know what you are doing: a neurophysiological study," *Neuron*, vol. 31, no. 1, pp. 155–165, 2001.

[17] M. A. Umilta, L. Escola, I. Intskirveli et al., "When pliers become fingers in the monkey motor system," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 6, pp. 2209–2213, 2008.

[18] K. Nelissen, E. Borra, M. Gerbella et al., "Action observation circuits in the macaque monkey cortex," *The Journal of Neuroscience*, vol. 31, no. 10, pp. 3743–3756, 2011.

[19] R. Mukamel, A. D. Ekstrom, J. Kaplan, M. Iacoboni, and I. Fried, "Single-neuron responses in humans during execution and observation of actions," *Current Biology*, vol. 20, no. 8, pp. 750–756, 2010.

[20] F. Binkofski, G. Buccino, K. M. Stephan, G. Rizzolatti, R. J. Seitz, and H. J. Freund, "A parieto-premotor network for object manipulation: evidence from neuroimaging," *Experimental Brain Research*, vol. 128, no. 1-2, pp. 210–213, 1999.

[21] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[22] F. Hamzei, M. S. Vry, D. Saur et al., "The dual-loop model and the human mirror neuron system: an exploratory combined fMRI and DTI study of the inferior frontal gyrus," *Cerebral Cortex*, vol. 26, no. 5, pp. 2215–2224, 2016.

[23] P. Molenberghs, R. Cunnington, and J. B. Mattingley, "Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies," *Neuroscience and Biobehavioral Reviews*, vol. 36, no. 1, pp. 341–349, 2012.

[24] G. Buccino, S. Vogt, A. Ritzl et al., "Neural circuits underlying imitation learning of hand actions: an event-related fMRI study," *Neuron*, vol. 42, no. 2, pp. 323–334, 2004.

[25] S. Vogt, G. Buccino, A. M. Wohlschlager et al., "Prefrontal involvement in imitation learning of hand actions: effects of practice and expertise," *NeuroImage*, vol. 37, no. 4, pp. 1371–1383, 2007.

[26] D. Ertelt, S. Small, A. Solodkin et al., "Action observation has a positive impact on rehabilitation of motor deficits after stroke," *Neuroimage*, vol. 36, pp. T164–T173, 2007.

[27] L. Fadiga, L. Fogassi, G. Pavesi, and G. Rizzolatti, "Motor facilitation during action observation: a magnetic stimulation study," *Journal of Neurophysiology*, vol. 73, no. 6, pp. 2608–2611, 1995.

[28] B. Calvo-Merino, D. E. Glaser, J. Grezes, R. E. Passingham, and P. Haggard, "Action observation and acquired motor skills: an FMRI study with expert dancers," *Cerebral Cortex*, vol. 15, no. 8, pp. 1243–1249, 2005.

[29] K. Stefan, L. G. Cohen, J. Duque et al., "Formation of a motor memory by action observation," *The Journal of Neuroscience*, vol. 25, no. 41, pp. 9339–9346, 2005.

[30] P. Celnik, K. Stefan, F. Hummel, J. Duque, J. Classen, and L. G. Cohen, "Encoding a motor memory in the older adult by action observation," *NeuroImage*, vol. 29, no. 2, pp. 677–684, 2006.

[31] P. Celnik, B. Webster, D. M. Glasser, and L. G. Cohen, "Effects of action observation on physical training after stroke," *Stroke*, vol. 39, no. 6, pp. 1814–1820, 2008.

[32] E. L. Altschuler, S. B. Wisdom, L. Stone et al., "Rehabilitation of hemiparesis after stroke with a mirror," *The Lancet*, vol. 353, no. 9169, pp. 2035-2036, 1999.

[33] C. Dohle, J. Pullen, A. Nakaten, J. Kust, C. Rietz, and H. Karbe, "Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial," *Neurorehabilitation and Neural Repair*, vol. 23, no. 3, pp. 209–217, 2008.

[34] H. Thieme, J. Mehrholz, M. Pohl, J. Behrens, and C. Dohle, "Mirror therapy for improving motor function after stroke," *Stroke*, vol. 44, no. 1, pp. e1–e2, 2012.

[35] G. Yavuzer, R. Selles, N. Sezer et al., "Mirror therapy improves hand function in subacute stroke: a randomized controlled trial," *Archives of Physical Medicine and Rehabilitation*, vol. 89, no. 3, pp. 393–398, 2008.

[36] F. Guo, Q. Xu, H. M. Abo Salem, Y. Yao, J. Lou, and X. Huang, "The neuronal correlates of mirror therapy: a functional magnetic resonance imaging study on mirror-induced visual illusions of ankle movements," *Brain Research*, vol. 1639, pp. 186–193, 2016.

[37] F. Hamzei, C. H. Lappchen, V. Glauche, I. Mader, M. Rijntjes, and C. Weiller, "Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere," *Neurorehabilitation and Neural Repair*, vol. 26, no. 5, pp. 484–496, 2012.

[38] C. H. Lappchen, T. Ringer, J. Blessin et al., "Optical illusion alters M1 excitability after mirror therapy: a TMS study," *Journal of Neurophysiology*, vol. 108, no. 10, pp. 2857–2861, 2012.

[39] V. S. Ramachandran and E. L. Altschuler, "The use of visual feedback, in particular mirror visual feedback, in restoring brain function," *Brain*, vol. 132, no. 7, pp. 1693–1710, 2009.

[40] K. Matthys, M. Smits, J. N. Van der Geest et al., "Mirror-induced visual illusion of hand movements: a functional magnetic resonance imaging study," *Archives of Physical Medicine and Rehabilitation*, vol. 90, no. 4, pp. 675–681, 2009.

[41] I. Nojima, T. Mima, S. Koganemaru, M. N. Thabit, H. Fukuyama, and T. Kawamata, "Human motor plasticity induced by mirror visual feedback," *The Journal of Neuroscience*, vol. 32, no. 4, pp. 1293–1300, 2012.

[42] I. Nojima, T. Oga, H. Fukuyama, T. Kawamata, and T. Mima, "Mirror visual feedback can induce motor learning in patients with callosal disconnection," *Experimental Brain Research*, vol. 227, no. 1, pp. 79–83, 2013.

[43] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, 1971.

[44] C. H. Läppchen, T. Ringer, J. Blessin et al., "Daily iTBS worsens hand motor training—a combined TMS, fMRI and mirror training study," *NeuroImage*, vol. 107, pp. 257–265, 2015.

[45] G. Atkinson and A. M. Batterham, "The use of ratios and percentage changes in sports medicine: time for a rethink?," *International Journal of Sports Medicine*, vol. 33, no. 7, pp. 505-506, 2012.

[46] L. V. Hedges and I. Olkin, *Statistical Methods for Meta-Analysis*, Academic press, Orlando, 1985.

[47] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences, L*, Erlbaum Associates, Hillsdale, NJ, USA, 1988.

[48] K. Numata, T. Murayama, J. Takasugi, M. Monma, and M. Oga, "Mirror observation of finger action enhances activity in anterior intraparietal sulcus: a functional magnetic resonance imaging study," *Journal of the Japanese Physical Therapy Association*, vol. 16, no. 1, pp. 1–6, 2013.

[49] G. Rizzolatti, L. Fogassi, and V. Gallese, "Motor and cognitive functions of the ventral premotor cortex," *Current Opinion in Neurobiology*, vol. 12, no. 2, pp. 149–154, 2002.

[50] G. A. Orban, "Functional definitions of parietal areas in human and non-human primates," *Proceedings of the Biological Sciences*, vol. 283, no. 1828, article 20160118, 2016.

[51] B. Calvo-Merino, J. Grezes, D. E. Glaser, R. E. Passingham, and P. Haggard, "Seeing or doing? Influence of visual and motor familiarity in action observation," *Current Biology*, vol. 16, no. 19, pp. 1905–1910, 2006.

[52] E. S. Cross, D. J. M. Kraemer, A. F. d. C. Hamilton, W. M. Kelley, and S. T. Grafton, "Sensitivity of the action observation network to physical and observational learning," *Cerebral Cortex*, vol. 19, no. 2, pp. 315–326, 2009.

[53] E. S. Cross, A. F. D. C. Hamilton, and S. T. Grafton, "Building a motor simulation de novo: observation of dance by dancers," *NeuroImage*, vol. 31, no. 3, pp. 1257–1267, 2006.

[54] B. Haslinger, P. Erhard, E. Altenmuller, U. Schroeder, H. Boecker, and A. O. Ceballos-Baumann, "Transmodal sensorimotor networks during action observation in professional pianists," *Journal of Cognitive Neuroscience*, vol. 17, no. 2, pp. 282–293, 2005.

[55] M. Iacoboni, "Imitation, empathy, and mirror neurons," *Annual Review of Psychology*, vol. 60, no. 1, pp. 653–670, 2009.

[56] V. Gazzola and C. Keysers, "The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data," *Cerebral Cortex*, vol. 19, no. 6, pp. 1239–1255, 2009.

[57] J. H. Maunsell and D. C. van Essen, "The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey," *Journal of Neuroscience*, vol. 3, no. 12, pp. 2563–2586, 1983.

[58] J. W. Lewis and D. C. Van Essen, "Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey," *The Journal of Comparative Neurology*, vol. 428, no. 1, pp. 112–137, 2000.

[59] C. L. Colby and J.-R. Duhamel, "Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey," *Neuropsychologia*, vol. 29, no. 6, pp. 517–537, 1991.

[60] E. G. Jones and D. P. Friedman, "Projection pattern of functional components of thalamic ventrobasal complex on monkey somatosensory cortex," *Journal of Neurophysiology*, vol. 48, no. 2, pp. 521–544, 1982.

[61] A. F. Hamilton and S. T. Grafton, "Goal representation in human anterior intraparietal sulcus," *The Journal of Neuroscience*, vol. 26, no. 4, pp. 1133–1137, 2006.

[62] E. Tunik, N. J. Rice, A. Hamilton, and S. T. Grafton, "Beyond grasping: representation of action in human anterior intraparietal sulcus," *Neuroimage*, vol. 36, pp. T77–T86, 2007.

[63] F. Binkofski and L. J. Buxbaum, "Two action systems in the human brain," *Brain and Language*, vol. 127, no. 2, pp. 222–229, 2013.

[64] R. P. Dum and P. L. Strick, "Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere," *The Journal of Neuroscience*, vol. 25, no. 6, pp. 1375–1386, 2005.

[65] U. Halsband and R. K. Lange, "Motor learning in man: a review of functional and clinical studies," *Journal of Physiology, Paris*, vol. 99, no. 4–6, pp. 414–424, 2006.

[66] S. S. Kantak, J. W. Stinear, E. R. Buch, and L. G. Cohen, "Rewiring the brain: potential role of the premotor cortex in motor control, learning, and recovery of function following brain injury," *Neurorehabilitation and Neural Repair*, vol. 26, no. 3, pp. 282–292, 2012.

[67] J. Reis, O. B. Swayne, Y. Vandermeeren et al., "Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control," *The Journal of Physiology*, vol. 586, no. 2, pp. 325–351, 2008.

[68] M. A. Perez, S. Tanaka, S. P. Wise et al., "Neural substrates of intermanual transfer of a newly acquired motor skill," *Current Biology*, vol. 17, no. 21, pp. 1896–1902, 2007.

[69] H. C. Sauerwein and M. Lassonde, "Cognitive and sensorimotor functioning in the absence of the corpus callosum: neuropsychological studies in callosal agenesis and callosotomized patients," *Behavioural Brain Research*, vol. 64, no. 1-2, pp. 229–240, 1994.

[70] M. I. Garry, A. Loftus, and J. J. Summers, "Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability," *Experimental Brain Research*, vol. 163, no. 1, pp. 118–122, 2005.

[71] N. Shinoura, Y. Suzuki, Y. Watanabe et al., "Mirror therapy activates outside of cerebellum and ipsilateral M1," *NeuroRehabilitation*, vol. 23, no. 3, pp. 245–252, 2008.

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Research Article

Optimal Combination of Anodal Transcranial Direct Current Stimulations and Motor Imagery Interventions

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Motor imagery contributes to enhance the (re)learning of motor skills through remapping of cortical networks. Combining motor imagery with anodal transcranial direct-current stimulation (a-tDCS) over the primary motor cortex has further been shown to promote its beneficial effects on postural control. Whether motor imagery should be performed concomitantly to a-tDCS (over depolarized membrane) or consecutively (over changing neurotransmitters activity) remains to be elucidated. In the present study, we measured the performance in a postural control task before and after three experimental conditions. Participants received a-tDCS before ($tDCS_{Before}$), during ($tDCS_{During}$), or both before and during motor imagery training ($tDCS_{Before + During}$). Performance was improved after $tDCS_{During}$, but not after both the $tDCS_{Before}$ and $tDCS_{Before + During}$ conditions. These results support that homeostatic plasticity is likely to operate following a-tDCS through decreasing cortical excitability and that motor imagery should be performed during anodal stimulation for optimum gains.

1. Introduction

Motor imagery–the mental simulation of an action–and actual execution of the corresponding movement are known to activate comparable neural networks [1–3]. Based on such partial neural substrates overlap, motor imagery (MI) has been shown to promote the capacity of neurons to adjust their connectivity to the cognitive/behavioral demand, thus eliciting activity-dependent plasticity [4] and significant effects on motor (re)learning [5]. During the last two decades, investigating the beneficial effects of MI on motor function recovery has been the subject of a compelling body of research [6–8]. Of specific interest, MI has been found to facilitate the ability to perform daily activities requiring an adequate postural control in young [9] and elderly persons [10] as well as in patients with stroke [11, 12].

Recent years witnessed a surge of interest in the brain stimulation delivered during MI. Applying anodal transcranial direct-current stimulation (a-tDCS), a non-invasive brain stimulation technique known to increase cortical excitability [13], over the primary motor cortex (M_1) during MI, has been found to yield additional performance gains in hand motor tasks compared to MI alone [14, 15]. Interestingly, Saruco et al. [16] further reported that combining MI with a-tDCS resulted in greater performance improvements in a task requiring strong postural regulations. Data showed that postural adjustments with low margins for performance improvement, and/or which were particularly difficult to acquire, were enhanced only when MI was combined with a-tDCS.

The effect of a-tDCS on cortical excitability may outlast the stimulation period and persist for up to 90 min [13]. Interestingly, while the modulation of cortical excitability

during stimulation stems from resting membrane potential modifications (i.e., depolarization [17]), the after-effects originate from changes in neuromodulators activity (increased intracortical facilitation and decreased intracortical inhibition [18]). Whether a MI session should ideally be scheduled over depolarized neuronal membranes (i.e., during a-tDCS) or during relevant neuromodulatory states (i.e., right after a-tDCS) requires further investigation. So far, research addressing the timing-dependent effects of a-tDCS on motor learning provided inconsistent results. Giacobbe et al. [19] found that motor performance of patients with stroke on a robotic wrist extension task improved when a-tDCS was delivered before training, but stagnated when applied concomitantly to the training session. Likewise, Kuntz et al. [20] observed that training on a digit serial reaction time task right after a-tDCS resulted in performance gains, whereas combining a-tDCS with actual practice had no significant effects on learning. Using a similar paradigm, Kuo et al. [21] reported divergent findings. They found that preconditioning cortical excitability through a-tDCS did not contribute to promote implicit motor learning. Other researchers further demonstrated that applying a-tDCS prior to a sequence-learning task even hindered explicit learning [22], whereas delivering the brain stimulation during actual practice improved performance [23]. To our knowledge, only Sriraman et al. [24] addressed similar timing-dependent effects of a-tDCS on a motor task with lower limbs. They found that delivering a-tDCS during practice better increased motor performance than applying a-tDCS prior to motor practice, without hindering the enhanced retention of motor performance. In addition, whether a further increase of cortical excitability triggered by membrane depolarization (during a-tDCS) on prefacilitated cortical activity (due to a-tDCS after-effects) could provide additional benefits on motor learning also remains unknown.

Aside from the context of physical training, the timing of a-tDCS delivery with reference to MI training has never been considered. The present study was therefore designed to determine whether MI should ideally be scheduled right after, during a-tDCS, or both right after and during a-tDCS.

2. Material and Methods

2.1. Participants. Sixteen right-handed and right-footed healthy students (7 men and 9 women, mean age 20 ± 2 years) voluntarily participated in this study. Participants had no contraindication to tDCS or a shoe size above 10.5 (US size), allowing a correct use of the postural tool. Each participant gave a written informed consent in agreement with the Declaration of Helsinki [25] before engaging in this double-blind experiment, which was approved by the local research ethics committee of the University.

2.2. Experimental Design. MI ability was first assessed using the revised version of the Movement Imagery Questionnaire (MIQ-R [26]). The test addresses the ease to perform MI in the visual and kinesthetic modalities, using four movements (hip abduction, squat jump, arm movement, and forward bending). For each item, participants read a description and physically performed the movement, before imagining through each modality. MI ease was rated on a 7-point Likert-type scale ranging from 1 *(very hard to see/feel)* to 7 *(very easy to see/feel)*. An average score for each modality and one for the entire questionnaire was calculated, with higher score representing greater ease of imaging. Despite its subjective nature, MI vividness assessment through a questionnaire is considered a reliable tool, as suggested in neurophysiological and neuroimaging studies [7]. MI vividness was also controlled after each experimental condition with a 5-point Likert-type scale. Specifically, participants self-reported from 1 (no sensation at all) to 5 (sensation as intense as during the actual execution) the intensity of the sensation perceived (i.e., kinesthetic MI vividness).

This double-blinding test-retest involved a MI session during which participants mentally rehearsed a postural task while being subjected to three conditions of M_1 stimulation. During the pretest, participants were first requested to actually perform a postural task (Figure 1(a)). Right after, they received 10 min of either sham or anodal stimulation and then performed 10 min of MI, which was also combined to a second sham or anodal stimulation. Three experimental conditions were therefore scheduled: (1) a-tDCS, then MI associated with sham stimulation ($tDCS_{Before}$), (2) sham stimulation, then MI associated to a-tDCS ($tDCS_{During}$), and (3) a-tDCS both before and during MI ($tDCS_{Before + During}$) (Figures 1(b) and 1(c)). A posttest session, strictly similar to the pretest, was performed immediately after completing the experimental conditions (Figure 1(d)). All participants randomly performed the three conditions, with a one-week delay between each session to avoid any carry-over effect [27]. Participants benefited from a familiarization with the task before starting the experimentation, allowing them to calibrate their postural skills.

2.2.1. Postural Task. During both the pre- and posttests, participants were required to perform a postural task which consisted in the validation of 16 targets that randomly appeared on a screen [16]. Data were collected from a Wii Balance Board, which reliability as a tool of postural assessment has been validated [28–32]. From a standing position on the balance board, participants received a continuous visual feedback of their center of pressure (CoP) on the screen, represented by a cross. By shifting their CoP without lifting any foot, the cross had to reach and stand into each target area during 3 s to complete its validation (Figure 2(a)). Targets were individually located in 8 different directions with two difficulty levels each, according to the distance from the initial position (Figure 2(b)). Difficulty thresholds were determined according to the sustentation polygon of each participant (Figure 2(c)). After each of the 16 targets (8 easy and 8 hard), a reference target (located in the center) had to be validated before shifting the CoP to the next target (Figure 2(a)). The duration of the task (i.e., validation of the 16 random and 16 reference targets), that depended on participants' individual postural abilities, ranged between 3 and 5 min.

2.2.2. Motor Imagery. As in Saruco et al.'s [16] study, participants performed MI while seating on a chair, positioned

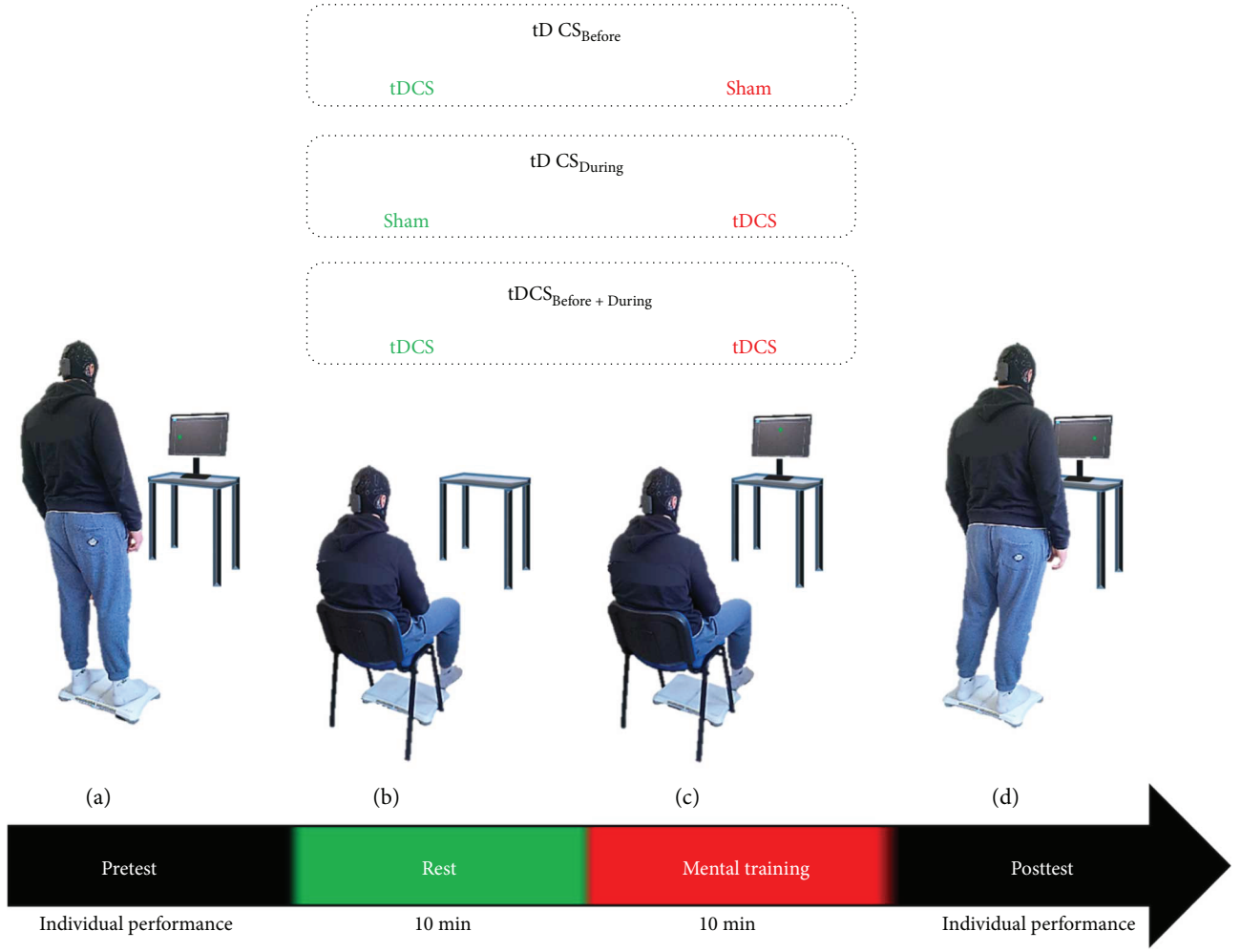

Figure 1: Time course of the experimental design. Participants performed the postural task during the pretest (a), immediately followed by 10 min of rest where participants relaxed while receiving either sham or anodal stimulation over M_1 (b). A 10 min MI session was then completed while participants received another sham or anodal stimulation (c). Finally, participants performed the posttest (d), which was strictly similar to the pretest.

exactly at the same place as the Wii Balance Board (i.e., where the pre- and posttests were performed, Figure 1(c)). During 10 consecutive minutes, participants were requested to mentally shift their CoP to the randomly assigned targets that appeared on the screen, which were identical to those presented during both pre- and posttests. Through kinesthetic MI, they were asked to mentally shift and keep their CoP from a standing position into the targets until their validation. Participants remained with their eyes opened during MI. Verbal indication was delivered by the participants at the end of each target validation, so that the experimenter was able to launch the next target. As during the pre- and posttests, a reference target had to be validated between two randomly assigned targets.

2.2.3. Brain Stimulation. Brain stimulation of 1 mA intensity was continuously delivered during 10 min through two saline-soaked sponge electrodes, with a constant-current stimulator (STARSTIM, Neuroelectrics, Barcelona, Spain). Such stimulation charge has been previously shown to induce after-effects on cortical excitability during 1 h [13]. For a bihemispheric stimulation of lower limbs, the 25 cm^2 anode electrode was fixed at Cz [33], with reference to the international 10/20 system. The 35 cm^2 cathode electrode was placed at the center of the forehead. This montage was previously shown as being relevant to enhance the beneficial effects of MI on postural control [16]. At the onset of the stimulation, intensity linearly increased during 30 s until reaching 1 mA, then ramped down to 0 during the last 30 s. For a good level of blinding, current also ramped up and down during the first and last 30 s of the sham stimulation, but was nil during MI.

2.3. Data Analysis. MIQ-R scores and participants' self-reports of MI vividness were the psychometric variables for MI ability. The time elapsed from the initial contact of the CoP with the target until it was validated (3 seconds inside the target) was the dependent variable for motor performance (Figure 2).

We used R [34], the packages *lme4* [35], and *ARTool* [36] to run a non-parametric analysis of validation times. Due to deviations from normality (visual inspection of Q-Q plots), we implemented a validated aligned rank transformation

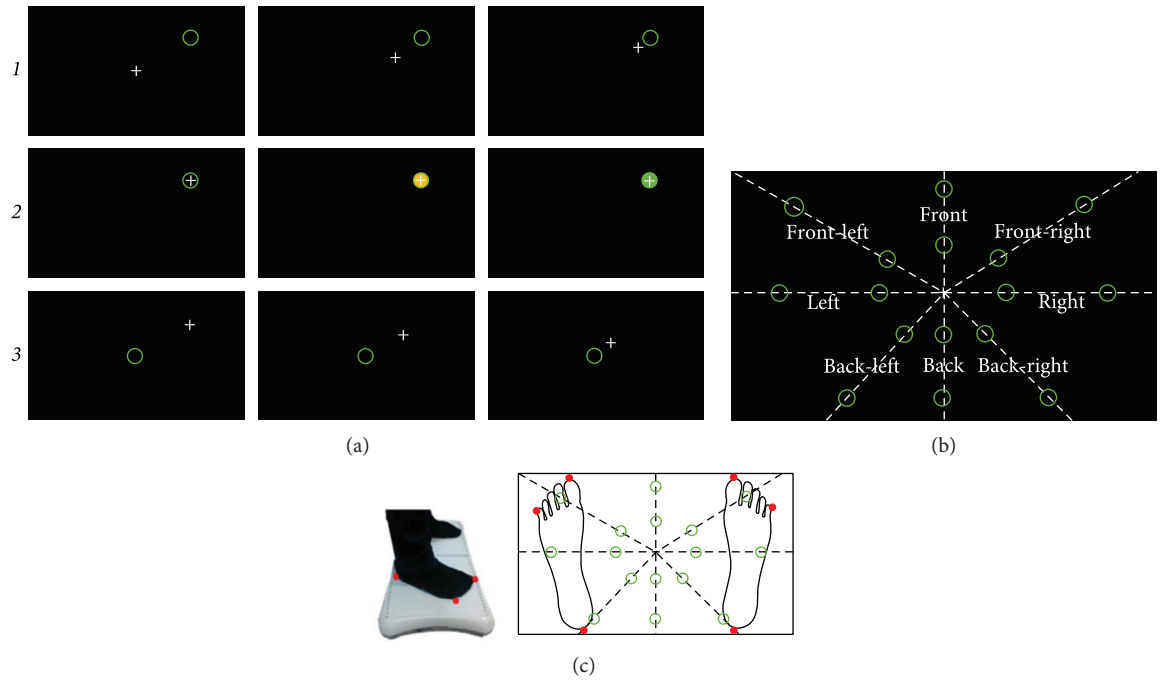

Figure 2: Postural task characteristics. (a_1) Shift of the CoP (white cross) from a reference position until reaching a randomly assigned target (green circle). (a_2) The target changed into yellow when the CoP remained within the target during 2 seconds, green after 3 seconds, and then disappeared (i.e., target validated). (a_3) Participants shift back their CoP to validate a reference target, before the next randomly assigned target appeared. (b) A total of 16 targets appeared on 8 different locations, with two levels of difficulty. Easy and hard targets were, respectively, located at 20% and 50% of the theoretical maximum stability limitation, previously individually delimitated according to the feet positions. (c) Comfortably standing on the Wii Balance Board, coordinates of the heels, and big and pinky toes were used to define the lines on which the targets appeared. Diagonals were calculated with the heel points and half of the distance between big and pinky toe points.

(ART) procedure [37]. This procedure consists in a preliminary step of data alignment based on the mean estimates of main/interaction effects of a given factorial model, followed by rank assignment. We applied the ART to a mixed linear model with validation times as the response variable. As fixed effects, we included condition ($tDCS_{Before}$, $tDCS_{During}$, and $tDCS_{Before + During}$), test (pretest; posttest), and difficulty (easy and hard targets). As random effect, we entered the by-subject and by-target random intercepts (front, front-right, front-left, back, back-left, and back-right locations). As post hoc investigations, we used contrast tests with ART (least square means difference) and ran a systematic investigation of main and interaction effects. The statistical significance threshold was set up for a type 1 error rate of 5%. We applied Holm's corrections for multiple comparisons to control the false discovery rate [38].

3. Results

3.1. MI Ability Data. Participants reported good MI ease and vividness with scores just above the median value. MIQ-R global score (M ± SD) was 5.07 ± 0.69. Visual and kinesthetic subscores were 5.52 ± 0.74 and 4.62 ± 0.98, respectively. Mean participants' self-report of MI vividness was 2.96 ± 0.70.

3.2. Performance Data. The linear mixed effect analysis with ART carried on validation times revealed a test × condition interaction ($F_{(2,1502)} = 2.60$, $p = 0.03$). Validation times were reduced during the posttest (4.25 s ± 1.36) compared to the pretest (4.67 s ± 1.97) in the $tDCS_{During}$ condition ($p_{(ART)} < 0.001$). However, there was no significant difference between pretest and posttest validation times in the $tDCS_{Before}$ (pretest: 4.60 s ± 1.58, posttest: 4.37 s ± 1.71, $p_{(Art)} = 0.11$) and $tDCS_{Before + During}$ (pretest: 4.41 s ± 1.50, posttest: 4.24 s ± 1.09, $p_{(Art)} = 0.50$) conditions (Figure 3). We also observed a test × difficulty interaction ($F_{(2,1502)} = 10.92$, $p < 0.001$). Difficult targets were validated more rapidly during the posttest than during the pretest (pretest: 5.03 s ± 2.00, posttest: 4.59 s ± 1.67, $p_{(Art)} < 0.001$), while there was no significant difference between the pretest (4.09 s ± 1.13) and the posttest (3.99 s ± 1.00) for easy targets ($p_{(ART)} = 0.20$).

The linear mixed effect analysis with ART also revealed a main effect of test ($F_{(2,1502)} = 19.79$, $p_{(Art)} < 0.001$) and difficulty ($F_{(2,1502)} = 150.80$, $p_{(Art)} < 0.001$). Posttest targets were overall validated faster than pretest targets (pretest: 4.56 s ± 1.69, posttest: 4.29 s ± 1.40), and easy targets were validated faster than hard targets (easy: 4.04 s ± 1.07, hard: 4.81 ± 1.86).

4. Discussion

This study aimed at investigating the optimal timing of a-tDCS delivery when designing a MI intervention for postural control training. Practically, we tried to determine whether MI should ideally be scheduled right after, during, or both

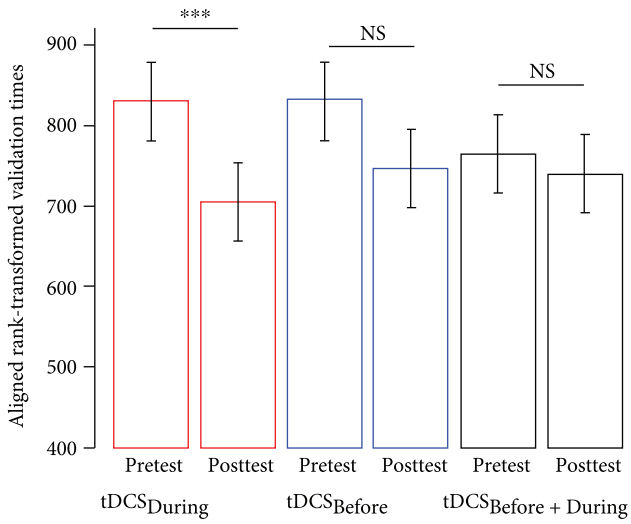

FIGURE 3: Behavioral outcomes. Least square mean estimates of validation times during the pretest and the posttest across experimental conditions. NS: no statistically significant difference (corrected $p_{(Art)}$ values), $^{***}p_{(Art)}$ value < 0.001.

right after and during a-tDCS, in order to evaluate the respective effects of changing neurotransmitters activity and membrane depolarization. While a performance improvement was observed after the concomitant use of a-tDCS and MI ($tDCS_{During}$), applying a-tDCS just before MI (either $tDCS_{Before}$ or $tDCS_{Before + During}$) did not significantly affect the motor performance.

Present data first provided evidence that applying a-tDCS during MI ($tDCS_{During}$) contributed to increase postural regulation to reach a target. This finding confirms previous data supporting that combining MI with a-tDCS can promote motor learning [14–16]. Using a comparable experimental design, Saruco et al. [16] reported that such combination yielded to better performance improvement compared to MI alone, hence supporting that performing MI while membrane potential modulation processes enhance cortical excitability might result in substantial performance gains.

In contrast, performing MI right after a-tDCS ($tDCS_{Before}$) did not significantly improve motor performance, hence suggesting that participants might not benefit from possible synaptic modulations fostering the long-term potentiation [39]. This latter finding is in line with previous results showing no effects [21, 24] or even deleterious effects of a-tDCS on motor learning when stimulation was delivered before physical practice [22, 23]. We thus extend this conclusion to motor learning by MI, confirming similar functional outcomes between actual execution and its mental representation. Interestingly, present result further suggests that applying stimulation just before practice might hinder the benefits observed after a MI session without tDCS [16].

The timing-dependent influence of a-tDCS on motor learning through MI might be explained by homeostatic plasticity processes as proposed by the Bienenstock-Cooper-Munro rule. This stipulates that synaptic modifications, based on the history of their activation, are operated in order to maintain neuronal connectivity within a useful range [40]. Motor learning relies on activity-dependent plasticity which can destabilize neural network properties [41]. The Bienenstock-Cooper-Munro rule postulates that a sliding of the modification threshold (i.e., the level of postsynaptic activity), negatively correlated to the previous neuronal firing rates, operates to avoid such destabilization. In other words, following high levels of neural activity, homeostatic plasticity processes raise the modification threshold for synaptic strengthening, hence fostering inhibition. Regulatory homeostatic plasticity, which occurs in M_1 following a-tDCS induction [42, 43], might therefore constitute a reliable explanation for the present results. Delivering an excitatory input through MI right after preconditioning a-tDCS might thus have elicited neural inhibition, hence hampering learning. The exact molecular functioning governing such homeostatic plasticity is not yet fully identified. Some studies highlighted the implication of the N-methyl-D-aspartate (excitatory neurotransmitter, NMDA) receptors' activity as an important process involved in homeostatic plasticity [44–46]. Amadi et al. [22] hypothesized that the homeostatic relationship between a-tDCS and motor learning might also occur at the level of gamma-aminobutyric acid- (inhibitory neurotransmitter, GABA-) ergic synapses. This suggests that the sliding of modification threshold may be governed by a modulation of both excitatory and inhibitory nervous processes.

Another original result is the lack of effect of combining a-tDCS with MI after a-tDCS preconditioning ($tDCS_{Before + During}$). As there was a possibility that $tDCS_{Before}$ would positively influence motor learning [20] and as positive effects of $tDCS_{During}$ were anticipated [16], it was relevant to test whether this combination could yield additional improvements. We postulate that further stimulation of the neural state (sparked by $tDCS_{During}$) contributed to trigger the sliding of the modification threshold towards inhibition processes. This result suggests that exogenous modulations of cortical excitability (i.e., a-tDCS) were not sufficient to overcome endogenous homeostatic plasticity processes. Moreover, as we did not find any difference when comparing the level of performance during the posttests of $tDCS_{Before}$ and $tDCS_{Before + During}$ conditions (Figure 1), we hypothesize that a greater input ($tDCS_{Before + During}$) did not lead to a greater reversibility of the neural state (i.e., decrease of the cortical excitability operated by homeostatic processes). Hence, irrespectively of the stimulation charge ($tDCS_{Before + During}$ or $tDCS_{Before}$ only), such processes would operate in a similar manner.

This study has some limitations that should be considered in future experiments. First, we did not include a control of cortical excitability modulations induced by a-tDCS and potential homeostatic plasticity processes. Such interaction has previously been considered by Siebner et al. [42] and Lang et al. [43]. The authors used repetitive transcranial magnetic stimulation (TMS), with the aim to increase cortical excitability. They showed that preconditioning with a-tDCS hampered the increase of cortical excitability induced by repetitive TMS. Measuring the amplitude of motor evoked potential through single-pulse TMS is a reliable method to assess the modulation of cortical excitability. Thus, an interesting perspective would be to collect such data during MI training for further evidence of a-tDCS impact on

homeostatic plasticity. Also, assessing the neurobiological factors involved in the relationship between a-tDCS and homeostatic plasticity processes certainly deserves further consideration [22]. From a practical perspective, this study addressed the short-term effects of preconditioning the neural state with a-tDCS, without scheduling a retention test. As Sriraman et al. [24] showed that a-tDCS applied before or during motor learning led to similar performance improvement 24 hours after practice, the effect of time on homeostatic plasticity should be investigated. Finally, there was no control group receiving no stimulation (e.g., sham stimulations before and during MI) in the design, hence preventing from drawing final conclusions regarding the relevance of delivering a-tDCS during MI in order to improve the postural control. However, such direct comparison of the benefits of simultaneous combination of a-tDCS with MI and those observed after MI alone (with sham a-tDCS) were assessed in a previous study [16]. It was found that although MI alone could improve the performance, additional gains were obtained when MI was combined with a-tDCS.

The aim of this experiment was to investigate whether a-tDCS should be applied before, during, or both before and during MI. Data revealed that a-tDCS scheduled before MI (either combined with sham or anodal stimulations) did not significantly improve motor performance, whereas a-tDCS delivered during MI was beneficial. Promising practical applications can be considered in the motor (re)learning domain, as present data support the relevance of applying a-tDCS during MI. This overall suggests that this timing should be regarded for optimal results. Considering the growing interest in brain stimulations and MI, specifically during the neurorehabilitation of patients suffering from locomotor and postural disorders, future studies should investigate in greater details how these two techniques might be adequately combined.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

References

[1] M. Lotze and U. Halsband, "Motor imagery," *Journal of Physiology-Paris*, vol. 99, no. 4-6, pp. 386–395, 2006.

[2] A. Guillot, C. Collet, V. A. Nguyen, F. Malouin, C. Richards, and J. Doyon, "Brain activity during visual versus kinesthetic imagery: an fMRI study," *Human Brain Mapping*, vol. 30, no. 7, pp. 2157–2172, 2009.

[3] J. Munzert, B. Lorey, and K. Zentgraf, "Cognitive motor processes: the role of motor imagery in the study of motor representations," *Brain Research Reviews*, vol. 60, no. 2, pp. 306–326, 2009.

[4] P. L. Jackson, M. F. Lafleur, F. Malouin, C. L. Richards, and J. Doyon, "Functional cerebral reorganization following motor sequence learning through mental practice with motor imagery," *NeuroImage*, vol. 20, no. 2, pp. 1171–1180, 2003.

[5] F. Di Rienzo, U. Debarnot, S. Daligault et al., "Online and offline performance gains following motor imagery practice: a comprehensive review of behavioral and neuroimaging studies," *Frontiers in Human Neuroscience*, vol. 10, p. 315, 2016.

[6] R. Dickstein and J. E. Deutsch, "Motor imagery in physical therapist practice," *Physical Therapy*, vol. 87, no. 7, pp. 942–953, 2007.

[7] F. Malouin and C. L. Richards, "Mental practice for relearning locomotor skills," *Physical Therapy*, vol. 90, no. 2, pp. 240–251, 2010.

[8] D. García Carrasco and J. Aboitiz Cantalapiedra, "Effectiveness of motor imagery or mental practice in functional recovery after stroke: a systematic review," *Neurología (English Edition)*, vol. 31, no. 1, pp. 43–52, 2016.

[9] J. H. Choi, Y. Choi, K. S. Nam, I. S. Cho, Y. T. Hwang, and Y. H. Kwon, "Effect of mental training on the balance control ability of healthy subjects," *Journal of Physical Therapy Science*, vol. 22, no. 1, pp. 51–55, 2010.

[10] M. F. Hamel and Y. Lajoie, "Mental imagery. Effects on static balance and attentional demands of the elderly," *Aging Clinical and Experimental Research*, vol. 17, no. 3, pp. 223–228, 2005.

[11] H. Cho, J. Kim, and G.-C. Lee, "Effects of motor imagery training on balance and gait abilities in post-stroke patients: a randomized controlled trial," *Clinical Rehabilitation*, vol. 27, no. 8, pp. 675–680, 2013.

[12] Y.-H. Bae, Y. Ko, H. Ha, S. Y. Ahn, W. Lee, and S. M. Lee, "An efficacy study on improving balance and gait in subacute stroke patients by balance training with additional motor imagery: a pilot study," *Journal of Physical Therapy Science*, vol. 27, no. 10, pp. 3245–3248, 2015.

[13] M. A. Nitsche and W. Paulus, "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans," *Neurology*, vol. 57, no. 10, pp. 1899–1901, 2001.

[14] Á. Foerster, S. Rocha, C. Wiesiolek et al., "Site-specific effects of mental practice combined with transcranial direct current stimulation on motor learning," *European Journal of Neuroscience*, vol. 37, no. 5, pp. 786–794, 2013.

[15] A. Saimpont, C. Mercier, F. Malouin et al., "Anodal transcranial direct current stimulation enhances the effects of motor imagery training in a finger tapping task," *European Journal of Neuroscience*, vol. 43, no. 1, pp. 113–119, 2016.

[16] E. Saruco, F. Di Rienzo, S. Nunez-Nagy et al., "Anodal tDCS over the primary motor cortex improves motor imagery benefits on postural control: a pilot study," *Scientific Reports*, vol. 7, no. 1, p. 480, 2017.

[17] M. A. Nitsche, K. Fricke, U. Henschke et al., "Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans," *The Journal of Physiology*, vol. 553, no. 1, pp. 293–301, 2003.

[18] M. A. Nitsche, A. Seeber, K. Frommann et al., "Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex," *The Journal of Physiology*, vol. 568, no. 1, pp. 291–303, 2005.

[19] V. Giacobbe, H. I. Krebs, B. T. Volpe et al., "Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: the dimension of timing," *NeuroRehabilitation*, vol. 33, no. 1, pp. 49–56, 2013.

[20] T. Kuntz, A. P. Sturm, V. Krause, B. Pollok, and A. Keitel, "EP 129. The effect of tDCS over M1 prior to and during implicit motor sequence learning," *Clinical Neurophysiology*, vol. 127, no. 9, article e295, 2016.

[21] M.-F. Kuo, M. Unger, D. Liebetanz et al., "Limited impact of homeostatic plasticity on motor learning in humans," *Neuropsychologia*, vol. 46, no. 8, pp. 2122–2128, 2008.

[22] U. Amadi, C. Allman, H. Johansen-Berg, and C. J. Stagg, "The homeostatic interaction between anodal transcranial direct current stimulation and motor learning in humans is related to $GABA_A$ activity," *Brain Stimulation*, vol. 8, no. 5, pp. 898–905, 2015.

[23] C. J. Stagg, G. Jayaram, D. Pastor, Z. T. Kincses, P. M. Matthews, and H. Johansen-Berg, "Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning," *Neuropsychologia*, vol. 49, no. 5, pp. 800–804, 2011.

[24] A. Sriraman, T. Oishi, and S. Madhavan, "Timing-dependent priming effects of tDCS on ankle motor skill learning," *Brain Research*, vol. 1581, pp. 23–29, 2014.

[25] World Medical Association, "World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," *JAMA*, vol. 310, no. 20, pp. 2191–2194, 2013.

[26] C. R. Hall and K. A. Martin, "Measuring movement imagery abilities: a revision of the Movement Imagery Questionnaire," *Journal of Mental Imagery*, vol. 21, no. 1-2, pp. 143–154, 1997.

[27] M. A. Nitsche, L. G. Cohen, E. M. Wassermann et al., "Transcranial direct current stimulation: state of the art 2008," *Brain Stimulation*, vol. 1, no. 3, pp. 206–223, 2008.

[28] R. A. Clark, A. L. Bryant, Y. Pua, P. McCrory, K. Bennell, and M. Hunt, "Validity and reliability of the Nintendo Wii Balance Board for assessment of standing balance," *Gait & Posture*, vol. 31, no. 3, pp. 307–310, 2010.

[29] B. E. Howells, R. A. Clark, C. L. Ardern et al., "The assessment of postural control and the influence of a secondary task in people with anterior cruciate ligament reconstructed knees using a Nintendo Wii Balance Board," *British Journal of Sports Medicine*, vol. 47, no. 14, pp. 914–919, 2013.

[30] J. D. Holmes, M. E. Jenkins, A. M. Johnson, M. A. Hunt, and R. A. Clark, "Validity of the Nintendo Wii® balance board for the assessment of standing balance in Parkinson's disease," *Clinical Rehabilitation*, vol. 27, no. 4, pp. 361–366, 2013.

[31] A. Dutta, S. Chugh, A. Banerjee, and A. Dutta, "Point-of-care-testing of standing posture with Wii balance board and Microsoft Kinect during transcranial direct current stimulation: a feasibility study," *NeuroRehabilitation*, vol. 34, no. 4, pp. 789–798, 2014.

[32] P. E. Jeter, J. Wang, J. Gu et al., "Intra-session test-retest reliability of magnitude and structure of center of pressure from the Nintendo Wii Balance Board™ for a visually impaired and normally sighted population," *Gait & Posture*, vol. 41, no. 2, pp. 482–487, 2015.

[33] Y.-S. Lee, H.-S. Yang, C.-J. Jeong et al., "The effects of transcranial direct current stimulation on functional movement performance and balance of the lower extremities," *Journal of Physical Therapy Science*, vol. 24, no. 12, pp. 1215–1218, 2012.

[34] R Core Team, *R: A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria, 2015, https://www.R-project.org.

[35] D. Bates, M. Maechler, B. Bolker, and S. Walker, "Fitting linear mixed-effects models using lme4," *Journal of Statistical Software*, vol. 67, no. 1, pp. 1–48, 2015.

[36] M. Kay and J. Wobbrock, "ARTool: aligned rank transform for nonparametric factorial ANOVAs. R package version 0.10.2. Retrieved from R package version 0.10.2," 2016, https://github.com/mjskay/ARTool.

[37] J. O. Wobbrock, L. Findlater, D. Gergle, and J. J. Higgins, "The aligned rank transform for nonparametric factorial analyses using only ANOVA procedures," in *Proceedings of the 2011 Annual Conference on Human Factors in Computing Systems - CHI '11*, pp. 143–146, Vancouver, BC, Canada, 2011.

[38] S. Holm, "A simple sequentially rejective multiple test procedure," *Scandinavian Journal of Statistics*, vol. 6, no. 2, pp. 65–70, 1979.

[39] C. J. Stagg and M. A. Nitsche, "Physiological basis of transcranial direct current stimulation," *The Neuroscientist*, vol. 17, no. 1, pp. 37–53, 2011.

[40] E. L. Bienenstock, L. N. Cooper, and P. W. Munro, "Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex," *Journal of Neuroscience*, vol. 2, no. 1, pp. 32–48, 1982.

[41] L. F. Abbott and S. B. Nelson, "Synaptic plasticity: taming the beast," *Nature Neuroscience*, vol. 3, pp. 1178–1183, 2000.

[42] H. R. Siebner, N. Lang, V. Rizzo et al., "Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex," *Journal of Neuroscience*, vol. 24, no. 13, pp. 3379–3385, 2004.

[43] N. Lang, H. R. Siebner, D. Ernst et al., "Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects," *Biological Psychiatry*, vol. 56, no. 9, pp. 634–639, 2004.

[44] M.-C. Lee, R. Yasuda, and M. D. Ehlers, "Metaplasticity at single glutamatergic synapses," *Neuron*, vol. 66, no. 6, pp. 859–870, 2010.

[45] W. C. Abraham and M. F. Bear, "Metaplasticity: the plasticity of synaptic plasticity," *Trends in Neurosciences*, vol. 19, no. 4, pp. 126–130, 1996.

[46] U. Ziemann and H. R. Siebner, "Modifying motor learning through gating and homeostatic metaplasticity," *Brain Stimulation*, vol. 1, no. 1, pp. 60–66, 2008.

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Research Article

Anodal tDCS over Primary Motor Cortex Provides No Advantage to Learning Motor Sequences via Observation

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When learning a new motor skill, we benefit from watching others. It has been suggested that observation of others' actions can build a motor representation in the observer, and as such, physical and observational learning might share a similar neural basis. If physical and observational learning share a similar neural basis, then motor cortex stimulation during observational practice should similarly enhance learning by observation as it does through physical practice. Here, we used transcranial direct-current stimulation (tDCS) to address whether anodal stimulation to M1 during observational training facilitates skill acquisition. Participants learned keypress sequences across four consecutive days of observational practice while receiving active or sham stimulation over M1. The results demonstrated that active stimulation provided no advantage to skill learning over sham stimulation. Further, Bayesian analyses revealed evidence in favour of the null hypothesis across our dependent measures. Our findings therefore provide no support for the hypothesis that excitatory M1 stimulation can enhance observational learning in a similar manner to physical learning. More generally, the results add to a growing literature that suggests that the effects of tDCS tend to be small, inconsistent, and hard to replicate. Future tDCS research should consider these factors when designing experimental procedures.

1. Introduction

Learning new motor skills is crucial for successful interactions with one's environment. However, the neural mechanisms that underlie skill learning in the human brain are not well known. Most prior neuroscience research has investigated skill acquisition through physical practice. For example, prior studies have shown that motor skill learning can be facilitated by applying anodal transcranial direct-current stimulation (tDCS) to the primary motor cortex (M1) during physical practice of new skills (for reviews, see [1–4]). These results suggest that M1 plays a functional role when learning novel motor skills through physical practice. However, motor learning also occurs when watching others perform actions in the absence of physical practice [5]. To date, the extent to which the motor system operates similarly in physical and observational learning remains unclear. In the present study, therefore, we use anodal tDCS over M1 to determine the extent to which stimulation of the motor system may also facilitate learning via observation.

Motor learning increases excitability of M1 and strengthens synaptic connections within M1 through long-term potentiation- (LTP-) like mechanisms [6–8]. Similarly, applying an anodal current over M1 via tDCS increases excitability of cortical neurons under the surface area of the electrode [9, 10] and the aftereffects of stimulation are believed to be related to LTP-like changes in synaptic plasticity [11]. In addition, combining anodal tDCS over M1 with a motor learning task (so-called "online" stimulation) has been shown to facilitate motor learning [1–4], which suggests that there may be additive effects of combining stimulation techniques with learning paradigms.

Physical practice of motor movements is not essential to learn new skills; motor skills can also be learned by watching others perform actions [5]. Although many studies have shown that motor skills can be learned via observation, the

specific neural mechanisms that are required to translate visual input into motor programs are not well understood [12, 13]. Several theories suggest that action observation engages an observer's own motor system by establishing internal representations of the motor programs required to perform the action (for a review, see [14]). Engagement of premotor and parietal cortices is consistently reported during both action execution and action observation, and these two brain regions form the core of the so-called human mirror system [15, 16].

Although M1 is not part of the premotor-parietal mirror system, accumulating evidence suggests that it plays an important role in action observation, as well as learning by observation. Electrophysiological recordings in monkeys have shown that cells in M1 exhibit mirror-like properties, meaning that they respond to both observed and executed movements [17–19]. In humans, repetitive transcranial magnetic stimulation (TMS) over M1, which temporarily disrupts function, effectively inducing a short-lived "virtual lesion," reduces the benefits of motor learning by observation [20]. Further, M1 engagement during observation might be a critical determinant for the success of motor learning via observation [21]. If M1 plays a similar functional role in observational learning as it does in physical learning, increasing M1 excitability during observational learning should facilitate skill acquisition in a similar manner as that reported for learning by physical practice.

Here, we investigate whether applying anodal tDCS over M1 during observational practice facilitates acquisition and retention of a keypress sequence learning task. We hypothesise that observational practice coupled with anodal tDCS should have beneficial effects on learning compared to observational practice alone, as has been previously reported for learning by physical practice [1–4]. Such a pattern of findings would support the view that M1 plays a similar functional role in learning via observation and physical practice, thus further illuminating the functional mechanisms supporting action and perception links in motor learning.

2. Method

2.1. Participants. Fifty-five participants consented to participate in the study. Five participants did not finish all sessions, including the posttraining testing sessions. These five participants were thus excluded from analyses as they did not have posttraining performance measures that were critical for testing our hypothesis. The final sample comprised 50 participants: 14 males and 36 females, 18 to 30 years old ($M = 20.60$ years, $SD = 2.40$). All participants were right-handed (based on self-report) Bangor University student volunteers with normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. Participants reported no contraindications to TMS or tDCS (personal/family history of epilepsy or seizures, metal or implants in the body, frequent headaches, history of serious head injury, heart disease, and possibility of being pregnant) and were not taking any medication that affects brain function (e.g., antiepileptic medication, tranquilizers, or antidepressants). Prior to the first stimulation session, participants were assigned to the sham ($N = 24$) or active stimulation ($N = 26$) group (see Section 2.4 for assignment procedure). No significant differences existed between the groups in terms of demographics and baseline performance (summarised in Table 1). Participants provided their written informed consent prior to beginning all experimental procedures and either received eight course credits or were paid £30 for their participation following completion. The study was conducted in accordance with the Declaration of Helsinki and all procedures were approved by the Ethics Committee of the School of Psychology at Bangor University (protocol 2016-15675) and the UK Ministry of Defence Research Ethics Committee (protocol 735/MODREC/15).

2.2. Stimuli. A keypress sequence learning paradigm was implemented, based on the task used by Wiestler and Diedrichsen [22]. A standard QWERTY black computer keyboard had the Q, 3, 4, 5, and Y keys covered with red tape and all surrounding keys removed. In pre- and posttraining sessions, participants were required to press the red keys with the five fingers of their left hand in a specified order. During the observational training tDCS sessions, participants watched videos of the experimenter performing the keypress task. For the video recordings, a similar keyboard was used with the only difference that the sides of the five keys were covered in yellow to improve the visibility of the key being pressed. Stimuli presentation and response recordings were performed using MATLAB 8.3.0 (The MathWorks, MA, USA) and Psychophysics Toolbox 3.0.12 [23].

2.2.1. Keypress Sequences. The same set of 12 five-element keypress sequences was used previously by Wiestler and Diedrichsen [22]. Each sequence required the five fingers of the left hand to be pressed once in a sequential order, with each of the 12 sequences featuring a different order with no more than three adjacent finger presses in a row. All sequences were matched for difficulty, based on a previous work [22]. For each participant, from the set of 12 sequences, four sequences were randomly allocated to the trained condition, and four other sequences were allocated to the untrained condition. The remaining four sequences remained unused.

2.2.2. Videos. For the observational training sessions, 13-second videos were created showing the experimenter's left hand from a first-person perspective, slightly tilted to the right (see Figure 1(a) and Supplementary 1). Each video showed the experimenter executing one sequence five times, with naturally varying breaks between each sequence repetition to ensure a more authentic presentation of the performance. For the same reason, for each sequence, five different video versions were recorded. This ensured closer to natural performance variation of the same sequence. An additional video version for each sequence was created where one of the five sequence executions was incorrect. This resulted in 72 videos in total.

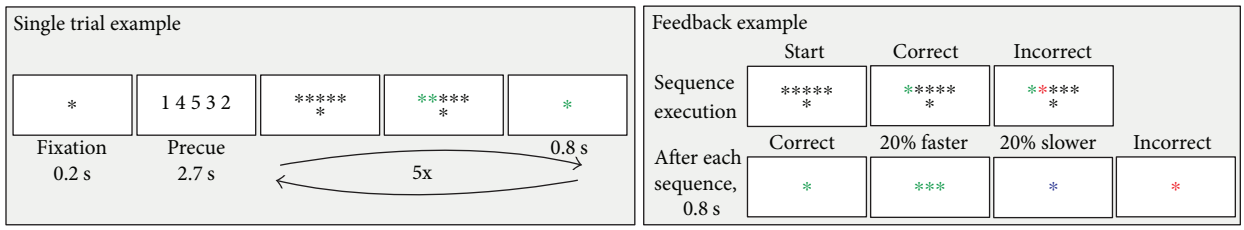
Sequences were executed at an intermediate performance level, which was determined by behavioural pilot test results,

Table 1: Group characteristics and self-reported sensations during training sessions.

	Sham ($N = 24$)	Active ($N = 26$)	Group difference (p value, effect size)
Demographics			
Gender (male/female)	8 : 16	6 : 20	0.623
Age (years; $M \pm SD$)	20.96 ± 2.97	20.27 ± 1.71	0.446, $d = 0.217$
Baseline performance			
Pretest initiation time (s; $M \pm SD$)	0.77 ± 0.25	$0.89 \pm .30$	0.117, $d = 0.455$
Pretest execution time (s; $M \pm SD$)	1.92 ± 0.57	2.02 ± 0.68	0.590, $d = 0.153$
Pretest error rate (%; $M \pm SD$)	25 ± 13	30 ± 15	0.203, $d = 0.366$
Sensations			
Strongest ($M \pm SD$)	1.23 ± 0.49	1.46 ± 0.79	0.478, $d = 0.202$
Affected ($M \pm SD$)	*0.16 ± 0.32*	*0.30 ± 0.36*	*0.037, $d = 0.618$*
Lasted ($M \pm SD$)	*1.14 ± 0.48*	*1.79 ± 0.71*	*0.001, $d = 1.04$*

Items in italics (last two rows) highlight variables that significantly differed between the sham and active stimulation groups. Strongest: the strongest reported sensation intensity level (0–4); affected: how much did sensations affect performance (0–4); lasted: when did the discomfort stop (0–3).

(a) Observation trial example



(b) Pretraining, posttraining, and retention test example

Figure 1: Sequence learning and testing elements. (a) Observation trial example. A sequence cue was followed by a video showing a hand executing the sequence five times, either correctly or incorrectly. Occasionally, a question was asked whether there was an error in any of the five repetitions, and a response had to be made. (b) Execution trial example. A cued sequence had to be memorised and then executed five times while receiving performance feedback.

where the average time to complete a correct sequence execution was 2.29 seconds (pilot: $N = 17$, $M = 2.29$ s, and SE = 0.14). Each original video, showing five repetitions of the same sequence, was slightly sped up or slowed down (±10%) to make it exactly 13 seconds long. Consequently, the authenticity of movement performance was somewhat reduced, but the relative variability within the video remained intact. The average length of time for a single sequence execution in the videos was 2.3 seconds. The videos were presented on a computer monitor in full colour on a black background. The frame rate was 29 frames per second with the resolution of 600×526 pixels, showing approximately natural hand size.

2.3. Procedure. Participants were required to watch and learn four different 5-element keypress sequences performed by a model with the left (nondominant) hand. Participants underwent six testing sessions (Figure 2). Consecutive multiple-day stimulation sessions were administered because they generally produce higher tDCS effects compared to single stimulation sessions [1], showing a cumulative increase in cortical excitability [24] and improved motor skill consolidation and retention [25, 26]. On the first day of testing (day 1), participants' left-hand motor area was localised with TMS (see below for details). After the localisation procedure, participants received task instructions and completed three single-sequence execution trials to ensure they understand the task. The familiarisation procedure was followed by a pretest, which was followed immediately by the first observational practice session. The observational practice sessions continued for the next three consecutive days (day 2 to day 4). For most participants, sessions were arranged at the same time of the day as the first practice session (with 1.5 to 2.5-hour difference for three participants in

Figure 2: Experimental procedure. The experiment involved pretest, four 20-minute-long training sessions coupled with tDCS, posttest, and retention test. In the pre-, post-, and retention tests, participants executed eight keypress sequences (four of them to be trained, the other four untrained) with the left (nondominant) hand. In the training sessions, participants watched videos of a model's left hand executing four of the eight sequences. During training, participants received either sham or active (1 mA) 20-minute stimulation over the right motor cortex (35 cm^2 large area centred on the left-hand motor area M1).

the sham group and 0.5 to 1.5-hour difference for four participants in the active stimulation group). The day after completing the final observational practice session, participants performed a posttest to assess learning (day 5). One week later, they returned to the lab one final time to perform a retention test to assess memory for the different sequences (day 12).

Stimuli presentation and response recordings were performed using MATLAB 8.3.0 (The MathWorks, MA, USA) and Psychophysics Toolbox 3.0.12 [23]). All scripts are available at Github (https://github.com/dcdace/2017_tDCS).

2.3.1. Testing Sessions. In the pre-, post-, and retention performance sessions, participants performed four trained and four untrained sequence execution trials in a random order with the left hand. Each trial consisted of five repetitions of the same sequence. All trial-related information was presented centrally at the bottom of the screen against a grey background. A trial started with a black fixation cross (0.2 s), followed by the sequence cue presented as five digits (2.7 s) that indicated from right to left which key to press: "1"—the right-most key pressed with the thumb and "5"—the left-most key pressed with the little finger (see Figure 1(b)). After the cue, the digits were replaced by the fixation cross and five black asterisks above it. This served as a "go" signal to execute the memorised sequence five times as quickly and accurately as possible. If the correct key was pressed, the corresponding asterisk on the screen turned green, if a wrong key was pressed, the asterisk turned red.

After executing a single sequence, the central fixation cross changed colour to provide feedback on the performance (0.8 s): green—correct sequence execution, red—incorrect sequence execution, blue—correct, but executed 20% slower than the median execution time (ET) in the previous trials, and three green asterisks—correct and executed 20% faster than the median ET in the previous trials. After this short feedback, all asterisks turned black signalling the start of the next execution trial. After five executions of the same sequence, the trial ended and the next sequence was cued.

Participants' performance was assessed as the average sequence initiation time, execution time, and error rate for the four trained (to-be-trained) and the four untrained sequences. The error rate was measured as the percentage of incorrect sequence executions. Incorrectly executed trials were excluded from initiation time and execution time measurements. The initiation time was measured as the duration between the "go" signal and the first keypress. The execution time was measured as the duration between the first and fifth keypresses.

2.3.2. Observational Training Sessions. During the observational training sessions, participants received either sham or active brain stimulation while watching videos of the model's left hand executing four sequences. Each video showed five repetitions of the same sequence. A trial started with a 5-digit cue (for 2.6 s), indicating the sequence to be executed, followed by a video (13 s) showing five executions of the cued sequence. Participants were instructed to watch whether the hand executed the correct sequence all five times. Occasionally, participants were asked whether there was an error in any of the five executions—the error question.

Each practice session was divided into three blocks, separated by a one-minute rest period. Within each block, 20 videos were presented in a random order: each sequence video four times and one "error video" (with at least one incorrect sequence execution) for each sequence. The error question was asked randomly 5–7 times per block. At the end of each block, participants received feedback on how accurately they spotted the incorrect sequence executions. During each session, participants saw a correct execution of each sequence at least 60 times (3 blocks, 4 videos per block, 5 repetitions per video, plus some correct repetitions in the "error video"). The whole training session lasted approximately 20 minutes and was coupled with 20 minutes of sham or active tDCS.

2.4. Motor Cortex Stimulation

2.4.1. Right M1 Localisation. Single-pulse TMS was used to localise the left-hand motor area. The TMS coil was positioned on the right hemisphere, slightly anterior and ventral to the vertex of the skull to induce a muscle twitch in the relaxed fingers of the left hand. The stimulator output was started at 45% and increased in steps of 2–5% until a visible twitch was observed. The stimulator output never exceeded 80% and participants received no more than 20 total pulses in total, with an interpulse interval kept to at least 5 seconds. The optimal location at which TMS evoked a just-noticeable finger twitch was marked on the participant's scalp with a surgical marker. For nine participants, a visible twitch was not observed following this procedure and the motor hand area was instead marked per position C4 of the EEG 10-20 system (after [27]). The localisation procedure was performed only on the first testing session and the marked M1 location was renewed with the surgical marker before each stimulation session.

The nine participants whose M1 area could not be localised using TMS were assigned to the sham group as the precise location of the stimulated area was not critical for sham stimulation. We acknowledge that random assignment, independent of localisation procedure, would have been a better approach. The reasons why we could not evoke a visible twitch in some participants may include extent of representation of the hand area and/or its accessibility via the cortical surface. To ensure that any group differences are not driven by the nonrandom assignment to groups, we repeated the main analyses of observational training and stimulation effects with the nine non-TMS-localised participants excluded. The results of this analysis (see Supplementary Materials 1) suggest that nonrandom group assignment did not systematically bias our findings.

2.4.2. Stimulation Parameters. We performed a single-blinded protocol. Participants were semirandomly assigned to the sham or active stimulation group, keeping gender balanced between the groups and ensuring that the motor hand area of the active group was localised using the TMS procedure described above. Participants were told that they would receive stimulation for up to 20 minutes, not specifying the exact length of the stimulation and not revealing the existence of two stimulation groups. During each practice session, the sham group received 30 seconds and the active group received 20 minutes of tDCS (cf. [28]).

A 1 mA constant current was delivered using a battery-driven DC-Stimulator Plus (neuroConn GmbH, Ilmenau, Germany) via a pair of conductive rubber electrodes placed into saline-soaked sponges (7×5 cm; 0.029 mA/cm^2 current density). The electrodes were secured with elastic bands. The contact impedance was monitored throughout the session to ensure it stays below 15 kΩ.

The anode was centred over the previously marked right M1. Due to the electrode size, the stimulation likely extended into premotor and anterior parietal cortices as well. The cathode was placed on the left supraorbital ridge (see photographs in Figure 2). The current was ramped up to 1 mA over 10 seconds, held constant for either 30 seconds (sham) or 20 minutes (active), and then ramped down over 10 seconds. This method is recommended to reliably blind participants to stimulation condition and ensure similar sensations for sham and active stimulation groups [28].

The observational training task started one minute after stimulation onset, to allow time for participants to adapt to the stimulation sensations and to ensure they felt comfortable with carrying on with the task. The stimulation ended about one minute before the end of the task.

2.4.3. Sensation Questionnaire. After each training session, participants provided information on the intensity of experienced sensations (itching, pain, burning, heat, pinching, metallic taste, and fatigue), the timing of any discomfort (when did the discomfort begin and how long did it last?), and the perceived impact of the stimulation on their performance (adapted from [29]). At the end of the experiment (day 12), participants were debriefed and asked whether they think they received sham or active stimulation.

2.5. Data Analysis. All statistical analysis was performed using R (v3.3.2, 2016-10-31) in RStudio (v1.0.136, 2016-12-21, RStudio Inc., Boston, MA). Graphs were produced in MS Excel 2016 (Microsoft, Redmond, WA, USA). The Excel files, raw data, and scripts with all analysis procedures and for reproducing results are available at https://github.com/dcdace/2017_tDCS.

Given the total sample size of 50, the study had 80% power to detect effects of tDCS that are conventionally considered large (Cohen's $d = 0.71$; the effect size was estimated with a *power.t.test* function in *R* for a two-sample, one-sided *t*-test with 25 observations per group). Three previous multiple stimulation session (3–5 consecutive days, 20–25 min per day, 1-2 mA, and ~12.5 participants per group) M1 anodal-tDCS physical training studies reported large tDCS effects ranging from 0.95 to 1.33 Cohen's *d* [25, 26, 30].

The effect of observational training on sequence-specific learning was assessed as a posttraining difference between the trained and untrained sequence initiation time, execution time, and error rate. For the sequence initiation time and execution time, we measured a percentage difference

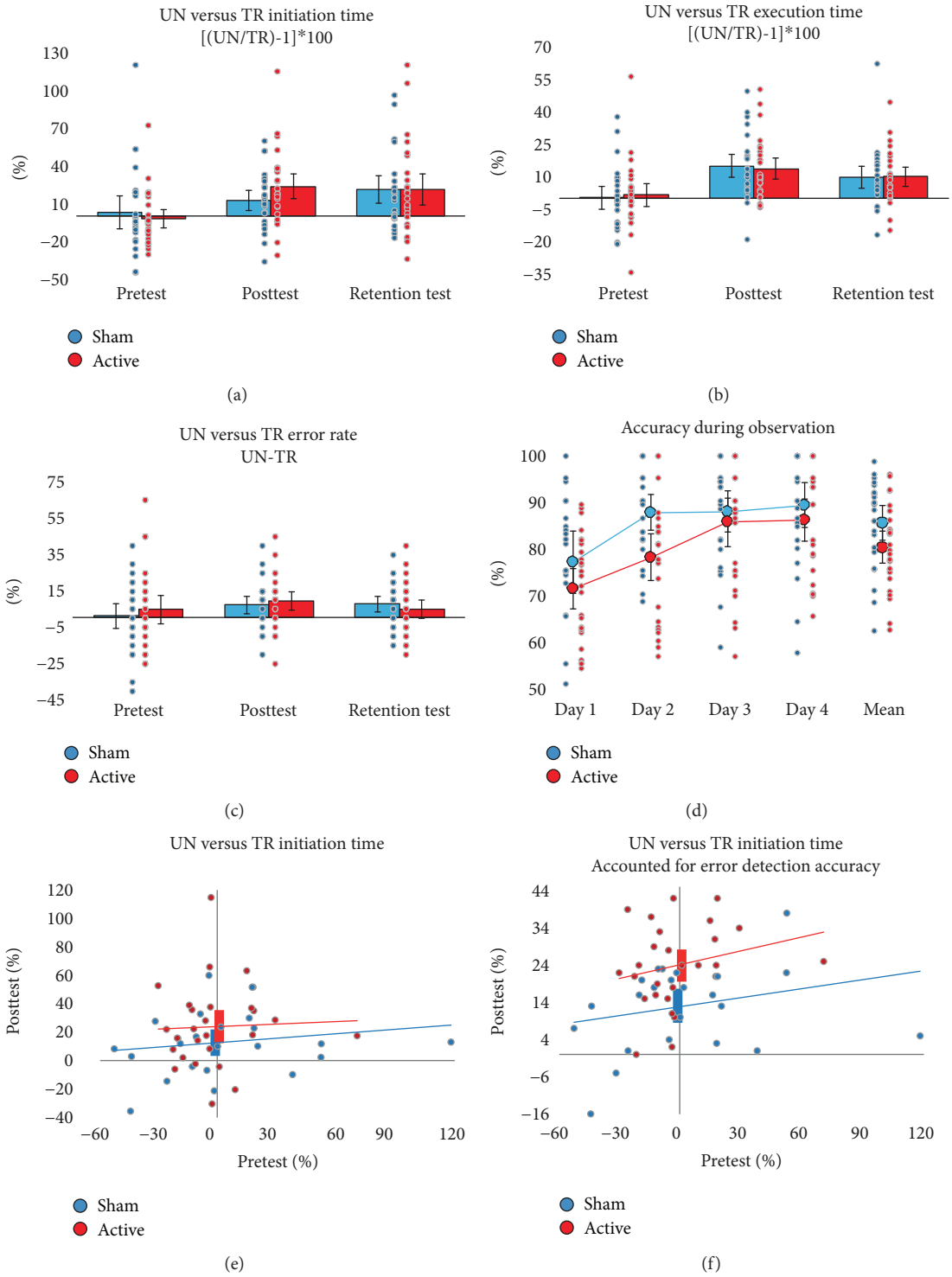


Figure 3: Performance results. Pre-, post-, and retention test differences in initiation time (a), execution time (b), and error rate (c) between trained (TR) and untrained (UN) sequences for sham (blue) and active (red) stimulation groups. (d) Error detection accuracy during observational practice sessions. (a–d) Bars and large dots: group averages; small dots: individual participant values; error bars: 95% CI (one-tailed for (a), (b), and (c); two-tailed for (d)). (e) Regression lines of pretest (predictor) and the posttest differences between trained and untrained sequence initiation times for the sham (blue) and active (red) stimulation groups. Intercepts of the regression lines represent the predicted posttest difference if the pretest difference is zero. Vertical bars represent 95% CIs (one-tailed) of intercepts (f). Same as (e), but posttest difference corrected for error detection accuracy during training sessions.

Table 2: Frequencies of self-reported sensations during the training sessions.

(a) The strongest intensity of discomforting sensations

Intensity level	Day 1					Day 2					Day 3					Day 4				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Sham	1	12	10	1	—	4	11	8	1	—	2	15	7	—	—	5	14	5	—	—
Active	2	11	8	3	2	2	18	2	3	1	2	15	4	2	3	3	16	5	2	—

0: none; 1: mild; 2: moderate; 3: considerable; 4: strong.

(b) How much did the sensations affect performance?

Intensity level	Day 1					Day 2					Day 3					Day 4				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Sham	19	5	—	—	—	20	4	—	—	—	22	2	—	—	—	21	2	1	—	—
Active	18	7	—	1	—	20	6	—	—	—	18	7	1	—	—	20	6	—	—	—

0: not at all; 1: slightly; 2: considerably; 3: much; 4: very much.

(c) When did the discomfort stop?

Intensity level	Day 1				Day 2				Day 3				Day 4			
	ns	1	2	3	ns	1	2	3	ns	1	2	3	ns	1	2	3
Sham	1	15	4	4	4	14	4	2	2	19	3	—	5	18	—	1
Active	2	6	9	9	2	11	7	6	2	8	7	9	3	9	8	6

ns: no sensations; 1: quickly; 2: middle of the block; 3: end of the block.

([(untrained/trained) − 1]*100), but for the error rate (to avoid dividing by zero), we calculated an absolute difference (untrained-trained) between the trained and untrained sequences. Results for all of these measures are plotted in Figures 3(a)–3(c) (raw performance measures are provided in Supplementary Materials 2). To correct for possible pretraining differences, we performed a linear regression between the pretraining difference (predictor) and the posttraining difference (outcome; see Figure 3(e) for an example plot). The intercept of the regression line was used as a measure of the posttraining difference between trained and untrained sequences, controlling for possible pretraining differences. This method reduces the noise of unwanted differences in the difficulty of trained and untrained sequences and thus allows a more accurate measurement of the training effect.

For the assessment of tDCS effects, we complemented null hypothesis significance testing with a Bayesian analysis to provide evidence for the null result. We used the *generalTestBF* function of the R package BayesFactor v0.9.12-2 [31] with its default parameters. The Bayesian test produced a Bayes factor to allow quantification of evidence in favour of either the alternative (BF_{10}) or null (BF_{01}) hypothesis based on prior beliefs and the present data. To describe the Bayes factor results, we used Jeffreys' [32] classification scheme and reported both BF_{10} and BF_{01}. Jeffreys proposed benchmarks for evaluating the strength of evidence as anecdotal (BF_{10} 0–3), substantial (BF_{10} 3–10), and strong (BF_{10} 10–30). These Bayes Factors can be readily interpreted as a ratio of evidence in favour of the experimental effect compared to the null effect. For example, a BF_{10} of 3 would represent that the experimental effect is three times more likely than the null, given the data.

The significance threshold for all statistical comparisons was $p < 0.05$. If not specified otherwise, all sample means are reported with their 95% confidence intervals in square brackets. Confidence intervals for two-tailed tests were calculated as SE * 2.07 for the sham group (df 23) and SE * 2.06 for the active group (df 25), whereas confidence intervals for one-sided tests were calculated as SE * 1.71 for df 23 and df 25 [33].

3. Results

3.1. Group Characteristics and Sensations during Training Sessions. Gender proportion between the sham and active stimulation groups was compared using a chi-square test. Mann–Whitney *U* tests were used to compare group age and experienced sensations during the training sessions. Participants' baseline performance (pretraining average of trained and untrained sequences) was compared using a two-tailed independent-measures *t*-test. Results are summarised in Table 1. The reported sensations for each training day are summarised in Table 2 and averages of all training days are plotted in Figure 4.

There were no differences in gender, age, and baseline performance between the groups. On average, both groups reported mild to moderate levels of discomfort during stimulation with no significant difference between the groups (Table 1; Figure 4(a)). Although the active stimulation group did report a small but significantly larger impact of stimulation on performance than the sham group, the

perceived impact for both groups was closest to zero ("no impact") (Table 1; Figure 4(b)). Finally, sensations lasted significantly longer for the active compared to the sham group (Figure 4(c)), with average sensations stopping between "quickly" and "in the middle of the block" across both groups.

The reported sensation data, therefore, shows that there were small but significant sensation differences between the sham and active stimulation groups. The sham protocol should provide comparable sensations to the active stimulation protocol [28]. However, small but significant sensation differences between the stimulation groups, using comparable protocols to ours, have been reported before [29], raising an issue that the widely accepted sham stimulation procedure may not be sufficiently effective.

Following the recommendation of Fertonani et al. [29], at the end of the experiment, we asked participants whether they think they received sham or active stimulation. In total, 54% thought they received active stimulation, 32% thought they received sham stimulation, and 14% did not know. There was no significant difference between the two groups in terms of which kind of stimulation they thought they received ($\chi^2 = 1.24$, $p = 0.538$), thus confirming the success of the blinding procedure.

3.2. Accuracy during Training Sessions. During the observational practice sessions, attention to the task was assessed by accurate responses to the error question (spotting incorrectly executed sequences). The overall accuracy was 83%, significantly higher than a 50% chance level (yes/no answers; $t_{49} = 24.61$, $p < 0.001$, two-tailed), confirming that participants paid attention to the task. The average accuracies for each group and day are plotted in Figure 3(d). On average, across the four training days, the sham group performed better ($M = 86\%$ (82%, 90%)) than the active group ($M = 81\%$ (77%, 85%)), with a marginally significant difference between the two groups (Welch two-sample t-test for nonequal variance: $t_{47.27} = 1.99$, $p = 0.052$, two-tailed, $d = 0.56$).

The small difference in error detection accuracy between the groups was an unexpected finding. It cannot be ruled out that anodal tDCS of M1 had some negative effects on the error detection accuracy. However, we do not have any a priori or theoretical grounds to support this suggestion. Another possibility is that the error detection accuracy was influenced by the discomforting sensations during the training sessions that, as reported above, affected the stimulation group more than the sham group. This possibility is supported by a significant negative correlation between the average error detection accuracy and the average self-report on how much performance was affected by the discomforting sensations (Kendall's tau-$b = -0.296$, $p = 0.008$, two-tailed; across both groups).

The lower error detection accuracy for the active stimulation group raises a possibility that the active group may not have been able to learn from the videos as well as the sham group due to stimulation-related discomfort and consequent impact on attention. To account for this possibility, we complement the planned analysis with an exploratory analysis that includes mean error detection accuracy as a covariate when assessing the stimulation effect.

3.3. Observational Training Effects on Sequence-Specific Learning. Both groups showed significant observational training effects at both posttest and retention test on all three performance measures, with medium to large effect sizes for the performance difference between trained and untrained sequences ($d_z = 0.52$–1.02; comparable to previous reports on keypress sequence learning by observation, e.g., [34–36]). The only exception to this pattern of results was that the active stimulation group demonstrated no effect on error rates at the retention test. Detailed results are provided in Table 3, columns I and II, where B_0 represents the percentage performance improvement from pretest. All tests in Table 3 are one-tailed as we were testing a directional prediction for the difference between trained and untrained sequences. Furthermore, Supplementary Materials 3 document the extent to which the training manipulation generalised to the untrained sequences, comparing the active and sham stimulation groups.

3.4. tDCS Effects on Sequence-Specific Learning by Observation

3.4.1. Primary Analysis. The effect of stimulation on sequence-specific learning was assessed by comparing observational training effects (the posttraining~pretraining regression line intercepts) between the sham and active stimulation groups. The performed analysis of covariance (ANCOVA) did not reveal any significant difference between the two groups on any of the three measures either at posttest or retention test (Figure 3(e) plots posttest initiation time results; see Supplementary Materials 4 for ANCOVA results of the raw means). The Bayes factor analyses yielded anecdotal to substantial evidence against the stimulation effect. Detailed results are provided in Table 3, column III (reporting significance of the group as a predictor variable for the training effect).

3.4.2. Secondary Analysis: Accounting for Error Detection Accuracy. Due to error detection differences between the groups, in an exploratory analysis, we added mean error detection accuracy as a covariate to the previous ANCOVA model and repeated the group comparison analysis. This exploratory analysis revealed evidence for the stimulation effect on the percentage difference between trained and untrained sequence initiation times at posttest. Compared to the sham group, the active stimulation group showed greater difference on this measure (see Figure 3(f)). The error detection accuracy significantly predicted the outcome ($\beta = 0.431$, $p = 0.003$; the better the accuracy during training, the faster initiation time of trained relative to untrained sequences at posttest). All other measures showed substantial to strong evidence against the stimulation effect when accounting for the error detection accuracy. Detailed results are provided in Table 3, column IV (reporting significance of the group as a predictor variable for the training effect accounting for the error detection accuracy).

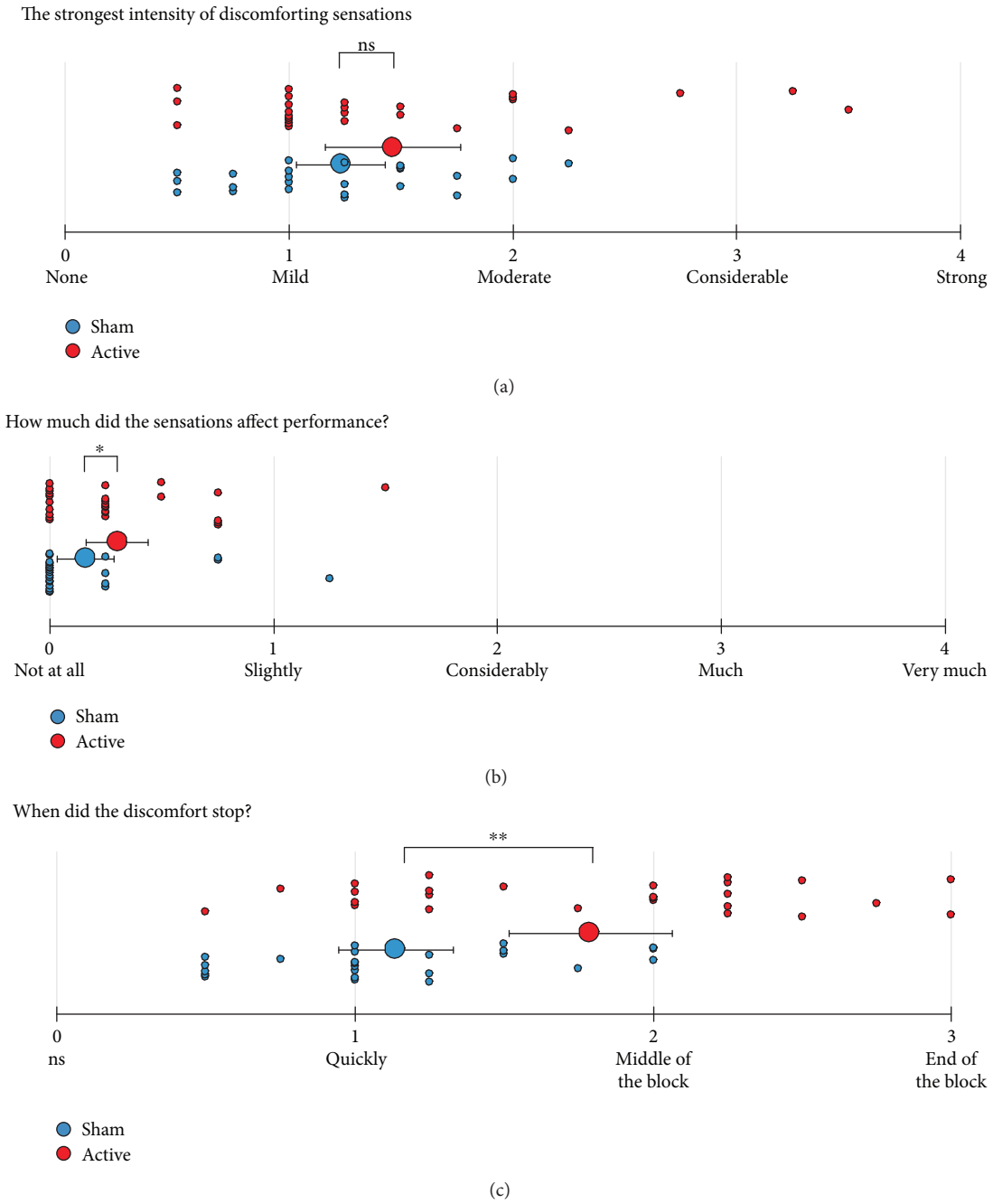


FIGURE 4: The 4-day average values of self-reported sensations during the training sessions. Large dots: group averages; small dots: individual participant values; red: active; blue: sham; error bars: 95% CI, two-tailed; $^{*}p < 0.05$, $^{**}p < 0.01$, two-tailed.

4. Discussion

We investigated the extent to which anodal tDCS over M1 facilitates motor sequence learning by observation, as previously reported for learning by physical practice [1–4]. Both the active and sham stimulation groups benefited from observational practice, replicating previous findings that motor skills can be learned by observation without overt physical practice [5, 34–39]. However, active stimulation over M1 did not provide an advantage to learning the motor sequences through observation over and above sham stimulation. Furthermore, Bayesian analyses revealed anecdotal to substantial evidence in favour of the null hypothesis across our dependent measures. Our findings therefore do not provide strong support for the hypothesis that excitatory M1 stimulation can enhance observational learning in a similar manner to physical learning.

4.1. Understanding the Role of the Motor System during Observational Learning. Although there is a consensus that shared mechanisms exist between action observation and

Table 3: Observational practice effects and tDCS effects on sequence-specific learning.

		I Observational training effect (trained versus untrained performance)		II Primary results	III Secondary results
		Sham	Active	tDCS effect (group difference)	tDCS effect (group difference), accounting for accuracy during training sessions
Initiation time	Post	$t_{(22)} = 2.65$, $p = 0.008$, $B_0 = 13\%$, $d_z = 0.54$	$t_{(24)} = 4.02$, $p < 0.001$, $B_0 = 24\%$, $d_z = 0.79$	*$t_{(47)} = 1.50$, $p = 0.072$, $d = 0.44$, anecdotal evidence against the effect ($BF_{10}/BF_{01} = 0.70/1.43$)*	$t_{(46)} = 2.48$, $p = 0.008$, $d = 0.73$, anecdotal evidence for the effect ($BF_{10}/BF_{01} = 2.41/0.41$)
	Ret.	$t_{(22)} = 3.21$, $p = 0.002$, $B_0 = 21\%$, $d_z = 0.66$	$t_{(24)} = 2.87$, $p = 0.004$, $B_0 = 21\%$, $d_z = 0.56$	*$t_{(47)} = 0.05$, $p = 0.480$, $d = 0.01$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.29/3.49$)*	*$t_{(46)} = 0.01$, $p = 0.496$, $d = 0$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.29/3.45$)*
Execution time	Post	$t_{(22)} = 5.02$, $p < 0.001$, $B_0 = 15\%$, $d_z = 1.02$	$t_{(24)} = 4.75$, $p < 0.001$, $B_0 = 14\%$, $d_z = 0.93$	*$t_{(47)} = -0.37$, $p = 0.355$, $d = 0.11$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.30/3.31$)*	*$t_{(46)} = -0.49$, $p = 0.312$, $d = 0.15$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.31/3.20$)*
	Ret.	$t_{(22)} = 4.02$, $p < 0.001$, $B_0 = 10\%$, $d_z = 0.82$	$t_{(24)} = 3.99$, $p < 0.001$, $B_0 = 10\%$, $d_z = 0.78$	*$t_{(47)} = -0.06$, $p = 0.475$, $d = 0.02$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.28/3.55$)*	*$t_{(46)} = -0.02$, $p = 0.492$, $d = 0.01$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.29/3.43$)*
Error rate	Post	$t_{(22)} = 2.56$, $p = 0.009$, $B_0 = 7\%$, $d_z = 0.52$	$t_{(24)} = 2.89$, $p = 0.004$, $B_0 = 9\%$, $d_z = 0.57$	*$t_{(47)} = 0.47$, $p = 0.322$, $d = 0.14$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.31/3.20$)*	*$t_{(46)} = 0.20$, $p = 0.422$, $d = 0.06$, substantial evidence against the effect ($BF_{10}/BF_{01} = 0.31/3.28$)*
	Ret.	$t_{(22)} = 2.99$, $p = 0.004$, $B_0 = 7\%$, $d_z = 0.61$	*$t_{(24)} = 1.45$, $p = 0.08$, $B_0 = 4\%$, $d_z = 0.28$*	*$t_{(47)} = -0.81$, $p = 0.210$, $d = 0.24$, anecdotal evidence against the effect ($BF_{10}/BF_{01} = 0.37/2.71$)*	*$t_{(46)} = -1.05$, $p = 0.149$, $d = 0.31$, anecdotal evidence against the effect ($BF_{10}/BF_{01} = 0.44/2.27$)*

Items in italics highlight nonsignificant effects. All p values reported reflect one-tailed tests as we had directional predictions for the influence of training and stimulation on our performance measures. Results are uncorrected for multiple comparisons.

execution [14], the role played by the motor system in observational learning is not clear [12, 13]. Indeed, several studies have questioned the notion of motor-driven learning by observation, arguing instead that it is driven by perceptual and cognitive processes [40–42]. It is possible, therefore, that primary motor areas might be engaged during action observation [43–45], but their involvement might not be *critical* in shaping observational learning.

Alternatively, it is possible that the effect of anodal tDCS over M1 during observational learning is smaller than during physical learning and subtler than we could detect in the current study. The current study had 80% power to detect an effect size that is typically considered large (0.71 Cohen's *d*). Therefore, we have reasonable confidence that we could detect large effects of stimulation, similar to what were reported previously during physical learning, should they exist. In addition, we followed recommended stimulation protocols by stimulating on consecutive days to enhance effects of stimulation [1] and skill learning [25, 26] (although, see work by Monte-Silva and colleagues [46] that demonstrates the abolishment of LTP-like plasticity in motor cortex when follow-up stimulation occurs 24 hours after initial stimulation). As such, we designed the experiment to increase the likely impact of tDCS on skill learning, but nonetheless report a null result. We suggest that future studies wishing to further explore the role of M1 in observational learning use a similar protocol, but with larger sample sizes, in order to increase statistical power to detect smaller effects.

The null result we report here adds to a growing set of null results using tDCS in tasks ranging from working memory [47, 48] to language [49, 50]. In addition, several recent meta-analyses document conflicting evidence regarding the efficacy of tDCS in a variety of paradigms where effects have previously been reported, as well as growing scepticism regarding a causal role of tDCS in performance enhancement [48, 50]. Given concerns over publication bias in general [51] and in the domain of tDCS in particular [52], it is important to report null results in order to provide a less biased estimate of the likely effect sizes that tDCS may have on behaviour. Therefore, balanced reporting of null results (in addition to positive results, such as those observed with tDCS over premotor cortex facilitating observational learning of a motor sequence [53]) will help to build a cumulative science of observational learning and tDCS. For instance, based on the details of the current study, researchers who wish to further explore the relationship between primary motor cortex activity and observational learning will have a more accurate estimate of the likely effect sizes that they might be targeting, which will directly inform power calculations and study design decisions.

The current study also provides a platform for future tDCS studies to build upon in other ways. Indeed, there are many avenues that future work could pursue in order to probe the relationship between the motor system and observational learning. For example, the effects of tDCS on observational learning may be task dependent. Aridan and Mukamel [21] reported a positive relationship between M1 activity during action observation and the success of motor skill learning via observation only if the observed model's performance was faster than the observer's performance at baseline. The current study used an intermediate model, which may not have been challenging enough to engage the motor system sufficiently. Future studies could use an expert model whose performance consistently exceeds the observer's baseline performance to test this possibility directly.

Follow-up work could also investigate the impact of different stimulation protocols. For example, several reports demonstrate a powerful effect of dual-M1 stimulation on motor learning [30, 54], which outperforms unilateral M1 stimulation montages [55–58]. Another possibility to explore with future work is the impact of tDCS intensity on motor learning effects. Recent work demonstrates that 1.5 mA, but not 1.0 mA, anodal tDCS over M1 reliably facilitates motor learning [59], which raises the possibility that our stimulation intensity was not optimised to induce reliable results. A further consideration is that small differences were observed in the sensations associated with active compared to sham stimulation, which is consistent with prior research [29]. The impact that such sensation differences have on task performance are worth studying in order to more effectively design sham protocols. Moreover, due to the electrode size (7×5 cm), the focality of tDCS stimulation is necessarily imprecise, and stimulation in our study may have extended beyond M1 into nearby premotor and anterior parietal brain regions as well. The modulation of cortical excitability under and between the electrodes is still under debate and investigation [10, 60]. As these suggestions demonstrate, many different lines of inquiry will be needed to better understand the relationship between motor system engagement and observational learning.

5. Conclusions

Our results do not support the hypothesis that anodal tDCS over M1 facilitates skill learning through observation to a large degree. The null finding does not necessarily imply that the motor system is not involved in sequence learning by observation. Rather, the results suggest that using the parameters employed in the current study, anodal tDCS over M1 does not reliably enhance observational learning. Given that no prior study has used tDCS over M1 in an attempt to enhance observational learning, this finding makes an important contribution to the literature by informing future brain stimulation studies and offering a platform upon which to base further investigation into the role of primary motor cortex in observational learning.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Richard Ramsey and Emily S. Cross contributed equally to this work.

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Supplementary Materials

Supplementary 1. The Supplementary Materials (videos) illustrate one example trial of an observational learning video stimulus.

Supplementary 2. Supplementary Materials 1 contains full results excluding the nine participants for whom TMS localisation of M1 was not possible. These supplementary materials contain a table of the observational practice effects and tDCS effects on sequence-specific learning, as well as a figure visualising all performance results excluding these nine participants. Supplementary Materials 2 is a figure visualising the mean and standard deviation values of participants' initiation time, execution time, and error rate, split into pre, post, and retention tests, and by the stimulation group (active versus sham). Supplementary Materials 3 includes a table documenting group differences in performance generalisation to the untrained sequences. Finally, Supplementary Materials 4 includes the tDCS effects on sequence-specific learning using ANCOVA.

References

[1] F. Hashemirad, M. Zoghi, P. B. Fitzgerald, and S. Jaberzadeh, "The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: a systematic review and meta-analysis," *Brain and Cognition*, vol. 102, pp. 1–12, 2016.

[2] J. Reis and B. Fritsch, "Modulation of motor performance and motor learning by transcranial direct current stimulation," *Current Opinion in Neurology*, vol. 24, no. 6, pp. 590–596, 2011.

[3] E. R. Buch, E. Santarnecchi, A. Antal et al., "Effects of tDCS on motor learning and memory formation: a consensus and critical position paper," *Clinical Neurophysiology*, vol. 128, no. 4, pp. 589–603, 2017.

[4] C. Ammann, D. Spampinato, and J. Márquez-Ruiz, "Modulating motor learning through transcranial direct-current stimulation: an integrative view," *Frontiers in Psychology*, vol. 7, pp. 3–6, 2016.

[5] S. Vogt and R. Thomaschke, "From visuo-motor interactions to imitation learning: behavioural and brain imaging studies," *Journal of Sports Sciences*, vol. 25, no. 5, pp. 497–517, 2007.

[6] D. Spampinato and P. Celnik, "Temporal dynamics of cerebellar and motor cortex physiological processes during motor skill learning," *Scientific Reports*, vol. 7, article 40715, 2017.

[7] M. S. Rioult-Pedotti, D. Friedman, and J. P. Donoghue, "Learning-induced LTP in neocortex," *Science*, vol. 290, no. 5491, pp. 533–536, 2000.

[8] J. N. Sanes and J. P. Donoghue, "Plasticity and primary motor cortex," *Annual Review of Neuroscience*, vol. 23, no. 1, pp. 393–415, 2000.

[9] M. A. Nitsche and W. Paulus, "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation," *The Journal of Physiology*, vol. 527, no. 3, pp. 633–639, 2000.

[10] M. A. Nitsche, L. G. Cohen, E. M. Wassermann et al., "Transcranial direct current stimulation: state of the art 2008," *Brain Stimulation*, vol. 1, no. 3, pp. 206–223, 2008.

[11] C. J. Stagg and M. A. Nitsche, "Physiological basis of transcranial direct current stimulation," *The Neuroscientist*, vol. 17, no. 1, pp. 37–53, 2011.

[12] D. J. Ostry and P. L. Gribble, "Sensory plasticity in human motor learning," *Trends in Neurosciences*, vol. 39, no. 2, pp. 114–123, 2016.

[13] H. R. McGregor, J. G. A. Cashaback, and P. L. Gribble, "Functional plasticity in somatosensory cortex supports motor learning by observing," *Current Biology*, vol. 26, no. 7, pp. 921–927, 2016.

[14] A. Gentsch, A. Weber, M. Synofzik, G. Vosgerau, and S. Schütz-Bosbach, "Towards a common framework of grounded action cognition: relating motor control, perception and cognition," *Cognition*, vol. 146, pp. 81–89, 2016.

[15] M. Iacoboni, I. Molnar-Szakacs, V. Gallese, G. Buccino, J. C. Mazziotta, and G. Rizzolatti, "Grasping the intentions of others with one's own mirror neuron system," *PLoS Biology*, vol. 3, no. 3, article e79, 2005.

[16] G. Rizzolatti and C. Sinigaglia, "The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations," *Nature Reviews Neuroscience*, vol. 11, no. 4, pp. 264–274, 2010.

[17] D. Tkach, J. Reimer, and N. G. Hatsopoulos, "Congruent activity during action and action observation in motor cortex," *Journal of Neuroscience*, vol. 27, no. 48, pp. 13241–13250, 2007.

[18] J. Dushanova and J. Donoghue, "Neurons in primary motor cortex engaged during action observation," *European Journal of Neuroscience*, vol. 31, no. 2, pp. 386–398, 2010.

[19] R. Wahnoun, J. He, and S. I. H. Tillery, "Selection and parameterization of cortical neurons for neuroprosthetic control," *Journal of Neural Engineering*, vol. 3, no. 2, pp. 162–171, 2006.

[20] L. E. Brown, E. T. Wilson, and P. L. Gribble, "Repetitive transcranial magnetic stimulation to the primary motor cortex interferes with motor learning by observing," *Journal of Cognitive Neuroscience*, vol. 21, no. 5, pp. 1013–1022, 2009.

[21] N. Aridan and R. Mukamel, "Activity in primary motor cortex during action observation covaries with subsequent behavioral changes in execution," *Brain and Behavior*, vol. 6, no. 11, article e00550, 2016.

[22] T. Wiestler and J. Diedrichsen, "Skill learning strengthens cortical representations of motor sequences," *eLife*, vol. 2, 2013.

[23] D. H. Brainard, "The psychophysics toolbox," *Spatial Vision*, vol. 10, no. 4, pp. 433–436, 1997.

[24] A. Alonzo, J. Brassil, J. L. Taylor, D. Martin, and C. K. Loo, "Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation," *Brain Stimulation*, vol. 5, no. 3, pp. 208–213, 2012.

[25] J. Reis, H. M. Schambra, L. G. Cohen et al., "Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 5, pp. 1590–1595, 2009.

[26] C. M. Saucedo Marquez, X. Zhang, S. P. Swinnen, R. Meesen, and N. Wenderoth, "Task-specific effect of transcranial direct current stimulation on motor learning," *Frontiers in Human Neuroscience*, vol. 7, 2013.

[27] A. F. DaSilva, M. S. Volz, M. Bikson, and F. Fregni, "Electrode positioning and montage in transcranial direct current stimulation," *Journal of Visualized Experiments*, no. 51, article e2744, 2011.

[28] A. J. Woods, A. Antal, M. Bikson et al., "A technical guide to tDCS, and related non-invasive brain stimulation tools," *Clinical Neurophysiology*, vol. 127, no. 2, pp. 1031–1048, 2016.

[29] A. Fertonani, C. Ferrari, and C. Miniussi, "What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects," *Clinical Neurophysiology*, vol. 126, no. 11, pp. 2181–2188, 2015.

[30] S. Waters-Metenier, M. Husain, T. Wiestler, and J. Diedrichsen, "Bihemispheric transcranial direct current stimulation enhances effector-independent representations of motor synergy and sequence learning," *The Journal of Neuroscience*, vol. 34, no. 3, pp. 1037–1050, 2014.

[31] R. Morey, J. Rouder, J. Love, and B. Marwick, "BayesFactor: 0.9.12-2 CRAN," *Zenodo*, 2015.

[32] H. Jeffreys, *Theory of Probability*, Clarendon Press, Oxford, 3rd ed. edition, 1961.

[33] G. Cumming, *Understanding the New Statistics: Effect Sizes, Confidence Intervals, and Meta-Analysis*, Routledge/Taylor & Francis Group, New York, NY, US, 2012.

[34] G. Bird and C. Heyes, "Effector-dependent learning by observation of a finger movement sequence," *Journal of Experimental Psychology: Human Perception and Performance*, vol. 31, no. 2, pp. 262–275, 2005.

[35] C. M. Heyes and C. L. Foster, "Motor learning by observation: evidence from a serial reaction time task," *The Quarterly Journal of Experimental Psychology Section A*, vol. 55, no. 2, pp. 593–607, 2002.

[36] M. Osman, G. Bird, and C. Heyes, "Action observation supports effector-dependent learning of finger movement sequences," *Experimental Brain Research*, vol. 165, no. 1, pp. 19–27, 2005.

[37] A. Lago-Rodríguez and B. Cheeran, "The role of mirror neurons in observational motor learning: an integrative review," *European Journal of Human Movement*, vol. 32, pp. 82–103, 2014.

[38] L. P. Kirsch and E. S. Cross, "Additive routes to action learning: layering experience shapes engagement of the action observation network," *Cerebral Cortex*, vol. 25, no. 12, pp. 4799–4811, 2015.

[39] T. Gardner, A. Aglinskas, and E. S. Cross, "Using guitar learning to probe the action observation network's response to visuomotor familiarity," *NeuroImage*, vol. 156, pp. 174–189, 2017.

[40] S. B. Lim, B. C. Larssen, and N. J. Hodges, "Manipulating visual–motor experience to probe for observation-induced after-effects in adaptation learning," *Experimental Brain Research*, vol. 232, no. 3, pp. 789–802, 2014.

[41] G. Vannuscorps and A. Caramazza, "Typical action perception and interpretation without motor simulation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 1, pp. 86–91, 2016.

[42] D. Maslovat, N. J. Hodges, O. E. Krigolson, and T. C. Handy, "Observational practice benefits are limited to perceptual improvements in the acquisition of a novel coordination skill," *Experimental Brain Research*, vol. 204, no. 1, pp. 119–130, 2010.

[43] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[44] T. T. de Beukelaar, K. Alaerts, S. P. Swinnen, and N. Wenderoth, "Motor facilitation during action observation: the role of M1 and PMv in grasp predictions," *Cortex*, vol. 75, pp. 180–192, 2016.

[45] L. Fadiga, L. Fogassi, G. Pavesi, and G. Rizzolatti, "Motor facilitation during action observation: a magnetic stimulation study," *Journal of Neurophysiology*, vol. 73, no. 6, pp. 2608–2611, 1995.

[46] K. Monte-Silva, M. F. Kuo, S. Hessenthaler et al., "Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation," *Brain Stimulation*, vol. 6, no. 3, pp. 424–432, 2013.

[47] J. Nilsson, A. V. Lebedev, A. Rydström, and M. Lövdén, "Direct-current stimulation does little to improve the outcome of working memory training in older adults," *Psychological Science*, vol. 28, no. 7, pp. 907–920, 2017.

[48] J. Medina and S. Cason, "No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations," *Cortex*, vol. 94, pp. 131–141, 2017.

[49] A. R. Price, H. McAdams, M. Grossman, and R. H. Hamilton, "A meta-analysis of transcranial direct current stimulation studies examining the reliability of effects on language measures," *Brain Stimulation*, vol. 8, no. 6, pp. 1093–1100, 2015.

[50] S. J. Westwood, A. Olson, R. C. Miall, R. Nappo, and C. Romani, "Limits to tDCS effects in language: failures to modulate word production in healthy participants with frontal or temporal tDCS," *Cortex*, vol. 86, pp. 64–82, 2017.

[51] U. Simonsohn, L. D. Nelson, and J. P. Simmons, "*P*-curve: a key to the file-drawer," *Journal of Experimental Psychology: General*, vol. 143, no. 2, pp. 534–547, 2014.

[52] M. E. Héroux, C. K. Loo, J. L. Taylor, and S. C. Gandevia, "Questionable science and reproducibility in electrical brain stimulation research," *PLoS One*, vol. 12, no. 4, article e0175635, 2017.

[53] S. Wade and G. Hammond, "Anodal transcranial direct current stimulation over premotor cortex facilitates observational learning of a motor sequence," *European Journal of Neuroscience*, vol. 41, no. 12, pp. 1597–1602, 2015.

[54] S. Koyama, S. Tanaka, S. Tanabe, and N. Sadato, "Dual-hemisphere transcranial direct current stimulation over primary motor cortex enhances consolidation of a ballistic thumb movement," *Neuroscience Letters*, vol. 588, pp. 49–53, 2015.

[55] S. Karok and A. G. Witney, "Enhanced motor learning following task-concurrent dual transcranial direct current stimulation," *PLoS One*, vol. 8, no. 12, article e85693, 2013.

[56] S. Karok, D. Fletcher, and A. G. Witney, "Task-specificity of unilateral anodal and dual-M1 tDCS effects on motor learning," *Neuropsychologia*, vol. 94, pp. 84–95, 2017.

[57] B. W. Vines, C. Cerruti, and G. Schlaug, "Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation," *BMC Neuroscience*, vol. 9, no. 1, p. 103, 2008.

[58] L. Mordillo-Mateos, L. Turpin-Fenoll, J. Millán-Pascual et al., "Effects of simultaneous bilateral tDCS of the human motor cortex," *Brain Stimulation*, vol. 5, no. 3, pp. 214–222, 2012.

[59] K. Cuypers, D. J. F. Leenus, F. E. van den Berg et al., "Is motor learning mediated by tDCS intensity?," *PLoS One*, vol. 8, no. 6, article e67344, 2013.

[60] M. Kuo, R. Polanía, and M. Nitsche, "Physiology of transcranial direct and alternating current stimulation," in *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders*, A. Brunoni, M. Nitsche and C. Loo, Eds., pp. 29–46, Springer International Publishing, Cham, 2016.

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Research Article

Motor Imagery during Action Observation of Locomotor Tasks Improves Rehabilitation Outcome in Older Adults after Total Hip Arthroplasty

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This study aimed at determining whether the combination of action observation and motor imagery (AO + MI) of locomotor tasks could positively affect rehabilitation outcome after hip replacement surgery. Of initially 405 screened participants, 21 were randomly split into intervention group ($N = 10$; mean age = 64 y; AO + MI of locomotor tasks: 30 min/day in the hospital, then 3×/week in their homes for two months) and control group ($N = 11$, mean age = 63 y, active controls). The functional outcomes (Timed Up and Go, TUG; Four Step Square Test, FSST; and single- and dual-task gait and postural control) were measured before (PRE) and 2 months after surgery (POST). Significant interactions indicated better rehabilitation outcome for the intervention group as compared to the control group: at POST, the intervention group revealed faster TUG ($p = 0.042$), FSST ($p = 0.004$), and dual-task fast-paced gait speed ($p = 0.022$), reduced swing-time variability ($p = 0.005$), and enhanced cognitive performance during dual tasks while walking or balancing ($p < 0.05$). In contrast, no changes were observed for body sway parameters ($p \geq 0.229$). These results demonstrate that AO + MI is efficient to improve motor-cognitive performance after hip surgery. Moreover, only parameters associated with locomotor activities improved whereas balance skills that were not part of the AO + MI intervention were not affected, demonstrating the specificity of training intervention. Overall, utilizing AO + MI during rehabilitation is advised, especially when physical practice is limited.

1. Introduction

Prolonged immobilization and inactivity after injury and/or surgery may lead to serious motor and cognitive dysfunctions, especially in older adults [1, 2]. More precisely, immobilization in the acute period after hip arthroplasty has become more and more frequent in this population due to the increasing amount of people suffering from osteoporosis, which can result in hip fractures [3]. Despite the knowledge that immobilization not only negatively affects cardiovascular and pulmonary parameters but also increases the risk of falls and movement disorders [1, 4], patients are generally inactive during this period due to their limited ability to participate in physical exercise. In addition, immobilization leads to several impairments of motor function [5]. Motor impairments that follow short periods of inactivity are believed to be principally driven by changes occurring at the cortical level rather than the muscular level [6–8]. Indeed, a significant reduction of the cortical motor area representing the immobilized limb could be observed [9].

To counteract at least some of these risk factors, mental simulation techniques such as action observation (AO) or motor imagery (MI) have been proposed as feasible alternatives to stimulate the motor system [10, 11]. The AO therapy

requires subjects to observe a video clip or watch actions performed by an operator [12, 13] while MI represents the mental simulation of motor actions without any corresponding motor output [14].

In the last decade, a growing number of AO- or MI-based interventions were successfully conducted that aimed at fostering rehabilitation of patients, for instance, after stroke [12, 15, 16], Parkinson's disease (for review, see [17]), or orthopedic injury and/or surgery [18, 19]. The use of AO in healthy participants has been shown to limit the reduction of brain area that is normally induced by immobilization [20]. Thus, activation of cerebral visuomotor systems during AO seems sufficient to counteract negative cortical plasticity induced by immobilization. Similarly, MI was demonstrated to counteract the slowdown of sensorimotor processes induced by short-term immobilization [21]. The reason for the efficiency of those mental simulation techniques is considered to rely on activation of overlapping brain areas during AO, MI, and physical execution of the motor task [14, 22]. Traditionally, AO and MI have been considered as independent intervention methods. Recently, however, more and more evidence emerged that proposes increased efficiency when combining AO with MI (AO + MI), meaning that MI is performed during AO (for reviews, see [23, 24]). In this context, AO + MI has revealed higher corticospinal excitability [25, 26] as well as greater activity in motor areas of the brain [27] compared to either AO or MI alone. Noteworthy some studies even reported oversummative activity [27, 28] compared to the sum of brain activity during independent AO and independent MI. These findings were interpreted as evidence that neural correlates of MI and AO might merge rather than compete with each other [24]. However, due to a lack of intervention studies, it is not clear to date whether the combination of AO and MI (AO + MI) in addition to common physical therapy has important implications for neurorehabilitation and motor (re-)learning in patients (for reviews, see [23, 24]).

The aim of the present study therefore was to evaluate AO + MI in a clinical setting by comparing the rehabilitation outcomes of patients undergoing an AO + MI intervention with those of patients that were treated in the conventional way only. One major aim of our study was to minimize the period of inactivity and to start with an early rehabilitation. Finally, our main hypothesis was that the combination of AO and MI (AO + MI) would result in better rehabilitation outcome than the conventional intervention alone.

2. Methods

2.1. Participants. Participants were recruited from the general database of Valdoltra Orthopaedic Hospital, University of Primorska, Ankaran, Slovenia. From 405 subjects that were assessed for eligibility, 26 volunteered to participate in the "*PANGeA hip study, Valdoltra 2015*." Finally, 21 participants successfully completed both (PRE and POST) measurements (for baseline characteristics, see Table 1). Due to primary osteoarthritis of the hip, the cementless total hip arthroplasty (THA) was performed through direct lateral approach in all participants. The enrolment, randomization, and final analysis procedures are shown in the CONSORT flow diagram (Figure 1). Prior to the study, all participants were physically screened by medical doctors and interviewed by the research team. The exclusion criteria were as follows: previous THA, severe acute metabolic, neuromuscular and cardiovascular diseases, excessive obesity (over 45% fat), elevated/high body temperature or other life-threatening situations, infectious diseases, cancer, bleeding, failure of vitally important organs, complete physical exhaustion, mild cognitive impairment or dementia, critical ischemia of the lower limbs, and patients unable to intend the measurement and rehabilitation protocols. All participants were right-handed and had normal or corrected-to-normal vision. All procedures were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and were approved by the National Medical Ethics Committee. Written informed consent was obtained from all participants prior to the study, and no payment was provided for participation in this study.

2.2. Nonphysical Training Intervention. Participants in the intervention group received next to a standard rehabilitation protocol with physiotherapists an additional nonphysical intervention (AO + MI of locomotor tasks) for approximately 30 minutes per day in the hospital, then 3 times per week in their homes, for a period of 2 months. At the same time and for the same amount of time, participants who were randomly allocated to the placebo control group were asked to actively observe the documentary videos on the television (in hospital and at home). Participants in both groups spent approximately 4–6 days in the hospital before being discharged. All hospital sessions were surveyed and supervised by the authors of the study. Home sessions were supervised by one experimenter during the beginning of the training and then by conference (Skype) video calls. Participants in the control group were also contacted via phone or Skype at least once per week within the period of two months to ensure a comparable level of commitment and to monitor their personal notes regarding the time they spent watching educational documentaries.

Each session of the nonphysical intervention program started with a short relaxation protocol. Afterwards, participants watched video clips presented on a 13-inch tablet PC showing a healthy person filmed from behind performing different locomotor tasks. The difficulty of the presented tasks was progressively increased from week 1 to 8: participants started observing a person walking slowly with assistive devices (e.g., walker and crutches), continuing with normal and fast-paced gait, walking upstairs and downstairs, and walking on narrow (normal and narrow sport bench) and unstable surfaces (soft mats, sand beach, and surfaces covered with snow). When participants reached the level where they could easily imagine themselves performing the presented tasks, an additional task was added such as performing the same locomotor task while holding a glass or a jug full of water. The videos were of different lengths (30 s to 60 s of cyclic locomotor tasks) and were displayed in blocks of 60 to 120 s (see also underneath for more details). Thus, the videos were repeated between two and four times while

Table 1: Baseline characteristics of PANGeA hip study participants.

	Intervention group ($N = 10$)	Control group ($N = 11$)	p value
Gender	2 women	5 women	
Age (y)	64.4 ± 4.1	63.1 ± 5.6	0.550
Height (cm)	171.8 ± 5.1	168.6 ± 13.8	0.528
Weight (kg)	86.6 ± 8.7	76.0 ± 15.7	0.088
Grip strength, dominant (kg)	35.3 ± 9.1	32.3 ± 15.6	0.605
Total hip replacement, (right side, N)	7/10	7/11	
MoCA score	27.9 ± 1.4	28.1 ± 1.4	0.755
Education duration (y)	12.4 ± 3.0	11.8 ± 2.4	0.636

Note: data are mean ± SD. MoCA: Montreal Cognitive Assessment.

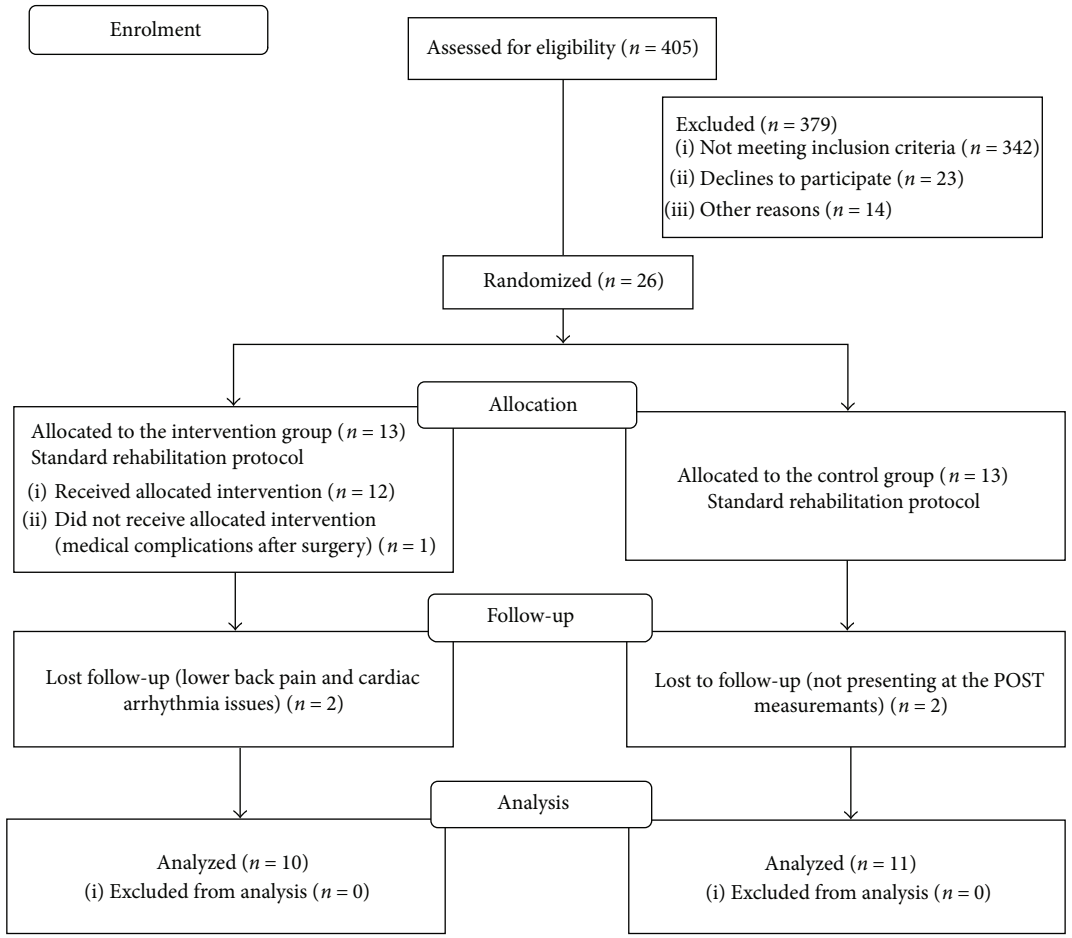

Figure 1: CONSORT flow diagram of the *PANGeA hip study, Valdoltra 2015*.

the participants watched the video and at the same time imagined performing the task that was shown in the video (AO + MI). However, as older adults indicated to have some problems to watch and at the same time "feel the sensations that arise from doing the task" (kinesthetic motor imagery), we presented first the video and asked them to do AO + MI followed by a period in which subjects should close their eyes and imagine the sensations that arise from doing the task (MI). First, this combination of AO + MI and MI was only foreseen in order to familiarize participants with AO + MI. However, this method proved very efficient to maintain the participants' motivation high, and therefore, the entire non-physical training was conceptualized to maintain blocks of AO + MI followed by the same amount of time for MI. Starting with 60 seconds of AO + MI and 60 seconds of MI, participants in the intervention group were encouraged to prolong their AO + MI and MI sessions up to 120 seconds for each task throughout the whole training period (two months). Altogether 30 different videos were used as shown in Table 2. Thus, during each training day, at least one to two

Table 2: Example of cognitive training intervention blocks for three successive trainings.

Length	AO + MI	Training 1	Training 2	Training 3
2 minutes each	AO + MI	Video 1	Video 2	Video 4
	MI			
	AO + MI			
	MI			
	Break			
	AO + MI	Video 1	Video 3	Video 4
	MI			
	AO + MI			
	MI			
	Break			
	AO + MI	Video 2	Video 3	Video 5
	MI			
	AO + MI			
	MI			

Note: each training session duration was approximately 30 minutes.

new videos were presented. Before watching the videos, the participants were instructed as follows: "On the following video you will see a locomotor task, which will be repeated several times. Observe this task and imagine performing the task yourself during the entire period of the video. After several repetitions (60–120 s) you will be asked to close your eyes and to continue performing mentally the task until you hear the stop sign. From time to time, I will encourage you performing the task. Now try to relax and when you are ready, press the spacebar to start the video while concentrating as much as possible on the task."

2.3. Outcome Measures. All measurements were carried out in a separate and quiet room to avoid any external disturbances from the hospital environment. All tests were performed twice, prior surgery (PRE measurements) and 60 days postsurgery (POST measurements).

2.3.1. Timed Up and Go Test (TUG). The TUG test was administered to quantify the functional mobility of patients [29]. Patients were asked to rise from the chair, walk around an obstacle that was 3 m away, and return to take a seat as quickly and safely. A practice trial was given, and then two timed trials were recorded and averaged [30]. Time to completion was monitored with a stopwatch.

2.3.2. Four Step Square Test (FSST). Patients were asked to perform stepping over 25 mm high obstacles in four different directions as quickly and safely as they could (FSST). A practice trial was given, and two timed trials were performed where the best of both was used for further analysis [31]. Time to completion was monitored with a stopwatch.

2.3.3. Single- and Dual-Task Walking. Spatiotemporal gait parameters were measured with the 2D OptoGait system (Microgate, Bolzano, Italy) in the following four 1-minute conditions in a randomized order: walking at their preferred, self-selected speed; brisk walking to the best of their capacity; and both speeds under a dual-task condition. The dual-task conditions were composed of walking and at the same time subtracting by threes from a randomly chosen number between 400 and 500 (serial 3s). Prior to walking, a familiarization trial was given to each participant. Participants were instructed to subtract as many numbers as possible, with their focus prioritized to task correctness prior to the speed of subtraction. Gait speed and swing-time variability were taken into further consideration [4]. For the cognitive task, the amount of subtracted numbers and errors was monitored for each condition.

2.3.4. Single- and Dual-Task Postural Control. The postural task consisted of standing as still as possible in a tandem foot placement position. Participants were asked to focus on a black point placed approximately one meter in front of them at eye level. A force plate (AMTI HE600600-2k, Advanced Mechanical Technology Inc., Watertown, MA, USA) was used to measure displacements of the center of pressure (COP) in both mediolateral and anteroposterior directions. From these values, total sway path, frequency, and amplitude were calculated separately for each direction. This postural task was either performed as a single task or combined with a secondary cognitive task. The cognitive task and its instructions were identical as for walking (see Section 2.3.3).

2.4. Statistical Analyses. The data were analyzed with IBM SPSS Statistics 24.0 software for Windows (SPSS Inc., Chicago, Il, USA). The Shapiro-Wilk test was performed to all datasets to test for normality of distribution. Baseline differences between both groups were assessed with independent sample t-test. Interactions were tested by a 2-way analysis of variance (ANOVA) where the group (intervention and control groups) was used as the between subject variable and time (PRE and POST measurements) as the within subject variable. In case of significance, post hoc comparisons with Bonferroni corrections were applied. For ordinal parameters and not-normally distributed data, a Friedman's ANOVA was used. Statistical significance was set at the level of $p < 0.05$.

3. Results

From all participants that were included and randomized, 10 participants from the intervention group (age: 64.4 ± 4.1 years; height: 171.8 ± 5.1 cm; weight: 86.6 ± 8.7 kg) and 11 participants from the control group (age: 63.1 ± 5.6 years; height: 168.6 ± 13.8 cm; weight: 76.0 ± 15.7 kg) were considered for statistical analyses. Functional outcome data did not violate normality of distribution as assessed by Shapiro-Wilk test (all $p \geq 0.106$). Furthermore, the independent sample t-test showed no significant differences between the intervention and control groups in any parameter of the baseline characteristics (see Table 1).

3.1. TUG Test. At PRE, the intervention group did not differ from the control group when performing the TUG ($p = 0.731$). However, there was a significant time × group interaction ($F_{1,19} = 4.770$, $p = 0.042$, $\eta^2 = 0.201$). Post hoc analyses revealed that the performance of the intervention group did not differ between PRE and POST ($-3.7 \pm 14.0\%$;

$p = 0.427$), while there was a trend toward deterioration in the control group, demonstrated as more time spent in TUG at POST ($+27.8 \pm 37.2\%$; $p = 0.061$) (see Figure 2). In addition, a significant difference between groups was observed at POST ($p = 0.031$).

3.2. FSST Test. At PRE, the intervention group did not differ from the control group when performing the FSST ($p = 0.498$). However, there was a significant time × group interaction ($F_{1,19} = 11.077$, $p = 0.004$, $\eta^2 = 0.368$). Post hoc analyses revealed that there was a trend toward an increase in time for completion of FSST in the control group ($+14.2 \pm 20.9\%$; $p = 0.071$) while there was a significant reduction in the intervention group at POST ($-12.6 \pm 12.3\%$; $p = 0.014$) (see Figure 2). Also, a significant difference between groups was observed at POST ($p = 0.001$).

3.3. Single- and Dual-Task Walking. At PRE, no significant differences were found between both groups for any of the assessed gait parameters (all $p \geq 0.284$). For the self-selected walking speed condition, there were neither significant main (all $p \geq 0.429$) nor interaction effects (all $p \geq 0.150$) for gait speed and swing-time variability parameters.

For the single-task fast-paced walking condition, there were no significant interaction effects for gait speed ($p = 0.132$) and swing-time variability ($p = 0.122$). In contrast, during dual-task fast-paced walking, there was a significant time × group interaction for gait speed ($F_{1,19} = 6.174$, $p = 0.022$, $\eta^2 = 0.245$). Post hoc tests indicated that the control group significantly decreased gait speed between PRE and POST ($-9.26 \pm 12.67\%$; $p = 0.029$) whereas the intervention group nonsignificantly increased their gait speed ($+5.15 \pm 15.91\%$; $p = 0.360$) (see Figure 2). Also, for the same parameter at POST, there was a nonsignificant trend between the two groups ($p = 0.097$).

For swing-time variability parameter, there was a significant time × group interaction ($F_{1,19} = 10.144$, $p = 0.005$, $\eta^2 = 0.348$). Post hoc tests revealed that the control group significantly increased swing-time variability between PRE and POST ($+25.54 \pm 23.39\%$; $p = 0.006$) while the intervention group nonsignificantly reduced swing-time variability ($-7.18 \pm 30.99\%$; $p = 0.315$) (see Figure 2). In addition, a significant difference between groups was observed at POST ($p = 0.004$).

For cognitive performance, there were no differences between the two groups at PRE for neither the subtracted numbers (all $p \geq 0.482$) nor the errors made (all $p \geq 0.124$). Friedman's ANOVA revealed a significant improvement in subtracted numbers at POST only for the intervention group during both self-selected ($\chi^2(1) = 8.000$, $p = 0.005$) and fast-paced walking ($\chi^2(1) = 6.000$, $p = 0.014$) while no changes were detected for the control group (self-selected: $p = 0.317$; fast-paced: $p = 0.480$). Similarly, for errors made during the serial threes subtraction task, there was a nonsignificant trend for both groups only in the self-selected walking condition: the intervention group nonsignificantly reduced errors ($\chi^2(1) = 3.000$, $p = 0.083$) while there was a trend for an increase in errors for the control group ($\chi^2(1) = 3.571$, $p = 0.059$). Finally, in the fast-paced walking condition, there was neither a change in the number of errors for the control group ($p = 0.705$) nor the intervention group ($p > 0.999$).

3.4. Single- and Dual-Task Postural Control. At PRE, no significant differences in any of the postural parameters were found between both groups (all $p \geq 0.105$).

There were no significant time × group interactions for any of the COP parameters (total sway path, frequency, and amplitude) in both mediolateral and anteroposterior directions, as well as in postural single- and dual-task conditions (all $p \geq 0.229$).

For the cognitive performance assessed during the serial threes subtraction task, there were no differences between the two groups at PRE, neither for the numbers calculated ($p = 0.810$) nor for the errors made ($p = 0.819$). However, Friedman's ANOVA revealed a significant improvement in subtracted numbers at POST for the intervention group only ($\chi^2(1) = 9.000$, $p = 0.003$) while no changes were observed in the control group ($p \geq 0.999$). For the errors made during the serial threes subtraction task, there was a nonsignificant trend for reduction of errors in the intervention group ($\chi^2(1) = 2.778$, $p = 0.096$) while there was a nonsignificant trend for an increase in the control group ($\chi^2(1) = 3.600$, $p = 0.058$).

4. Discussion

The principal finding of the current study is that two months of additional nonphysical training resulted in better functional and cognitive rehabilitation outcomes in patients with unilateral total hip replacement than with the standard rehabilitation program alone. More specifically, our study supports the feasibility of AO + MI combined with kinesthetic MI in order to accelerate and improve the acute phase of rehabilitation (up to two months after the surgery). The intervention group had better outcomes than the control subjects in physical tests that measured functional mobility and stepping over obstacles, tasks that were actually part of the mental training. In contrast, no differences between the intervention and control groups were found in tasks that were not mentally trained such as static balance. This underlines the task specificity of the mental training intervention.

There is increasing evidence that the combination of AO and MI (AO + MI) leads to greater brain activity in motor areas than either AO or MI alone (for reviews, see [23, 24]). However, the functional implications of these observations for rehabilitation are not clear, yet, as the applicability and effectiveness of AO + MI was scarcely investigated in functional settings. Some of the first studies that concentrated on behavioral outcomes were conducted in the sports domain, where AO + MI was initially entitled "video-guided imagery." In this context, it was demonstrated that training with AO + MI was more effective in order to learn golf putting [32] or increase elbow flexors strength [33] than the same training with MI. Similarly, Sun et al. [34] demonstrated better rehabilitative outcome in a group practicing concurrent AO + MI than a group that first observed and then imagined the same actions. However, less clear results were

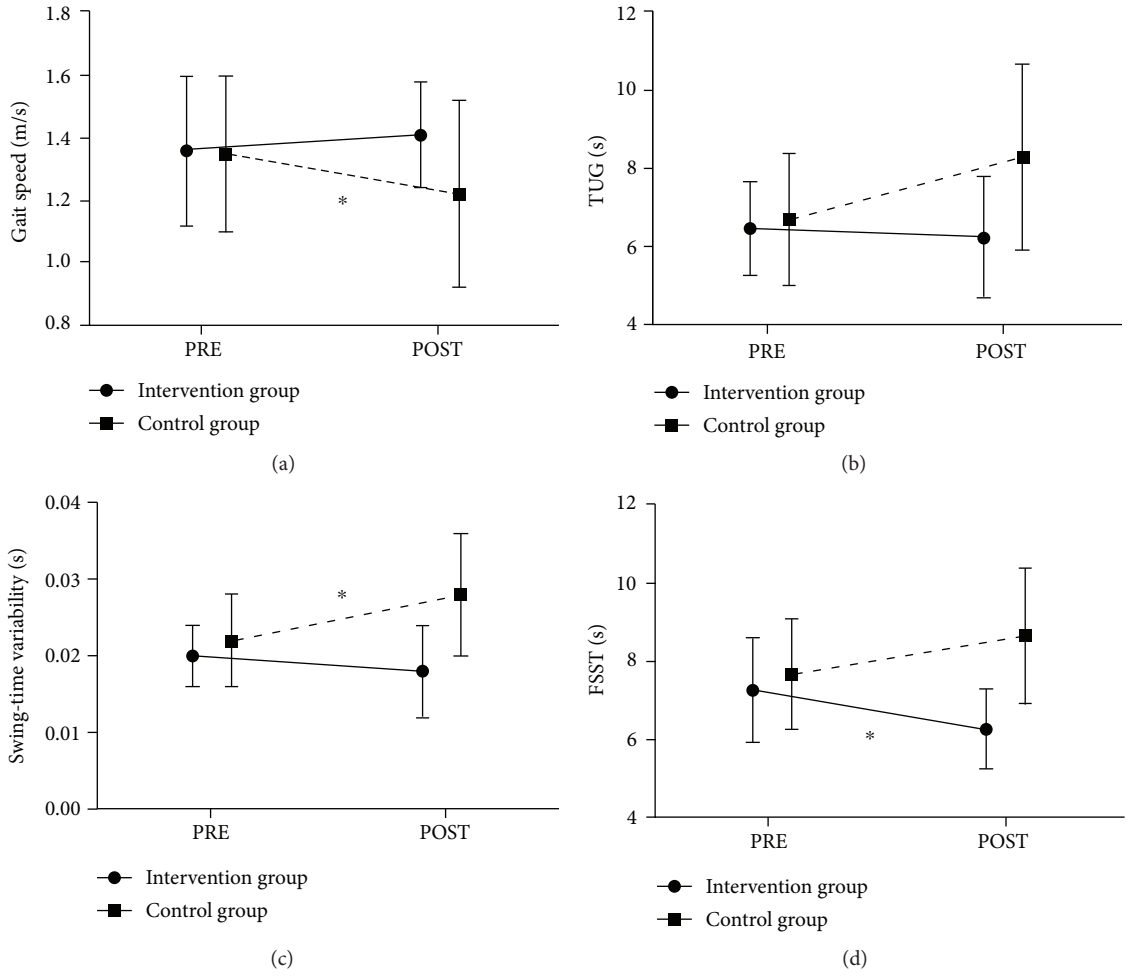

Figure 2: Results from functional locomotor outcome measures (mean ± standard deviation): (a) gait speed in the fast-paced dual-task walking condition; (b) results for the Timed Up and Go test (TUG); (c) swing-time variability in the fast-paced dual-task walking condition; (d) the results for the Four Step Square Test (FSST). Note: * indicates a significant change ($p < 0.05$) in the Bonferroni-corrected post hoc test from PRE to POST.

obtained after nonphysical balance training with comparable outcomes when using either AO + MI or MI alone [35].

In the present study, we initially wanted to evaluate the influence of AO + MI in a clinical setting by comparing AO + MI with the normal rehabilitation procedure. However, as subjects indicated difficulties to watch and at the same time "feel the sensations that arise from doing the task" (kinesthetic motor imagery), we presented first the video and asked them to do AO + MI followed by a period in which subjects should close their eyes and imagine the sensations that arise from doing the task (MI). Although this kind of mental training intervention intermingles AO + MI and MI, and consequently, the influence of each single mental simulation technique cannot be differentiated, we considered it most important to apply a motivating, comprehensive, and feasible mental training intervention. Furthermore, out of the 405 screened patients, we expected to recruit a higher number of "suitable" participants for the current study that would have allowed the comparison of the current two groups with an additional group performing solely MI. However, although this was not possible, the current approach nevertheless allows the comparison between the standardized (best practice) rehabilitation procedures with the same rehabilitation process amplified with mental simulation of locomotor tasks.

From the behavioral perspective, the current mental simulation training of locomotor tasks in THA patients was highly efficient (a) to counteract surgery-induced impairments that became obvious in the control group (TUG; gait speed and swing-time variability during dual-task walking) and (b) to even improve some motor-cognitive skills already two months after surgery (FSST; cognitive performance during postural tasks and during walking). Another interesting point is the task specificity of the mental simulation approach. Only in tasks that were part of the mental training, participants demonstrated improved task performance compared to the control group whereas in tasks that were not mentally trained, no differences between groups were obvious. Furthermore, the AO + MI training-related effects were mostly seen in the more demanding tasks, such as dual-task walking, where participants needed to perform a secondary cognitive task while walking. The present results are in

general agreement with one of our previous studies where nonphysical training led to enhanced performance only in the most attention-demanding walking condition [4].

The underlying mechanisms of mental simulation programs are believed to rely on overlapping brain areas during motor execution and MI as well as during motor execution and AO [14, 22]. In this context, Jeannerod postulated the well-accepted hypothesis that "the motor system is part of a simulation network that is activated under a variety of conditions in relation to action, either self-intended or observed from other individuals" [36]. Recent studies proposed the combination of AO and MI (AO + MI) as this combined approach was found to elicit greater [25, 37] and in some cases even oversummative activity [27, 28] compared to the sum of brain activity during independent AO and independent MI. These findings were interpreted as evidence that neural correlates of MI and AO might merge rather than compete with each other [24]. In this sense, the involvement of distinct brain structures that can solely be activated by either MI or AO [38, 39] would provide supplementary and complementary activation compared to one or the other modality alone. In addition, the activation of common AO and MI brain regions, mostly premotor and motor areas, may induce an overlapping activity [22, 40] that would further augment brain activity with AO + MI. Concerning the execution of AO + MI, it was suggested that the mental simulation of a movement would be facilitated by visual guidance, which allows the participants to update their internal representations. In addition, the visual stimulus generated by AO may help participants to create a visual image, allowing them to focus on kinesthetic modality [41], known to be more effective to activate the motor neural processes than visual imagery only [42]. In line with this, patients in our intervention group reported to be able to perform better kinesthetic MI directly after having seen a video of the task.

With advanced age mental imagery capacities can be altered, especially the temporal features of the imagined action [43]. Our training therefore started with relatively short videos, and the task exposure time was progressively increased. It has been argued that the lack of sensory feedback might be one of the main reasons to explain the decreased ability to perform motor imagery with age [44]. This argues in favor of using AO + MI approaches, since AO may help old adults to compensate for MI ability deficiencies. This is further supported by the finding in elderly subjects that revealed better effectiveness of AO + MI in activating brain areas, than either AO or MI alone [25].

5. Conclusion

The present study highlights the benefits of AO + MI interventions for rehabilitation purposes, especially when participants are immobilized after surgery. The results demonstrate that the integrated AO + MI approach was an efficient tool to enhance the functional rehabilitation outcomes of postsurgical orthopedic patients. Remarkably, gains were shown to be exclusively improving the tasks that were actually mentally simulated during the training so that future nonphysical training studies should take into account this task specificity.

In conclusion, AO + MI approaches represent an affordable, safe, and not very time-consuming tool to optimize individual's rehabilitation process. Furthermore, it allows starting the rehabilitation process in the early phase following surgery, when the patient is not able to perform a regular physical training. Once mastered, short sessions of AO + MI performed at home on a regular basis can significantly improve the outcomes of the rehabilitation process, even in frail populations.

Disclosure

An earlier version of this work was partly presented at the 21st Annual Congress of the European College of Sport Science (ECSS), Vienna, Austria, in July 2016.

Conflicts of Interest

The authors have no conflicts to report.

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References

[1] R. Pišot, U. Marusic, G. Biolo et al., "Greater loss in muscle mass and function but smaller metabolic alterations in older compared with younger men following 2 wk of bed rest and recovery," *Journal of Applied Physiology*, vol. 120, no. 8, pp. 922–929, 2016.

[2] E. E. Devore, T. G. Fong, E. R. Marcantonio et al., "Prediction of long-term cognitive decline following postoperative delirium in older adults," *The Journals of Gerontology: Series A*, vol. 72, no. 12, pp. 1697–1702, 2017.

[3] J. Y. Reginster, P. Gillet, and C. Gosset, "Secular increase in the incidence of hip fractures in Belgium between 1984 and 1996: need for a concerted public health strategy," *Bulletin of the World Health Organization*, vol. 79, no. 10, pp. 942–946, 2001.

[4] U. Marusic, V. Kavcic, B. Giordani, M. Gerževič, R. Meeusen, and R. Pišot, "Computerized spatial navigation training during 14 days of bed rest in healthy older adult men: effect on gait performance," *Psychology and Aging*, vol. 30, no. 2, pp. 334–340, 2015.

[5] M. Bassolino, M. Bove, M. Jacono, L. Fadiga, and T. Pozzo, "Functional effect of short-term immobilization: kinematic changes and recovery on reaching-to-grasp," *Neuroscience*, vol. 215, pp. 127–134, 2012.

[6] S. Facchini, M. Romani, M. Tinazzi, and S. M. Aglioti, "Time-related changes of excitability of the human motor system contingent upon immobilisation of the ring and little fingers," *Clinical Neurophysiology*, vol. 113, no. 3, pp. 367–375, 2002.

[7] R. Huber, M. F. Ghilardi, M. Massimini et al., "Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity," *Nature Neuroscience*, vol. 9, no. 9, pp. 1169–1176, 2006.

[8] L. Avanzino, M. Bassolino, T. Pozzo, and M. Bove, "Use-dependent hemispheric balance," *Journal of Neuroscience*, vol. 31, no. 9, pp. 3423–3428, 2011.

[9] J. Liepert, M. Tegenthoff, and J.-P. Malin, "Changes of cortical motor area size during immobilization," *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, vol. 97, no. 6, pp. 382–386, 1995.

[10] T. Mulder, S. de Vries, and S. Zijlstra, "Observation, imagination and execution of an effortful movement: more evidence for a central explanation of motor imagery," *Experimental Brain Research*, vol. 163, no. 3, pp. 344–351, 2005.

[11] S. Grospretre, C. Ruffino, and F. Lebon, "Motor imagery and cortico-spinal excitability: a review," *European Journal of Sport Science*, vol. 16, no. 3, pp. 317–324, 2016.

[12] D. Ertelt, S. Small, A. Solodkin et al., "Action observation has a positive impact on rehabilitation of motor deficits after stroke," *NeuroImage*, vol. 36, pp. T164–T173, 2007.

[13] E. Sarasso, M. Gemma, F. Agosta, M. Filippi, and R. Gatti, "Action observation training to improve motor function recovery: a systematic review," *Archives of Physiotherapy*, vol. 5, no. 1, p. 14, 2015.

[14] M. Jeannerod, "The representing brain: neural correlates of motor intention and imagery," *Behavioral and Brain Sciences*, vol. 17, no. 2, pp. 187–202, 1994.

[15] A. J. Butler and S. J. Page, "Mental practice with motor imagery: evidence for motor recovery and cortical reorganization after stroke," *Archives of Physical Medicine and Rehabilitation*, vol. 87, no. 12, pp. 2–11, 2006.

[16] M. Franceschini, M. Agosti, A. Cantagallo, P. Sale, M. Mancuso, and G. Buccino, "Mirror neurons: action observation treatment as a tool in stroke rehabilitation," *European Journal of Physical and Rehabilitation Medicine*, vol. 46, no. 4, pp. 517–523, 2010.

[17] D. Caligiore, M. Mustile, G. Spalletta, and G. Baldassarre, "Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis," *Neuroscience & Biobehavioral Reviews*, vol. 72, pp. 210–222, 2017.

[18] N. Schott, M. O. Frenkel, H. Korbus, and K. L. Francis, "Mental practice in orthopedic rehabilitation: where, what, and how? A case report," *Movement & Sport Sciences - Science & Motricité*, vol. 82, pp. 93–103, 2013.

[19] J. H. Villafañe, C. Pirali, M. Isgrò, C. Vanti, R. Buraschi, and S. Negrini, "Effects of action observation therapy in patients recovering from total hip arthroplasty arthroplasty: a prospective clinical trial," *Journal of Chiropractic Medicine*, vol. 15, no. 4, pp. 229–234, 2016.

[20] M. Bassolino, M. Campanella, M. Bove, T. Pozzo, and L. Fadiga, "Training the motor cortex by observing the actions of others during immobilization," *Cerebral Cortex*, vol. 24, no. 12, pp. 3268–3276, 2014.

[21] A. Meugnot, N. F. Agbangla, Y. Almecija, and L. Toussaint, "Motor imagery practice may compensate for the slowdown of sensorimotor processes induced by short-term upper-limb immobilization," *Psychological Research*, vol. 79, no. 3, pp. 489–499, 2015.

[22] J. Grèzes and J. Decety, "Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis," *Human Brain Mapping*, vol. 12, no. 1, pp. 1–19, 2001.

[23] S. Vogt, F. D. Rienzo, C. Collet, A. Collins, and A. Guillot, "Multiple roles of motor imagery during action observation," *Frontiers in Human Neuroscience*, vol. 7, p. 807, 2013.

[24] D. L. Eaves, M. Riach, P. S. Holmes, and D. J. Wright, "Motor imagery during action observation: a brief review of evidence, theory and future research opportunities," *Frontiers in Neuroscience*, vol. 10, p. 514, 2016.

[25] A. Mouthon, J. Ruffieux, M. Wälchli, M. Keller, and W. Taube, "Task-dependent changes of corticospinal excitability during observation and motor imagery of balance tasks," *Neuroscience*, vol. 303, pp. 535–543, 2015.

[26] D. J. Wright, S. A. McCormick, J. Williams, and P. S. Holmes, "Viewing instructions accompanying action observation modulate corticospinal excitability," *Frontiers in Human Neuroscience*, vol. 10, p. 17, 2016.

[27] W. Taube, M. Mouthon, C. Leukel, H. M. Hoogewoud, J. M. Annoni, and M. Keller, "Brain activity during observation and motor imagery of different balance tasks: an fMRI study," *Cortex*, vol. 64, Supplement C, pp. 102–114, 2015.

[28] M. Sakamoto, T. Muraoka, N. Mizuguchi, and K. Kanosue, "Combining observation and imagery of an action enhances human corticospinal excitability," *Neuroscience Research*, vol. 65, no. 1, pp. 23–27, 2009.

[29] D. Podsiadlo and S. Richardson, "The timed "Up & Go": a test of basic functional mobility for frail elderly persons," *Journal of the American Geriatrics Society*, vol. 39, no. 2, pp. 142–148, 1991.

[30] M. Jakovljević, "Časovno merjeni test vstani in pojdi: pregled literature," *Fizioterapija*, vol. 21, no. 1, pp. 38–47, 2013.

[31] N. Sonc and D. Rugelj, "Normativne vrednosti časovno merjenega testa korakanja v štirih kvadratih," *Fizioterapija*, vol. 22, no. 1, pp. 31–37, 2014.

[32] D. Smith and P. Holmes, "The effect of imagery modality on golf putting performance," *Journal of Sport and Exercise Psychology*, vol. 26, no. 3, pp. 385–395, 2004.

[33] C. J. Wright and D. Smith, "The effect of PETTLEP imagery on strength performance," *International Journal of Sport and Exercise Psychology*, vol. 7, no. 1, pp. 18–31, 2009.

[34] Y. Sun, W. Wei, Z. Luo, H. Gan, and X. Hu, "Improving motor imagery practice with synchronous action observation in stroke patients," *Topics in Stroke Rehabilitation*, vol. 23, no. 4, pp. 245–253, 2016.

[35] W. Taube, M. Lorch, S. Zeiter, and M. Keller, "Non-physical practice improves task performance in an unstable, perturbed environment: motor imagery and observational balance training," *Frontiers in Human Neuroscience*, vol. 8, 2014.

[36] M. Jeannerod, "Neural simulation of action: a unifying mechanism for motor cognition," *NeuroImage*, vol. 14, no. 1, pp. S103–S109, 2001.

[37] K. L. Macuga and S. H. Frey, "Neural representations involved in observed, imagined, and imitated actions are dissociable and hierarchically organized," *NeuroImage*, vol. 59, no. 3, pp. 2798–2807, 2012.

[38] F. Filimon, J. D. Nelson, D. J. Hagler, and M. I. Sereno, "Human cortical representations for reaching: mirror neurons for execution, observation, and imagery," *NeuroImage*, vol. 37, no. 4, pp. 1315–1328, 2007.

[39] B. Lorey, T. Naumann, S. Pilgramm et al., "How equivalent are the action execution, imagery, and observation of intransitive movements? Revisiting the concept of somatotopy during action simulation," *Brain and Cognition*, vol. 81, no. 1, pp. 139–150, 2013.

[40] S. Hétu, M. Grégoire, A. Saimpont et al., "The neural network of motor imagery: an ALE meta-analysis," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 5, pp. 930–949, 2013.

[41] P. Holmes and C. Calmels, "A neuroscientific review of imagery and observation use in sport," *Journal of Motor Behavior*, vol. 40, no. 5, pp. 433–445, 2008.

[42] C. M. Stinear, W. D. Byblow, M. Steyvers, O. Levin, and S. P. Swinnen, "Kinesthetic, but not visual, motor imagery modulates corticomotor excitability," *Experimental Brain Research*, vol. 168, no. 1-2, pp. 157–164, 2006.

[43] P. Personnier, A. Kubicki, D. Laroche, and C. Papaxanthis, "Temporal features of imagined locomotion in normal aging," *Neuroscience Letters*, vol. 476, no. 3, pp. 146–149, 2010.

[44] X. Skoura, P. Personnier, A. Vinter, T. Pozzo, and C. Papaxanthis, "Decline in motor prediction in elderly subjects: right versus left arm differences in mentally simulated motor actions," *Cortex*, vol. 44, no. 9, pp. 1271–1278, 2008.

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Research Article

Dynamic Neuro-Cognitive Imagery Improves Mental Imagery Ability, Disease Severity, and Motor and Cognitive Functions in People with Parkinson's Disease

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People with Parkinson's disease (PD) experience kinesthetic deficits, which affect motor and nonmotor functions, including mental imagery. Imagery training is a recommended, yet underresearched, approach in PD rehabilitation. Dynamic Neuro-Cognitive Imagery (DNI™) is a codified method for imagery training. Twenty subjects with idiopathic PD (Hoehn and Yahr stages I–III) were randomly allocated into DNI training (experimental; $n = 10$) or in-home learning and exercise program (control; $n = 10$). Both groups completed at least 16 hours of training within two weeks. DNI training focused on anatomical embodiment and kinesthetic awareness. Imagery abilities, disease severity, and motor and nonmotor functions were assessed pre- and postintervention. The DNI participants improved ($p < .05$) in mental imagery abilities, disease severity, and motor and spatial cognitive functions. Participants also reported improvements in balance, walking, mood, and coordination, and they were more physically active. Both groups strongly agreed they enjoyed their program and were more mentally active. DNI training is a promising rehabilitation method for improving imagery ability, disease severity, and motor and nonmotor functions in people with PD. This training might serve as a complementary PD therapeutic approach. Future studies should explore the effect of DNI on motor learning and control strategies.

1. Introduction

Parkinson's disease (PD) affects sensory and cognitive [1–3] as well as motor functions, resulting in impaired proprioception and kinesthesia [3–6]. These deficits manifest as impaired motion sensitivity, joint position sense, spatial cognition, and haptic acuity; altered attention to action; and inaccurate center of gravity [1, 2, 6, 7]. Forty to 63% of people with PD report sensory/perceptual deficits [8, 9] which are more disabling than cardinal PD motor symptoms (e.g., rigidity, tremor, and bradykinesia) during the "off" state (i.e., when anti-Parkinsonian medications are not functioning satisfactorily) [10].

Proprioceptive and kinesthetic deficits are closely linked to [3, 11] and underlie [12] motor deficits in PD. This information composes one's body schema ("body image" [13, 14]) [15], that is, the mental images and proprioceptive representations of the body in relation to the environment [14, 16] that serve as a vital component for perception, action, and motor control [15, 17]. PD-related sensory deficits may facilitate inaccurate body schema [1, 3], further affecting the use and interpretation of proprioceptive information [1, 12, 18] and exacerbating PD motor and cognitive deficits [1, 11, 19]. However, proprioceptive and kinesthetic deficits in PD are often underdiagnosed [20] and have received little attention in PD rehabilitation [12].

Mental imagery (herein referred to as "imagery") is the cognitive process of creating visual, auditory, or kinesthetic experiences in the mind [21] with or without overt physical execution [22] and is an important tool for cognitive and

motor performance [23]. In fact, imagery is a recommended and promising, yet underresearched, tool in PD rehabilitation [24–29], with kinesthetic imagery being particularly recommended [24, 30]. The positive effects of imagery training on people with PD are potentially derived from facilitating conscious motor planning and performance [31]. Imagery relies on [15] and uses [32] proprioceptive and kinesthetic information, including body schema [14, 33–37], thus potentially improving awareness towards body perception and schema [33]. However, proprioceptive and kinesthetic deficits and body schema misperception [13, 16] may affect imagery use in people with PD [19, 25, 38], thus limiting its therapeutic potential for this population. Although PD affects movement speed during imagery [25], imagery ability is generally well preserved in people with PD [25, 39, 40] and was not found to be correlated with the most or least affected side [25, 40]. As a trainable skill driven by internal stimuli [28], imagery ability may be capable of being improved following imagery practice in people with PD [40]. Although not investigated to date, kinesthesia-based imagery interventions may improve imagery ability and use and kinesthetic deficits. This may potentially attenuate cognitive deficits and promote physical performance [30].

Such imagery interventions conform with recommendations in the PD literature [24, 37] because they incorporate sensory information and body awareness for optimizing motor learning [41] and develop correct image properties of actual motor movements [31].

Reports on imagery interventions for people with PD are sparse. A case report describing a 3-month motor imagery (MI; i.e., the cognitive process of mentally rehearsing motor tasks without overt physical movements [42–44]) intervention reported gains in balance, PD motor symptoms, and pain reduction [45]. Furthermore, imagery interventions for people with PD specifically focusing on body schema and kinesthetic could not be found despite being recommended [6, 13].

Reports on imagery interventions embedded within conventional rehabilitation protocols for people with PD are limited and focus on enhancing motor functions through MI [37, 46]. Moreover, the imagery component in these reports is implemented to a limited extent (i.e., 15–20% of the total intervention [37]). In a study assessing the effects of a combined regimen of physical and MI practice (1-hour, biweekly intervention for 12 weeks) with no details regarding the time dedicated to imagery training in a cohort of 23 people with PD [46], the combined MI group showed significant improvements in functional motor task performance times (e.g., standing up and lying down), including the Timed Up and Go (TUG) test (~2.5 sec), the "number of steps required to rotate in a circle," and UPDRS scores (especially the mentation segment) [46]. Another study assessed the effects of a single session of imagery practice with physical practice versus a single session of physical practice on gait in 20 people with PD. The authors reported that the added imagery practice session did not have a significant effect [47]. Other forms of imagery training, however, have not been explored in PD to date.

Dynamic Neuro-Cognitive Imagery (DNI) (also known as "The Franklin Method" [48–51]) is a codified imagery-based training method for enhancing motor and nonmotor performance. DNI emphasizes correct anatomical and biomechanical embodiment and kinesthetic awareness for mindful and safe movement and function. DNI uses multisensorial, anatomical, and metaphorical imagery techniques [48, 49, 51]. DNI's potential for people with PD lies in compensating for specific PD-related sensory and cognitive mechanisms underlying motor and nonmotor impairments, through enhanced internal imagery-based body representations and sensory information. However, its application to people with PD has not been investigated. Training in DNI has shown gains in biomechanical (i.e., range of motion) (Abraham et al., in preparation) and qualitative (e.g., jump height) aspects [36, 52] of dance performance in university-level dance students, as well as gains in imagery ability and use (Abraham et al., in preparation).

The goals of the study were (1) to assess the feasibility of delivering an intensive, 2-week DNI training for people with PD, (2) to investigate the effects of DNI training versus an in-home learning and exercise program that included frequent staff checkups (herein referred to as "learning/exercise") on imagery abilities and disease severity and symptoms in a cohort of individuals with mild-moderate PD, and (3) to explore DNI impact on motor, spatial cognitive, and psychological function.

Our hypotheses were as follows: (1) delivering intensive, 2-week DNI training for people with PD will be feasible with high (>80%) retention and adherence rates; (2) participants randomly assigned to DNI training will exhibit greater gains in imagery abilities and disease severity and symptoms compared to participants engaged in the same amount of time in an in-home learning/exercise program over a matched time period; and (3) participants in DNI training will improve more in motor, spatial cognitive, and psychological functions compared to participants in an in-home learning/exercise program.

2. Materials and Methods

The study was approved by the Emory University School of Medicine Institutional Review Board. All participants provided written informed consent prior to the beginning of the study.

2.1. Participants. Twenty participants with idiopathic PD (Hoehn and Yahr stages I–III) were recruited from the local community through patient support groups, educational events, word of mouth, and the Michael J. Fox Finder website. Inclusion criteria were adults (18 years and more) with a clinical diagnosis of PD based upon established criteria [53] and determined by a board-certified neurologist with specialty training in movement disorders. To clarify, diagnosis of PD required the individual who originally presented with asymmetric symptoms that included at least 3 of the cardinal signs of PD (rigidity, bradykinesia, tremor, and postural instability); must have shown clear symptomatic benefit (e.g., alleviated rigidity, bradykinesia, and tremor)

Table 1: Multisensorial DNI for enhancing anterior and posterior pelvic tilt.

	DNI exercises
Anatomical embodiment	Self-touch: touching the iliac crests and innominates and imagining/feeling them moving throughout pelvic tilting
Kinesthetic	Pushing the low back (in PPT) and abdomen (in APT) into a big pillow (Figure 1)
Visual-cognitive	Watching a pelvic model and visualizing the different parts (i.e., two innominates and sacrum) moving in the desired manner (Figure 2)
Auditory-cognitive	Saying out loud: "pelvis is tilting forward" (for APT) and "pelvis is tilting backward" (for PPT)
Metaphorical	The pelvis is a bowl pouring water anteriorly (in APT) and posteriorly (in PPT) (Figure 3)
Auditory	Listening to the sound of pouring water (using 2 cups filled with water)

Note: APT = anterior pelvic tilt; PPT = posterior pelvic tilt. All drawings are presented with permission from Mr. E. Franklin.

from anti-Parkinsonian medications, for example, levodopa [54]; and must have had unilateral onset of symptoms. For this study, participants also needed to score greater than 17 on the Montreal Cognitive Assessment (MoCA) to be included. Exclusion criteria were any other medical conditions prior to the PD onset potentially causing persistent disability. Participants were aged 40 and older, were stages I–III in the Hoehn and Yahr scale, and could walk 3 meters or more with or without assistance. At the initial assessment, participants were evaluated for general health, self-rated ability to perform activities of daily living, fall risk, age, and education.

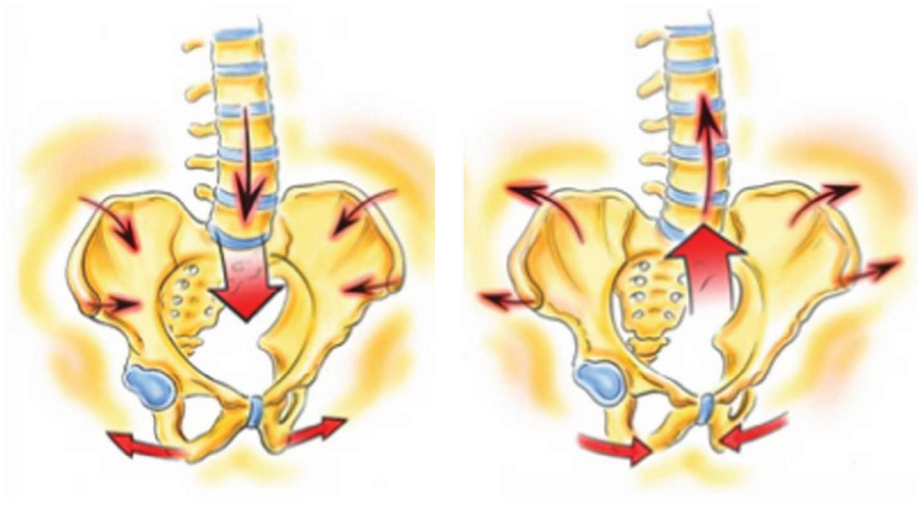
2.2. Design. Participants were randomly allocated with a computer into either DNI (experimental; $n = 10$) or a learning/exercise (control; $n = 10$) training. Both interventions were conducted simultaneously for 2 weeks and consisted of 5 sessions per week (a total of 10 sessions). Participants were "on," that is, optimally medicated, during all intervention sessions. Participants were asked to attend a minimum of 4 sessions per week (a total of 8 sessions) and underwent assessments within 1 week before intervention (pretesting) and 2–5 days after the intervention ended (posttesting). Participants and research assistants were blinded to group allocation at pretesting. Participants were asked to maintain their regular medical regimen and all activities during the study.

2.3. Experimental Intervention. The DNI intervention was intended to develop participants' imagery skills, kinesthetic and proprioceptive sense, and motor self-awareness. All sessions were delivered in a group by a physical therapist who specialized in imagery training and was also a certified DNI educator. The DNI program was planned by a qualified, experienced instructor (AA), to address PD-specific kinesthetic and proprioceptive deficits, and was developed in line with previous imagery- and PD-related literature [24, 37]. The protocol focused on (1) acquiring imagery skills and techniques (e.g., applying different types, modalities, integration of imagery, and physical movement); (2) correcting anatomical and biomechanical embodiment and kinesthetic and proprioceptive awareness (i.e., understanding the design and function of anatomical structures and identifying their location and motion), focusing on the pelvis, hips, and spine; and (3) using imagery for postural, balance, and coordination enhancement. These contents included, among others, concepts such as dynamic alignment [48] and center of gravity [6] and were all introduced using a broad spectrum of multisensory imagery [48, 49]. An example is given in Table 1. The first session was dedicated to introduction to imagery [34], based on previous literature emphasizing the importance and beneficial effect of introducing imagery as part of an imagery-based intervention in neurorehabilitation [55, 56]. All DNI sessions were conducted at the same time of the day (i.e., mornings) with each session lasting 2 hr (including a break). All DNI sessions followed the same structure: DNI warm-up (15 min), DNI concept introduction and practice part A (35 min), a break (10 min), DNI concept introduction and practice part B (35 min), DNI movement session (20 min), and a DNI cool-down/wrap-up (5 min). The movement session focused on the integration of DNI into movement and exercise and included the use of elastic bands and balls, accompanied by music. Content was practiced individually, in pairs, and in a group. Participants were encouraged to perform according to their ability while trying to "push their boundaries" without risking safety. Able-bodied volunteers who have experience in fall detection and prevention participated in all sessions to assure participants' safety and offered them manual assistance, if needed. Participants were encouraged to practice the DNI techniques and tools at home while performing activities of daily living (ADLs) as well as specific DNI exercises.

2.4. Control Intervention. The in-home learning and exercise program, which included staff checkups [57], matched the required time engagement of the DNI group (i.e., 2 hr per day, 5 days per week for two weeks, with a minimum required of 4 sessions per week). Participants were provided with a binder of 8th-grade reading-level lessons related to health and wellness and a 30-minute exercise video, consisting of standing and stepping gross and fine motor exercises that target PD impairments [58]. Participants were instructed to read one lesson per day (estimated time: 1.5 hr) and also make a 30-minute video provided via a secured internet website. All participants had access to the website, but if they had not had such access, we would have provided a DVD for viewing. Lesson topics included the following: research, creativity, exercise, nutrition, infectious diseases, family caregiving, kidney diseases, and health disparities. A research assistant called participants on the

(a) (b)

Figure 1: DNI "pushing the pelvis into a big pillow."



(a) (b)

Figure 2: DNI pelvic parts moving in APT (a) and PPT (b).

telephone 3 times over the 2 weeks (evenly spaced) to confirm compliance and discuss educational content from the lessons. One participant received only 2 calls because they could not be reached for the third phone call. Each call lasted approximately 10 minutes (range: 3 to 20 minutes).

2.5. Testing Protocol. The same measurement protocol was administered at pre- and posttesting, using a standardized script with instructions for each task. Participants were assessed with a battery of measures that assessed mental imagery, disease severity and symptoms, and motor and

(a) (b)

Figure 3: DNI "pelvis as a bowl and water pouring out of it to the front (in APT (a)) and to the back (in PPT (b))."

spatial cognitive functions. At posttesting, participants from both groups completed an exit questionnaire to assess their experiences and enjoyment of the intervention [59, 60]. Participants were tested while they were taking medications at a standardized time of day (on state) to reduce potential medication-related fluctuations in performance and came for their visit at a self-determined optimal state.

2.6. Cognitive and ADL Status Measures. The *Montreal Cognitive Assessment* (MoCA) is a 30-point test providing a measure of the global status of cognitive impairment through the assessment of a range of executive functions including orientation, memory recall, visuospatial function, attention/concentration, and language. The MoCA achieves high sensitivity and specificity for detecting mild cognitive dysfunction [61] and is valid and reliable in people with PD [62]. If an individual had fewer than 12 years of education, they received an additional point. A score of 27 or greater is considered a normal screen for cognition [61, 63].

The *Composite Physical Function Scale* (CPF) [64] asks 12 questions about an individual's functional ability as related to basic ADLs, intermediate ADLs, and advanced activities. Participants are asked to rate activities as "can do," "can do with difficulty or assistance," or "cannot do." This 24-point scale can provide estimates of risk for loss of function.

2.7. Imagery Measures. The *Movement Imagery Questionnaire-Revised Second Version* (MIQ-RS) [65, 66] is a 14-item questionnaire that assesses visual (7 items) and kinesthetic (7 items) imagery ability in people with movement limitations, using gross movements of the trunk and extremities. The examiner first reads the task, participants execute the movement physically and then imagine performing the movement visually or kinesthetically, and then participants score their imagery ease/difficulty. A Visual Analogue Scale (VAS) ranging from 1 ("very hard to see/feel") to 7 ("very easy to see/feel") is used with higher scores representing better ability/increased ease.

The *Kinesthetic and Visual Imagery Questionnaire* (KVIQ-20) [67] is a 20-item questionnaire that assesses visual (10 items) and kinesthetic (10 items) imagery ability in people with restricted mobility, using gross and fine motor tasks of the trunk and extremities. The examiner first describes the movement, then demonstrates it, and then the participant is asked to perform the movement, imagine it (using a first-person perspective), and then rate the clarity of the visual imagery or the intensity of the sensations associated with a movement imaged, using a VAS ranging from 1 ("no image/sensation") to 5 ("image as clear as seeing/as intense as executing the action") with higher scores reflecting greater imagery ability. The KVIQ-20 was previously used to assess imagery ability in people with PD [25, 31, 40, 68].

The *Vividness of Movement Imagery Questionnaire-Revised Version* (VMIQ-2) [69], previously used in PD [39], is a 36-item questionnaire that assesses the vividness of 3 modes (i.e., external visual, internal visual, and kinesthetic) of movement imagery using 12 actions. VAS ranging from 1 ("perfectly clear and as vivid as normal vision or feel of movement") to 5 ("no image at all, you only 'know' that you are thinking of the skill") is used. Low scores reflect greater imagery ability.

2.8. Disease Severity and Psychological Measures. PD-specific measures included the *Movement Disorder Society-Unified Parkinson's Disease Rating Sub-Scales I–IV* (UPDRS I–IV) [70].

Balance confidence was measured with the *Activities-Specific Balance Confidence Scale* (ABC) [71]. The ABC asks 16 questions about an individual's confidence in "not losing his/her balance" in life situations. Participants rate their confidence for each situation on a scale of 0% to 100% confidence. Scores are averaged, and the overall percent confidence was used for analysis.

The *Impact on Participation and Autonomy Scale Questionnaire* (IPA) [72] is a reliable and valid instrument for assessing autonomy and participation in chronic disorders. The IPA measures self-perceived participation in five aspects of life: autonomy indoors, autonomy outdoors, social life, family role, and work/education.

Subjective pain experience was measured with the *Brief Pain Inventory* (BPI; pain severity and interference with daily life) [73], and depression was measured with the *Beck Depression Inventory-II* (BDI-II) [74].

2.9. Motor Function Measures. Mobility measures include the *Single and Dual Timed Up and Go* (TUG) test [75] that measures mobility and dual tasking ability [76] with baseline, cognitive (counting backwards by 3 s), and manual (carrying a full glass of water) conditions. Participants rise from a chair, walk 3 meters away, turn, and walk back to the chair and sit down.

Forward (Fwd) *Gait Speed* [77] was assessed with a stopwatch. Participants walk 20 feet (~6 meters) and are given a meter of space before and after the 20-foot distance. Gait time and number of steps were measured, allowing for gait speed calculation. Three trials from each condition were averaged.

The *6-Minute Walk Test* (6MWT) measures overall mobility in older people and those with PD [78].

The *30-Second Chair Stand* [79] is a test in which participants rise from a chair to full standing as many times as possible in 30 seconds, without using their hands. The examiner counts aloud the number of repetitions completed.

The *360° Turn Test (Time and Number of Steps)* [80] is a test in which the participant is asked to complete a 360° turn while time to complete and number of steps required to turn are recorded. Right and left directions were tested.

The *Push and Release Test* (PRT) [81] rates the postural response of the participant to a sudden release of the participant pushing backwards on the examiner's hands placed on the participant's back. The VAS scale ranging from 0 ("falls without attempting a step or unable to stand without assistance") to 4 ("recovers independently with 1 step of normal length and width") is used.

2.10. Cognitive Function Measures. The *Trail Making Test Parts A and B* [82] is a cognitive function test of visual attention, processing speed, executive function, and set switching. In Trail A, a test of visual motor speed and numeric sequencing, the participant connects numbers scattered on the page in ascending order. In Trail B, a test of global frontal lobe dysfunction and executive function, the participant connects numbers and letters on a page in alternating ascending order (i.e., 1-A-2-B-3-C). Participants are required to connect the letters and/or numbers as quickly as possible, without lifting the writing utensil from the paper. They also receive a practice attempt for both Trails A and B. Errors made while completing the task are pointed out immediately so the participant can correct them. Time to complete each trial (up to a maximum of 300 seconds) is recorded. The time difference between Trails A and B (Trail difference = Trail B – Trail A) is considered for analyses.

The *Reverse Corsi Blocks Visuospatial Task* [83] is a test of visuospatial function which requires participants to watch the examiner point to a series of blocks and then repeat the pattern backwards. The examiner begins with two moves and progresses to a maximum of nine moves, with two trials per level. Each level consists of two trials with the same number of moves. At each subsequent level, the number of required moves increases by one move. Participants are given one practice trial of two moves. A participant will advance to the next level if he or she successfully completes at least one of the trials in a level. Once a participant gets both trials of a level incorrect, the task is concluded. The span (total number of moves remembered) and number of trials successfully completed are considered for analyses.

The Brooks Spatial Memory Task (BSM) [84] is a test of visuospatial mental imagery in which the participant is asked to visualize a 4×4 grid in which the location of numbers 1 through 8 is described. Next, the participant is requested to repeat the numbers' location. Participants practice with three instructions and progress up to 8 instructions. All levels are completed regardless of errors in performance, and percentages correct (out of 50) were used for analysis.

The *Body Position Spatial Task* (BPST) [59] is modelled after the Corsi Blocks task [83], which assesses visuospatial short-term working memory. Whereas with Corsi Blocks the examiner points to a sequence of blocks in a particular spatial pattern coded by numbers, in BPST, the examiner demonstrates (verbally and visually) a sequenced pattern of steps to the side, forward, and turning (in place). The participant then repeats the pattern exactly. The examiner begins with two moves and progresses to a maximum of nine moves. At each subsequent level, the number of required moves increases by one move, with two trials per level. Participants are given one practice trial of two moves. Participants advance to the next level if they correctly complete at least one of the trials in a level. Once a participant misses both trials of a level, the task is concluded. The span (number of moves remembered) and number of trials performed correctly are used for analyses. Participants are allowed to use their assistive device (i.e., a cane or a walker) if they use it habitually.

2.11. Participants' Satisfaction Measures. An exit questionnaire [59, 60] was administered to all participants after the intervention for assessing whether participants enjoyed the intervention or would continue and whether they noted improvements in aspects of well-being. A VAS ranging from 1 ("strongly agree") to 5 ("strongly disagree") was used.

Table 2: Baseline participants' demographics (*M*, SD).

	DNI ($n = 10$) *M* (SD)	Learning/exercise ($n = 10$) *M* (SD)	p[a]
Sex	1 woman, 9 men	3 women, 7 men	.58[b]
Age (years)	66.4 (12.5)	65.1 (7.5)	.78
UPDRS Motor Subscale III	38.4 (13.8)	32.1 (12.2)	.29
Hoehn and Yahr stage (median (first, third quartiles))	2.0 (1.8, 2.5)	2.0 (2.0, 2.5)	.80
Duration of PD (years)	6.1 (3.8)	8.5 (4.5)	.21
MoCA (/30)	28.3 (1.4)	26.6 (2.0)	.04*
CPF (/24)	19.9 (4.6)	20.3 (3.71)	.83
Education (years)	16.2 (2.2)	16.4 (2.0)	.83
Number of comorbidities	3.4 (1.7)	2.6 (1.7)	.32
Number of prescription medications	5.7 (3.4)	3.1 (3.1)	.09[c]
Use of assistive device (yes/no)	3/7	4/6	1.00[b]
History of ≥1 falls in the past year (yes/no)	6/4	4/6	.65[b]
Previous experience with imagery (yes/no)	4/6	1/9	.30[b]

Note: values are mean (SD), unless otherwise noted. PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Sub-Scale; MoCA = Montreal Cognitive Assessment; CPF = Composite Physical Function Scale. [a]Independent *t*-tests' compared groups. [b]Fisher's exact test. [c]Equal variance not assumed. *$p < .05$.

2.12. Statistical Analysis. The last observation was carried forward for participants who did not complete a minimum of 8 of the 10 offered sessions for their group assignment (DNI or learning/exercise) before posttesting ($n = 2$). Data were analyzed using SPSS (Version 19.0, IBM Corp., Armonk, NY). Descriptive statistics and two-way [group (DNI, learning/exercise) × time (pre, post)] mixed-design analysis of variance (ANOVA) were used to assess the effect of the interventions. Two-tailed hypotheses were used with a p value of .05 or less regarded as significant. Effect sizes (η_p^2) and confidence intervals (95% CI) were also calculated. For the 360° Turn Test, data were analyzed for the right side only after conducting paired-sample *t*-tests which yielded nonsignificant differences ($p > .05$) between sides for both time and number of steps.

3. Results

Participants' demographics are displayed in Table 2. At pretesting, the groups had normal cognition (as assessed by MoCA), there were more males, about half of them had experienced falls in the previous year or used an assistive device, they were at low risk for losing function (as measured by the CPF), and they had mild-moderate PD. The groups differed slightly in cognitive function as assessed by MoCA (Table 2), but both groups were within the normal range for cognition (i.e., >26 points). There were no significant differences between groups in imagery ability, as measured by MIQ-RS, KVIQ-20, and VMIQ-2 (not shown) nor between visual and kinesthetic imagery abilities at pretesting (Table 3).

Delivering both the DNI and learning/exercise interventions was feasible with high adherence and compliance. Two participants did not complete the intervention and posttesting: One DNI participant fell at home while skateboarding recreationally, resulting in back pain that prevented him from attending, and one learning/exercise participant could not complete assignments because of Parkinsonian complications.

Table 3: Visual and kinesthetic imagery abilities at pretesting.

	Visual *M* (SD)	Kinesthetic *M* (SD)	p[a]
MIQ-RS (/7)	4.86 (1.64)	4.68 (1.63)	.72
KVIQ-20 (/5)	3.19 (1.04)	2.86 (.93)	.28
VMIQ-2[†] (12–70)	External: 29.30 (12.68) Internal: 30.35 (13.86)	32.05 (13.55)	.47[b]

[a]Paired-sample *t*-tests' compared categories. [b]Paired-sample *t*-tests' compared internal-visual and kinesthetic categories. [†]Lower values represent better scores.

Compliance for the DNI group was 100%. All participants in learning/exercise read the information and discussed with staff (verified by staff), but 4 out of 9 learning/exercise participants did not complete the exercise video 8 times as requested. All participants used the video at least twice.

3.1. Outcome Measures. Results for all outcome measures are detailed in Table 4. There was a group × time interaction in the mental imagery measures. The DNI group improved more than the learning/exercise group did in all mental imagery measures except for the kinesthetic MIQ-RS and kinesthetic VMIQ-2.

There were significant group × time interactions in the UPDRS-III, the TUG-manual, time and number of steps to turn 360°, reactive postural control, and BPST span. The DNI group improved more than the learning/exercise group did.

There was a significant group × time interaction in the IPA score. The learning/exercise group improved more.

Both groups strongly agreed that they enjoyed their program and strongly agreed that they were more mentally active and would continue the program if possible. DNI

Table 4: Outcome measures at pre- and posttesting.

	DNI *M* (SD) [range] {95% CI}	Learning/exercise *M* (SD) [range] {95% CI}	$F_{(1,18)}$!	*p*	η_p^2
Mental imagery					
MIQ-RS (/7)					
Visual					
Pre	4.98 (1.56) [1.86–6.71] {3.86–6.10}	4.74 (1.79) [1.00–6.43] {3.62–5.86}	5.84	.02*	.245
Post	5.85 (.79) [4.71–7.00] {4.89–6.81}	4.31 (1.88) [1.00–6.57] {3.35–5.27}			
Kinesthetic					
Pre	5.07 (1.43) [2.29–6.57] {3.99–6.15}	4.30 (1.79) [1.00–6.29] {3.22–5.38}	1.69	.20	.086
Post	5.47 (1.48) [2.29–7.00] {4.31–6.62}	4.05 (1.96) [1.00–6.57] {2.90–5.21}			
Total					
Pre	5.02 (1.14) [3.36–6.64] {4.21–5.83}	4.52 (1.29) [2.50–6.36] {3.71–5.33}	5.30	.03*	.228
Post	5.66 (.96) [4.14–7.00] {4.85–6.47}	4.18 (1.43) [2.21–6.57] {3.37–4.99}			
KVIQ-20 (/5)					
Visual					
Pre	3.29 (1.22) [1.30–4.80] {2.58–3.99}	3.10 (.88) [1.50–4.00] {2.39–3.80}	6.12	.02*	.254
Post	3.95 (.63) [3.00–4.90] {3.31–4.58}	2.67 (1.18) [1.00–4.20] {2.03–3.30}			
Kinesthetic					
Pre	3.07 (1.10) [1.00–4.70] {2.44–3.69}	2.66 (.72) [1.30–3.50] {2.03–3.28}	6.58	.01*	.268
Post	3.65 (1.18) [1.00–5.00] {2.94–4.35}	2.39 (.92) [1.00–4.10] {1.68–3.09}			
Total					
Pre	3.18 (.89) [2.00–4.75] {2.69–3.66}	2.88 (.51) [2.10–3.75] {2.39–3.36}	9.62	.00**	.348
Post	3.80 (.80) [2.50–4.90] {3.27–4.32}	2.53 (.77) [1.25–3.45] {2.00–3.05}			
VMIQ-2† *(/12–70)*					
External visual					
Pre	26.10 (11.68) [12.00–47.00] {17.73–34.46}	32.50 (13.42) [20.00–60.00] {24.13–40.86}	6.70	.01*	.271
Post	21.20 (6.64) [12.00–31.00] {15.10–27.29}	36.40 (11.13) [19.00–60.00] {30.30–42.49}			
Internal visual					
Pre	27.70 (15.09) [12.00–56.00] {18.42–36.97}	33.00 (12.73) [19.00–60.00] {23.72–42.27}	5.79	.02*	.244
Post	20.00 (7.39) [12.00–35.00] {12.66–27.33}	36.30 (13.76) [17.00–60.00] {28.96–43.63}			
Kinesthetic					
Pre	29.40 (14.53) [12.00–53.00] {20.33–38.46}	34.70 (12.69) [14.00–60.00] {25.63–43.76}	1.96	.17	.098
Post	22.10 (11.44) [12.00–48.00] {14.02–30.17}	34.70 (12.83) [15.00–60.00] {26.62–42.77}			
Disease severity and psychological					
UPDRS-I†					
Pre	11.90 (5.19) {7.67–16.12}	15.00 (7.34) {10.77–19.22}	.00	1.00	.000
Post	10.40 (5.58) {6.15–14.64}	13.50 (7.10) {9.25–17.74}			
UPDRS-II†					
Pre	16.50 (5.87) {12.82–20.17}	18.20 (5.18) {14.52–21.87}	.01	.90	.001
Post	14.10 (6.17) {10.33–17.86}	15.60 (5.12) {11.83–19.36}			
UPDRS-III†					
Pre	38.40 (13.87) {29.70–47.09}	32.10 (12.24) {23.40–40.79}	4.08	.05*	.185
Post	31.60 (13.85) {22.96–40.23}	31.20 (12.06) {22.56–39.83}			
UPDRS-IV†					
Pre	3.50 (4.11) {0.89–6.10}	4.60 (3.71) {1.99–7.20}	.02	.87	.001
Post	4.50 (5.03) {1.84–7.15}	5.40 (2.54) {2.74–8.05}			
ABC (%)					
Pre	78.20 (18.31) {67.14–89.26}	73.20 (14.79) {62.14–84.26}	.00	.94	.000
Post	74.23 (18.02) {67.61–90.27}	74.23 (18.02) {62.90–85.57}			

Table 4: Continued.

	DNI *M* (SD) [range] {95% CI}	Learning/exercise *M* (SD) [range] {95% CI}	$F_{(1,18)}$!	*p*	η_p^2
IPA†					
Pre	32.60 (21.80) {14.96–50.23}	43.50 (30.54) {25.86–61.13}	5.20	.03*	.224
Post	35.00 (22.28) {20.03–49.96}	36.20 (22.75) {21.23–51.16}			
BPI-severity†					
Pre	2.82 (2.25) {1.22–4.42}	3.03 (2.56) {1.23–4.82}	.95	.34	.056
Post	2.55 (2.25) {1.05–4.04}	3.28 (2.20) {1.60–4.95}			
BPI-interference†					
Pre	2.44 (1.79) {.86–4.01}	2.21 (2.90) {.45–3.97}	2.48	.13	.134
Post	1.41 (1.24) {.40–2.42}	2.14 (1.79) {1.01–3.27}			
BDI-II†					
Pre	12.90 (8.41) {6.93–18.86}	14.50 (9.51) {8.53–20.46}	.75	.39	.040
Post	9.20 (5.82) {4.73–13.66}	12.40 (7.50) {7.93–16.86}			
Motor function					
Fwd gait† (meters/sec)					
Pre	1.08 (.18) {.95–1.21}	1.06 (.20) {.93–1.19}	.00	.92	.001
Post	1.09 (.15) {.98–1.20}	1.07 (.16) {.96–1.17}			
6MWT (meters)					
Pre	410.52 (127.05) {348.89–472.14}	393.34 (32.61) {331.72–454.96}	2.46	.13	.120
Post	447.32 (84.22) {399.53–495.11}	370.05 (57.06) {322.26–417.85}			
30-Second Chair Stand (reps)					
Pre	14.20 (6.52) {10.60–17.80}	11.10 (4.01) {7.50–14.70}	1.49	.23	.077
Post	16.00 (5.61) {12.69–19.30}	11.40 (4.24) {8.09–14.70}			
Mini-BEST (/28)					
Pre	22.50 (4.37) {19.68–25.31}	21.80 (4.10) {18.68–25.31}	1.60	.22	.082
Post	23.30 (3.30) {20.86–25.73}	21.20 (3.99) {18.76–23.63}			
TUG† (sec)					
Pre	9.00 (2.18) {7.61–10.40}	9.85 (2.02) {8.45–11.25}	2.21	.15	.110
Post	8.40 (1.85) {7.00–9.80}	10.26 (2.32) {8.86–11.66}			
TUG-cognitive† (sec)					
Pre	13.72 (8.07) {9.57–17.87}	12.76 (3.57) {8.61–16.91}	3.07	.09	.146
Post	11.14 (3.21) {6.65–15.63}	15.61 (9.01) {11.12–20.11}			
TUG-manual† (sec)					
Pre	13.61 (5.44) {10.75–16.46}	12.69 (2.71) {9.83–15.55}	4.43	.05*	.198
Post	11.16 (2.76) {9.28–13.03}	12.99 (2.87) {11.11–14.87}			
360° Turn Test (steps)†					
Pre	10.20 (5.57) {7.43–12.96}	6.90 (1.91) {4.13–9.66}	6.63	.01**	.269
Post	9.00 (2.53) {6.26–11.73}	9.70 (5.22) {6.96–12.43}			
360° Turn Test (sec)†					
Pre	4.23 (2.98) {2.75–5.70}	3.12 (.95) {1.64–4.59}	7.58	.01**	.296
Post	3.38 (1.46) {1.96–4.80}	4.69 (2.64) {3.27–6.11}			
PRT (/4)					
Pre	2.80 (1.31) {2.07–3.52}	2.70 (.82) {1.97–3.42}	5.68	.02*	.240
Post	3.40 (.84) {2.82–3.97}	2.10 (.87) {1.52–2.67}			
Cognitive function					
Trail A† (sec)					
Pre	27.46 (10.33) {20.64–34.28}	30.44 (10.19) {23.62–37.26}	1.24	.27	.065
Post	28.19 (7.03) {23.51–32.88}	27.68 (7.06) {23.00–32.37}			

Table 4: Continued.

	DNI M (SD) [range] {95% CI}	Learning/exercise M (SD) [range] {95% CI}	$F_{(1,18)}$!	p	η_p^2
Trail B† (sec)					
Pre	78.26 (52.49) {32.03–124.49}	95.79 (83.23) {49.56–142.02}	.01	.90	.001
Post	68.29 (29.35) {28.34–108.23}	87.52 (79.80) {47.58–127.47}			
Trails B-A† (sec)					
Pre	50.79 (45.11) {8.70–92.89}	65.34 (77.42) {23.24–107.44}	.18	.66	.010
Post	40.09 (25.35) {2.91–77.27}	59.84 (74.97) {22.66–97.02}			
Corsi-trials					
Pre	6.30 (1.82) {4.91–7.68}	6.70 (2.31) {5.31–8.08}	1.87	.18	.094
Post	7.30 (1.49) {5.97–8.62}	6.80 (2.39) {5.47–8.12}			
Corsi-span					
Pre	4.70 (1.15) {3.98–5.41}	4.90 (.99) {4.18–5.61}	1.05	.31	.055
Post	5.30 (1.05) {4.47–6.13}	5.00 (1.41) {4.17–5.83}			
BSM					
Pre	72.40 (14.07) {58.92–85.87}	66.40 (24.99) {52.92–79.87}	.19	.66	.011
Post	77.60 (14.56) {65.53–89.66}	68.20 (21.15) {56.13–80.26}			
BPST-trials					
Pre	4.10 (1.52) {3.14–5.05}	4.40 (1.34) {3.44–5.35}	.48	.49	.026
Post	4.70 (1.56) {3.48–5.91}	4.60 (2.06) {3.38–5.81}			
BPST-span					
Pre	3.40 (.69) {2.60–4.19}	4.20 (1.54) {3.40–4.99}	6.68	.01**	.271
Post	3.90 (.99) {3.19–4.60}	3.80 (1.13) {3.09–4.50}			

Note: values represent group × time interactions. MIQ-RS = Movement Imagery Questionnaire-Revised Second Version; KVIQ = Kinesthetic and Visual Imagery Questionnaire; VMIQ = Vividness of Movement Imagery Questionnaire-Revised Version; UPDRS = Unified Parkinson's Disease Rating Sub-Scales; ABC = Activities-Specific Balance Confidence Scale; IPA = Impact on Participation and Autonomy Scale Questionnaire; BPI = Brief Pain Inventory; BDI = Beck Depression Inventory; 6MWT = 6-Minute Walk Test; TUG = Timed Up and Go; FAB = Fullerton Advanced Balance Scale; DGI = Dynamic Gait Index; PRT = Push and Release Test; BSM = Brooks Spatial Memory Task; BPST = Body Position Spatial Task. !Differences were calculated using mixed-design ANOVA. *$p < .05$. **$p < .01$. †Lower values represent better scores.

participants agreed that they noted improvements in balance, walking, mood, and coordination, and they were more physically active. Median and interquartile values are reported for exit questionnaire responses in Table 5.

4. Discussion

This study represents one of the first efforts to examine the effects of imagery training on imagery ability, disease severity, motor, and nonmotor functions in people with mild-to-moderate PD. The DNI intervention provided participants with imagery information based on correct body biomechanics and encouraged them to use this knowledge for increasing self-awareness and improving motor performance. This is different from other approaches to imagery, in which participants' existing motor experiences serve as the foundation for the imagery training [37]. Further, the DNI intervention included imagery contents only (unlike previous reports using combined imagery and conventional therapies), thus resulting in a high volume of imagery training (100 min per session) in comparison to previous reports (e.g., 15–20 minutes [46] and 20 minutes [37]).

Delivering intensive, 2-week DNI training was feasible with high adherence and compliance rates, thus confirming our first hypothesis. Participants in the DNI group enjoyed the training, attended sessions beyond the minimum required, and commented that the training was very useful for them in improving their ADLs. The DNI group benefitted significantly more from the training versus the learning/exercise group and exhibited greater improvements in measures of imagery ability, disease severity, and motor and nonmotor functions.

The lack of significant differences between visual and kinesthetic imagery ability found at pretesting agrees with previous findings [40] but contradicts other findings suggesting visual imagery to be better than kinesthetic imagery in PD [25, 68]. Kinesthetic and visual imagery trainings may be equally relevant and potentially beneficial for people with PD. Future studies, however, should compare between the two modalities in terms of their effectiveness in this population.

MIQ-RS and KVIQ-20 scores in the current study could not be compared with previous reports of people with PD due to significant differences in delivery protocol [68] or VAS scales [25, 31, 40]. There is therefore a need for homogenous delivery protocols in this population. VMIQ-2 scores in the current study (23.30 ± 12.68, 30.35 ± 13.86, and 32.05 ± 13.55 for external-visual, internal-visual, and kinesthetic abilities, resp.) were higher than previous published values (27.5 ± 7.4 and 28.3 ± 6 for internal-visual and

Table 5: Participants' satisfaction from intervention.[†]

Question	DNI (median (1st, 3rd quartiles))	Learning/exercise (median (1st, 3rd quartiles))
(1) Did you enjoy?	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)
(2) Balance improved	2.00 (1.00, 3.00)	3.00 (3.00, 3.00)
(3) Walking improved	2.00 (1.50, 2.00)	3.00 (2.50, 3.50)
(4) Mood improved	2.00 (1.00, 3.00)	3.00 (2.00, 3.50)
(5) Coordination improved	2.00 (2.00, 3.00)	3.00 (3.00, 4.00)
(6) Strength improved	3.00 (1.00, 3.00)	3.00 (3.00, 3.00)
(7) Endurance improved	3.00 (3.00, 3.00)	3.00 (3.00, 3.50)
(8) I would continue	1.00 (1.00, 1.00)	2.00 (1.00, 3.50)
(9) More physically active	2.00 (1.00, 2.50)	3.00 (2.00, 3.50)
(10) More mentally active	1.00 (1.00, 2.00)	2.00 (1.50, 3.50)

[†]Lower values represent better scores.

kinesthetic) in a group of 15 people with PD [39]. In another study, a mean score of 24.4 ± 7.1 was reported, with no specifications regarding the imagery modality [85].

The DNI group improved significantly in all three modalities of imagery ability (i.e., external-visual, internal-visual, and kinesthetic) following the intervention, whereas the learning/exercise group did not exhibit these improvements, which match, and may be explained by, the multi-imagery perspectives (i.e., 1st- and 3rd-person) and multisensorial imagery approach (i.e., visual, auditory, and kinesthetic) used by DNI. This finding supports the notion that imagery ability can be enhanced following imagery training in people with PD and suggests that imagery performance (e.g., vividness) in people with PD can improve not only with actual visual cues (i.e., a target on a screen) [31] but also with imagery training.

Previous literature suggests that people with PD are less likely to use a "first-person" strategy for imagery (i.e., kinesthetic or internal-visual), which involves internal-visual or kinesthetic information [29], possibly reflecting kinesthetic and proprioceptive deficits [1, 4, 7] and altered body schema [6, 16, 86] associated with PD. Therefore, the improvements in kinesthetic and internal-visual and imagery abilities noticed following the DNI training may suggest an enhanced ability to access kinesthetic, internal information, thus potentially more likely to use a first-person imagery modality. Such improvements in kinesthetic and internal-visual imagery ability may lead to better somatosensory integration and body schema [14, 33], as well as reduced external (e.g., auditory and visual) cue or feedback dependency, frequently observed in PD [18]. Being more available and not dependent on space and time constraints, relying on internally guided, kinesthetic stimuli and cues, has potential for enhancing independence and decreased reliance on externally provided cues in ADLs for people with PD, thus improving the quality of life [31, 41]. Future studies should investigate the effect of DNI training on the ability of people with PD to spontaneously generate and use internally generated cues [87]. Such insights, once demonstrated, could be translated into clinical guidelines and embedded within PD rehabilitation protocols, as previously suggested with imagery [26, 27].

This study is the first, to our knowledge, to demonstrate significant improvement in UPDRS-III, that is, motor symptoms, following imagery training. A previous study reported a significant improvement in the mental subscale (UPDRS-I) following a combined physical and motor imagery training [46]. Gaps in knowledge prohibit explaining the relationships between different types of imagery training or contents and the effects on aspects of disease severity, as measured by the UPDRS.

The DNI group improved significantly more than the learning/exercise group did in selected measures of motor and cognitive functions, including TUG-manual and 360° turns. These improvements are especially notable because the DNI intervention focused on anatomical and biomechanical embodiment and kinesthetic-proprioceptive imagery and not on the training of specific functions/tasks to be measured as outcome measures (e.g., TUG-manual and 6MW), as is the case in previous reports [37, 46]. As such, the current findings might suggest changes in motor control and planning strategies, involved in such functions, following relevant DNI contents, such as imagery for embodying the center of mass and central axis. These aspects were not within the scope of this study and should be looked at in future works.

The mechanisms of effect of DNI are not fully revealed to date and should be examined in light of previous literature highlighting brain strategies and compensatory mechanisms involved with imagery in PD [88]. Specifically, such investigations should take into account previous reports suggesting that performance of an imagery task (i.e., mental rotation of body parts; as measured by reaction time and brain activity) in people with PD is affected by various factors, such as visual information (e.g., image orientation), the affected/nonaffected limb, and the presence of tremor [88, 89]. Moreover, it was concluded that people with PD used first-person, kinesthetic imagery to solve the imagery task [89].

The improvements noted in the DNI group in motor and nonmotor functions could be explained, in part, by the following: (1) imagery plays an important role in motor and nonmotor functions [23], and gains in imagery ability could contribute to enhanced motor and nonmotor

capabilities; (2) correcting (and enhancing) body posture and biomechanics is important for proper motor performance [90, 91]; and (3) providing additional sensory information could optimize motor learning in people with PD [41]. In addition, the imagery-cognitive strategies used in DNI could potentially serve to bypass the basal ganglia-supplementary motor area circuit [46] and contribute to the establishment of a more clear and accurate body schema [14].

This study has limitations: (1) it evaluated only a small sample, (2) differences existed between groups on the MoCA and imagery experience, (3) the intervention was only two weeks long, and (4) there was a lack of follow-up testing to evaluate the retention effect. In addition, four out of the 9 participants in the learning/exercise group reported that they did not complete the exercise video 8 times as requested, which resulted in a reduced volume of the control intervention for these participants. All of these limitations have affected the results in unknown ways; therefore, the current findings should be interpreted cautiously. Future studies should investigate the effects of DNI training with larger samples and longer interventions with long-term follow-up measurements.

Future research should also explore the potential for beneficial effects of DNI in people with PD in other circumstances, for example, during the off state [40] and when combined with other training approaches, for example, physical therapy group exercise.

5. Conclusion

This study provides preliminary evidence for the clinical application and effectiveness of imagery training in PD. The demonstrated gains in imagery ability and motor and non-motor functions in people with PD following DNI training further support the incorporation of imagery training in PD rehabilitation. Research into imagery and motor control and planning in PD is warranted.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

[1] J. Konczak, D. M. Corcos, F. Horak et al., "Proprioception and motor control in Parkinson's disease," *Journal of Motor Behavior*, vol. 41, no. 6, pp. 543–552, 2009.

[2] J. Konczak, A. Sciutti, L. Avanzino et al., "Parkinson's disease accelerates age-related decline in haptic perception by altering somatosensory integration," *Brain*, vol. 135, no. 11, pp. 3371–3379, 2012.

[3] A. Conte, N. Khan, G. Defazio, J. C. Rothwell, and A. Berardelli, "Pathophysiology of somatosensory abnormalities in Parkinson disease," *Nature Reviews Neurology*, vol. 9, no. 12, pp. 687–697, 2013.

[4] H. Teasdale, E. Preston, and G. Waddington, "Proprioception of the ankle is impaired in people with Parkinson's disease," *Movement Disorders Clinical Practice*, vol. 4, no. 4, pp. 524–528, 2017.

[5] L. Ribeiro, T. M. e Souza, L. Bizarro, and A. Oliveira, "Proprioceptive deficits in Parkinson's disease: from clinical data to animal experimentation," *Psychology & Neuroscience*, vol. 4, no. 2, pp. 235–244, 2011.

[6] J. H. Friedman, "Misperceptions and Parkinson's disease," *Journal of the Neurological Sciences*, vol. 374, pp. 42–46, 2017.

[7] S. Zia, F. Cody, and D. O'Boyle, "Joint position sense is impaired by Parkinson's disease," *Annals of Neurology*, vol. 47, no. 2, pp. 218–228, 2000.

[8] W. C. Koller, "Sensory symptoms in Parkinson's disease," *Neurology*, vol. 34, no. 7, pp. 957–959, 1984.

[9] L. M. Shulman, C. Singer, J. A. Bean, and W. J. Weiner, "Internal tremor in patients with Parkinson's disease," *Movement Disorders*, vol. 11, no. 1, pp. 3–7, 1996.

[10] T. Witjas, E. Kaphan, J. P. Azulay et al., "Nonmotor fluctuations in Parkinson's disease: frequent and disabling," *Neurology*, vol. 59, no. 3, pp. 408–413, 2002.

[11] M. Vaugoyeau, S. Viel, C. Assaiante, B. Amblard, and J. P. Azulay, "Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease," *Neuroscience*, vol. 146, no. 2, pp. 852–863, 2007.

[12] M. Demirci, S. Grill, L. McShane, and M. Hallett, "A mismatch between kinesthetic and visual perception in Parkinson's disease," *Annals of Neurology*, vol. 41, no. 6, pp. 781–788, 1997.

[13] L. Bissolotti, F. Isacco-Grassi, C. Orizio et al., "Spinopelvic balance and body image perception in Parkinson's disease: analysis of correlation," *European Spine Journal*, vol. 24, Supplement 7, pp. 898–905, 2015.

[14] F. de Vignemont, "Body schema and body image—pros and cons," *Neuropsychologia*, vol. 48, no. 3, pp. 669–680, 2010.

[15] K. McCormick, N. Zalucki, M. L. Hudson, and G. Lorimer Moseley, "Faulty proprioceptive information disrupts motor imagery: an experimental study," *Australian Journal of Physiotherapy*, vol. 53, no. 1, pp. 41–45, 2007.

[16] A. H. E. Gamarra, C. S. Molski, A. Hilbig, C. K. Valentini, V. L. W. Striebel, and C. R. de Mello Rieder, "Evaluation of body image and self-concept and their correlation with depressive symptoms in Parkinson's disease," *Arquivos de Neuro-Psiquiatria*, vol. 67, no. 3a, pp. 585–590, 2009.

[17] J. T. Shenton, J. Schwoebel, and H. B. Coslett, "Mental motor imagery and the body schema: evidence for proprioceptive dominance," *Neuroscience Letters*, vol. 370, no. 1, pp. 19–24, 2004.

[18] J. V. Jacobs and F. B. Horak, "Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease," *Neuroscience*, vol. 141, no. 2, pp. 999–1009, 2006.

[19] R. G. Cohen, A. Chao, J. G. Nutt, and F. B. Horak, "Freezing of gait is associated with a mismatch between motor imagery and motor execution in narrow doorways, not with failure to judge doorway passability," *Neuropsychologia*, vol. 49, no. 14, pp. 3981–3988, 2011.

[20] J. Jankovic, "Parkinson's disease: clinical features and diagnosis," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 79, no. 4, pp. 368–376, 2008.

[21] S. M. Kosslyn, G. Ganis, and W. L. Thompson, "Neural foundations of imagery," *Nature Reviews Neuroscience*, vol. 2, no. 9, pp. 635–642, 2001.

[22] A. Fusco, M. Iosa, M. C. Gallotta, S. Paolucci, C. Baldari, and L. Guidetti, "Different performances in static and dynamic imagery and real locomotion. An exploratory trial," *Frontiers in Human Neuroscience*, vol. 8, p. 760, 2014.

[23] C. Papadelis, C. Kourtidou-Papadeli, P. Bamidis, and M. Albani, "Effects of imagery training on cognitive performance and use of physiological measures as an assessment tool of mental effort," *Brain and Cognition*, vol. 64, no. 1, pp. 74–85, 2007.

[24] C. Gabbard and A. Fox, "Using motor imagery therapy to improve movement efficiency and reduce fall injury risk," *Journal Novel Physiotherapies*, vol. 3, no. 6, p. 186, 2013.

[25] E. Heremans, P. Feys, A. Nieuwboer et al., "Motor imagery ability in patients with early- and mid-stage Parkinson disease," *Neurorehabilitation and Neural Repair*, vol. 25, no. 2, pp. 168–177, 2011.

[26] M. E. Morris, C. L. Martin, and M. L. Schenkman, "Striding out with Parkinson disease: evidence-based physical therapy for gait disorders," *Physical Therapy*, vol. 90, no. 2, pp. 280–288, 2010.

[27] A. Mirelman, I. Maidan, and J. E. Deutsch, "Virtual reality and motor imagery: promising tools for assessment and therapy in Parkinson's disease," *Movement Disorders*, vol. 28, no. 11, pp. 1597–1608, 2013.

[28] D. Caligiorea, M. Mustilea, G. Spalletta, and G. Baldassarre, "Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis," *Neuroscience & Biobehavioral Reviews*, vol. 72, pp. 210–222, 2017.

[29] G. Abbruzzese, L. Avanzino, R. Marchese, and E. Pelosin, "Action observation and motor imagery: Innovative cognitive tools in the rehabilitation of Parkinson's disease," *Parkinson's Disease*, vol. 2015, Article ID 124214, 9 pages, 2015.

[30] V. K. Lim, M. A. Polych, A. Holländer, W. D. Byblow, I. J. Kirk, and J. P. Hamm, "Kinesthetic but not visual imagery assists in normalizing the CNV in Parkinson's disease," *Clinical Neurophysiology*, vol. 117, no. 10, pp. 2308–2314, 2006.

[31] E. Heremans, A. Nieuwboer, P. Feys et al., "External cueing improves motor imagery quality in patients with Parkinson disease," *Neurorehabilitation and Neural Repair*, vol. 26, no. 1, pp. 27–35, 2012.

[32] C. A. Porro, M. P. Francescato, V. Cettolo et al., "Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study," *Journal of Neuroscience*, vol. 16, no. 23, pp. 7688–7698, 1996.

[33] J. Schwoebel and H. B. Coslett, "Evidence for multiple, distinct representations of the human body," *Journal of Cognitive Neuroscience*, vol. 17, no. 4, pp. 543–553, 2005.

[34] E. Franklin, *Inner Focus Outer Strength*, Princeton Book Company, Canada, 2006.

[35] E. Franklin, *The Art and Science of Cueing*, OPTP, Minneapolis, MN, USA, 2016.

[36] T. Heiland and R. Rovetti, "Examining effects of Franklin Method metaphorical and anatomical mental images on college dancers' jumping height," *Research in Dance Education*, vol. 14, no. 2, pp. 141–161, 2013.

[37] S. Braun, A. Beurskens, M. Kleynen, J. Schols, and D. Wade, "Rehabilitation with mental practice has similar effects on mobility as rehabilitation with relaxation in people with Parkinson's disease: a multicentre randomised trial," *Journal of Physiotherapy*, vol. 57, no. 1, pp. 27–34, 2011.

[38] S. Thobois, P. F. Dominey, J. Decety et al., "Motor imagery in normal subjects and in asymmetrical Parkinson's disease: a PET study," *Neurology*, vol. 55, no. 7, pp. 996–1002, 2000.

[39] J. Crémers, K. D'Ostilio, J. Stamatakis, V. Delvaux, and G. Garraux, "Brain activation pattern related to gait disturbances in Parkinson's disease," *Movement Disorders*, vol. 27, no. 12, pp. 1498–1505, 2012.

[40] A. Maillet, S. Thobois, V. Fraix et al., "Neural substrates of levodopa-responsive gait disorders and freezing in advanced Parkinson's disease: a kinesthetic imagery approach," *Human Brain Mapping*, vol. 36, no. 3, pp. 959–980, 2015.

[41] A. Nieuwboer, L. Rochester, L. Müncks, and S. P. Swinnen, "Motor learning in Parkinson's disease: limitations and potential for rehabilitation," *Parkinsonism & Related Disorders*, vol. 15, Supplement 3, pp. S53–S58, 2009.

[42] J. Decety, "The neurophysiological basis of motor imagery," *Behavioural Brain Research*, vol. 77, no. 1-2, pp. 45–52, 1996.

[43] A. Abraham, A. Dunsky, and R. Dickstein, "Motor imagery practice for enhancing eleve performance among professional dancers: a pilot study," *Medical Problems of Performing Artists*, vol. 31, no. 3, pp. 132–139, 2016.

[44] A. Abraham, A. Dunsky, and R. Dickstein, "The effect of motor imagery practice on elevé performance in adolescent female dance students: a randomized controlled trial," *Journal of Imagery Research in Sport and Physical Activity*, vol. 12, no. 1, 2017.

[45] F. Zangrando, G. Piccinini, A. Pelliccioni, V. M. Saraceni, and T. Paolucci, "Neurocognitive rehabilitation in Parkinson's disease with motor imagery: a rehabilitative experience in a case report," *Case Reports in Medicine*, vol. 2015, Article ID 670385, 4 pages, 2015.

[46] R. Tamir, R. Dickstein, and M. Huberman, "Integration of motor imagery and physical practice in group treatment applied to subjects with Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 21, no. 1, pp. 68–75, 2007.

[47] L. M. de Melo Santiago, D. A. de Oliveira, L. G. L. de Macêdo Ferreira et al., "Immediate effects of adding mental practice to physical practice on the gait of individuals with Parkinson's disease: randomized clinical trial," *NeuroRehabilitation*, vol. 37, no. 2, pp. 263–271, 2015.

[48] E. Franklin, *Dynamic Alignment through Imagery*, Human Kinetics, Champaign, IL, USA, 1996.

[49] E. Franklin, *Pelvic Power*, Princeton Book, Hightstown, NJ, USA, 2002.

[50] E. Franklin, *Conditioning for Dance*, Human Kinetics, Champaign, IL, USA, 2004.

[51] E. Franklin, *Dance Imagery for Technique and Performance*, Human Kinetics, Champaign, IL, USA, 2014.

[52] T. Heiland, R. Rovetti, and J. Dunn, "Effects of visual, auditory, and kinesthetic imagery interventions on dancers' plié arabesques," *Journal of Imagery Research in Sport and Physical Activity*, vol. 7, no. 1, p. 5, 2012.

[53] B. A. Racette, M. Rundle, A. Parsian, and J. S. Perlmutter, "Evaluation of a screening questionnaire for genetic studies of Parkinson's disease," *American Journal of Medical Genetics*, vol. 88, no. 5, pp. 539–543, 1999.

[54] A. J. Hughes, S. E. Daniel, L. Kilford, and A. J. Lees, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 55, no. 3, pp. 181–184, 1992.

[55] T. J. H. Bovend'Eerdt, H. Dawes, C. Sackley, and D. T. Wade, "Practical research-based guidance for motor imagery practice in neurorehabilitation," *Disability and Rehabilitation*, vol. 34, no. 25, pp. 2192–2200, 2012.

[56] C. Wondrusch and C. Schuster-Amft, "A standardized motor imagery introduction program (MIIP) for neuro-rehabilitation: development and evaluation," *Frontiers in Human Neuroscience*, vol. 7, p. 477, 2013.

[57] A. R. Hart, R. Dillard, M. M. Perkins et al., "The DREAMS team: creating community partnerships through research advocacy training for diverse older adults," *Educational Gerontology*, vol. 43, no. 9, pp. 440–450, 2017.

[58] M. E. Hackney and K. McKee, "Community-based adapted tango dancing for individuals with Parkinson's disease and older adults," *Journal of Visualized Experiments*, no. 94, article e52066, 2014.

[59] M. E. Hackney, C. D. Hall, K. V. Echt, and S. L. Wolf, "Dancing for balance: feasibility and efficacy in oldest-old adults with visual impairment," *Nursing Research*, vol. 62, no. 2, pp. 138–143, 2013.

[60] K. E. McKee and M. E. Hackney, "The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease," *Journal of Motor Behavior*, vol. 45, no. 6, pp. 519–529, 2013.

[61] Z. S. Nasreddine, N. A. Phillips, V. Bédirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[62] K. L. Chou, M. M. Amick, J. Brandt et al., "A recommended scale for cognitive screening in clinical trials of Parkinson's disease," *Movement Disorders*, vol. 25, no. 15, pp. 2501–2507, 2010.

[63] S. Hoops, S. Nazem, A. D. Siderowf et al., "Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease," *Neurology*, vol. 73, no. 21, pp. 1738–1745, 2009.

[64] R. E. Rikli and C. J. Jones, "The reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults," *Journal of Aging and Physical Activity*, vol. 6, no. 4, pp. 363–375, 1998.

[65] M. Gregg, C. Hall, and A. Butler, "The MIQ-RS: a suitable option for examining movement imagery ability," *Evidence-based Complementary and Alternative Medicine*, vol. 7, no. 2, pp. 249–257, 2010.

[66] A. J. Butler, J. Cazeaux, A. Fidler et al., "The movement imagery questionnaire-revised, second edition (MIQ-RS) is a reliable and valid tool for evaluating motor imagery in stroke populations," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 497289, 11 pages, 2012.

[67] F. Malouin, C. L. Richards, P. L. Jackson, M. F. Lafleur, A. Durand, and J. Doyon, "The kinesthetic and visual imagery questionnaire (KVIQ) for assessing motor imagery in persons with physical disabilities: a reliability and construct validity study," *Journal of Neurologic Physical Therapy*, vol. 31, no. 1, pp. 20–29, 2007.

[68] B. Randhawa, S. Harris, and L. A. Boyd, "The kinesthetic and visual imagery questionnaire is a reliable tool for individuals with Parkinson disease," *Journal of Neurologic Physical Therapy*, vol. 34, no. 3, pp. 161–167, 2010.

[69] R. Roberts, N. Callow, L. Hardy, D. Markland, and J. Bringer, "Movement imagery ability: development and assessment of a revised version of the vividness of movement imagery questionnaire," *Journal of Sport & Exercise Psychology*, vol. 30, no. 2, pp. 200–221, 2008.

[70] C. G. Goetz, B. C. Tilley, S. R. Shaftman et al., "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results," *Movement Disorders*, vol. 23, no. 15, pp. 2129–2170, 2008.

[71] L. E. Powell and A. M. Myers, "The activities-specific balance confidence (ABC) scale," *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, vol. 50A, no. 1, pp. M28–M34, 1995.

[72] M. Cardol, R. J. de Haan, B. A. de Jong, G. A. M. van den Bos, and I. J. M. de Groot, "Psychometric properties of the impact on participation and autonomy questionnaire," *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 2, pp. 210–216, 2001.

[73] A. G. Beiske, J. H. Loge, A. Rønningen, and E. Svensson, "Pain in Parkinson's disease: prevalence and characteristics," *Pain*, vol. 141, no. 1, pp. 173–177, 2009.

[74] C. D. Silberman, J. Laks, C. F. Capitão, C. S. Rodrigues, I. Moreira, and E. Engelhardt, "Recognizing depression in patients with Parkinson's disease: accuracy and specificity of two depression rating scale," *Arquivos de Neuro-Psiquiatria*, vol. 64, no. 2b, pp. 407–411, 2006.

[75] A. Shumway-Cook, S. Brauer, and M. Woollacott, "Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test," *Physical Therapy*, vol. 80, no. 9, pp. 896–903, 2000.

[76] S. Morris, M. E. Morris, and R. Iansek, "Reliability of measurements obtained with the timed "Up & Go" test in people with Parkinson disease," *Physical Therapy*, vol. 81, no. 2, pp. 810–818, 2001.

[77] R. W. Bohannon, "Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants," *Age and Ageing*, vol. 26, no. 1, pp. 15–19, 1997.

[78] M. J. Falvo and G. M. Earhart, "Six-minute walk distance in persons with Parkinson disease: a hierarchical regression model," *Archives of Physical Medicine and Rehabilitation*, vol. 90, no. 6, pp. 1004–1008, 2009.

[79] R. Rikli and C. Jones, *Senior Fitness Test Manual*, Human Kinetics, Champaign, IL, USA, 2001.

[80] M. Schenkman, T. Ellis, C. Christiansen et al., "Profile of functional limitations and task performance among people with early- and middle-stage Parkinson disease," *Physical Therapy*, vol. 91, no. 9, pp. 1339–1354, 2011.

[81] J. V. Jacobs, F. B. Horak, K. Van Tran, and J. G. Nutt, "An alternative clinical postural stability test for patients with Parkinson's disease," *Journal of Neurology*, vol. 253, no. 11, pp. 1404–1413, 2006.

[82] C. R. Bowie and P. D. Harvey, "Administration and interpretation of the Trail Making Test," *Nature Protocols*, vol. 1, no. 5, pp. 2277–2281, 2006.

[83] R. P. C. Kessels, E. van den Berg, C. Ruis, and A. M. A. Brands, "The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span," *Assessment*, vol. 15, no. 4, pp. 426–434, 2008.

[84] L. R. Brooks, "The suppression of visualization by reading," *Quarterly Journal of Experimental Psychology*, vol. 19, no. 4, pp. 289–299, 1967.

[85] M. U. Ferraye, B. Debû, L. Heil, M. Carpenter, B. R. Bloem, and I. Toni, "Using motor imagery to study the neural substrates of dynamic balance," *PLoS One*, vol. 9, no. 3, article e91183, 2014.

[86] R. Sandyk, "Reversal of a body image disorder (macrosomatognosia) in Parkinson's disease by treatment with AC pulsed electromagnetic fields," *The International Journal of Neuroscience*, vol. 93, no. 1-2, pp. 43–54, 1998.

[87] M. E. Hackney, H. L. Lee, J. Battisto, B. Crosson, and K. M. McGregor, "Context-dependent neural activation: internally and externally guided rhythmic lower limb movement in individuals with and without neurodegenerative disease," *Frontiers in Neurology*, vol. 6, p. 251, 2015.

[88] R. C. Helmich, F. P. de Lange, B. R. Bloem, and I. Toni, "Cerebral compensation during motor imagery in Parkinson's disease," *Neuropsychologia*, vol. 45, no. 10, pp. 2201–2215, 2007.

[89] R. C. Helmich, B. R. Bloem, and I. Toni, "Motor imagery evokes increased somatosensory activity in Parkinson's disease patients with tremor," *Human Brain Mapping*, vol. 33, no. 8, pp. 1763–1779, 2012.

[90] C. M. Powers, "The influence of abnormal hip mechanics on knee injury: a biomechanical perspective," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 40, no. 2, pp. 42–51, 2010.

[91] N. Bogduk and S. Mercer, "Biomechanics of the cervical spine. I: Normal kinematics," *Clinical Biomechanics*, vol. 15, no. 9, pp. 633–648, 2000.

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Research Article

Age-Related Differences in Cortical and Subcortical Activities during Observation and Motor Imagery of Dynamic Postural Tasks: An fMRI Study

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Age-related changes in brain activation other than in the primary motor cortex are not well known with respect to dynamic balance control. Therefore, the current study aimed to explore age-related differences in the control of static and dynamic postural tasks using fMRI during mental simulation of balance tasks. For this purpose, 16 elderly (72 ± 5 years) and 16 young adults (27 ± 5 years) were asked to mentally simulate a static and a dynamic balance task by motor imagery (MI), action observation (AO), or the combination of AO and MI (AO + MI). Age-related differences were detected in the form of larger brain activations in elderly compared to young participants, especially in the challenging dynamic task when applying AO + MI. Interestingly, when MI (no visual input) was contrasted to AO (visual input), elderly participants revealed deactivation of subcortical areas. The finding that the elderly demonstrated overactivation in mostly cortical areas in challenging postural conditions with visual input (AO + MI and AO) but deactivation in subcortical areas during MI (no vision) may indicate that elderly individuals allocate more cortical resources to the internal representation of dynamic postural tasks. Furthermore, it might be assumed that they depend more strongly on visual input to activate subcortical internal representations.

1. Introduction

Aging is associated with deterioration of postural control [1]. This is indicated by an increased variation of the center of pressure, an increase of postural sway, and a higher risk of falls in the elderly [2]. This deterioration has been related to structural and functional changes in the central nervous system [3].

When considering postural control in general, early studies believed that mainly spinal and brainstem structures were involved in postural control [4, 5], although more recent studies showed the crucial importance of cortical and subcortical brain regions [6, 7]. For instance, studies applying transcranial magnetic stimulation (TMS) reported the importance of the primary motor cortex (M1) in the control of dynamic and static postural tasks [7, 8] and showed adaptations in M1 that were correlated with adaptations in balance control [9]. In line with this, structural changes assessed by magnetic resonance imaging (MRI) in the supplementary motor area (SMA) and prefrontal cortex (PFC) were shown to be correlated with changes in postural control, underlining the importance of these cortical areas for postural control [10].

Considering subcortical structures, the cerebellum and basal ganglia were shown to play a fundamental role in balance control. For instance, lesions in those brain regions resulted in severe deterioration of balance [11–14]. Moreover, larger brain activation was found in the cerebellum

when a more challenging static postural task was performed [15]. In addition, Goble et al. [16] observed that the level of activation of the basal ganglia during stimulation of the foot muscle spindle was correlated with balance performance indicating that the sensory processing in the basal ganglia is also important for an adequate postural control.

Based on these aforementioned studies, it can be concluded that postural control relies on a brain network involving the PMC, SMA, PFC, M1, brainstem, basal ganglia, and cerebellum. It is important to note that these regions are influenced by aging. For manual motor tasks, numerous functional MRI (fMRI) studies showed greater cortical activity in M1, PMC, and PFC in elderly adults compared to young adults [17–20]. This phenomenon of greater and more diffuse cortical activity in the elderly was observed for both cognitive function and motor function, and it is still debated whether this so-called (cortical) overactivation is related to compensatory processes or dedifferentiation of (i.e., less distinctive) representations [21, 22]. Irrespective of its exact nature, it is reasonable to assume that this age-related overactivation can also be found during the performance of balance tasks. In line with this, changes in the activation of M1 were recently shown by means of TMS during postural tasks. Papegaaij et al. [23] observed a reduction of intracortical inhibition when elderly people were standing on foam compared to standing on a rigid surface while young people displayed unchanged intracortical inhibition. Moreover, a facilitation of motor-evoked potentials during upright stance was observed in the elderly compared to young participants [24, 25], suggesting that aging is accompanied by disinhibition of M1.

In a first step, the current study therefore aimed to clarify whether different ways of mentally simulating postural tasks (action observation = AO, motor imagery = MI, and combination of AO and MI = AO + MI) could reproduce the phenomenon of cortical overactivation known from studies investigating the actual execution of postural tasks. So far, only MI of gait and upright stance was compared between young and elderly subjects using fMRI.

Compared to young adults, elderly participants displayed increased activity in the multisensory vestibular cortices, motion-sensitive visual cortices (MT/V5), and somatosensory cortices (right postcentral gyrus) during motor imagery (MI) of upright stance [26]. The authors supposed that the observed overactivation in the elderly was the result of a reduced reciprocal inhibitory sensory interaction, which may be a compensatory mechanism and may reflect a more conscious postural control. Similarly, an age-related overactivation in the right supplementary motor area (SMA, BA6), the right orbitofrontal cortex (BA11), and the left dorsolateral frontal cortex (BA10) was observed during MI of gait [27].

Taken together, TMS and fMRI studies convincingly demonstrated age-related cortical overactivation during motor tasks in general and postural tasks in particular. However, little is known about differences in subcortical brain regions between young and elderly adults.

Functional MRI studies of the upper extremity reported divergent results when comparing subcortical brain activity in young and elderly participants. Some described reduced activity in the cerebellum or the basal ganglia [28–30] while others observed higher activation levels in subcortical regions in the elderly [19, 20]. With respect to balance control, there is no study to date that compared (subcortical) brain activation levels in young and elderly subjects. This seems important as challenging postural tasks are differently organized than easy postural tasks [31] and age-related differences become more pronounced in complex (e.g., more dynamic) postural tasks [31, 32]. Thus, to better understand postural control and to better tailor nonphysical balance training interventions, it is important to gain a better understanding of age-related changes in the neural processing while mentally simulating postural tasks. In particular, there is a need to clarify the activation of subcortical centers in the aging brain, which is considered to be essential for a more automatic movement execution (e.g., [33]).

Therefore, the main aim of the current study was to explore age-related differences in the internal representation of dynamic postural tasks by means of fMRI in order to detect not only cortical but also subcortical changes. For this purpose, young and older participants were asked to mentally simulate balance tasks by either MI, AO, or the combination of the two (AO + MI) while lying in the scanner. Two postural tasks were simulated: quiet upright stance (static) and the compensation of a mediolateral perturbation (dynamic). As the dynamics of actual balance tasks limit brain accessibility, mental simulation was chosen, which is certainly not a perfect effigy of real task execution but, nevertheless, demonstrates important parallels. It was shown, for instance, that physical task performance and mental simulation activate similar brain areas in a similar manner [34–37]. Based on the activation of overlapping brain areas, Jeannerod [36] postulated the well-accepted theory that "the motor system is part of a simulation network that is activated under a variety of conditions in relation to action, either self-intended or observed from other individuals" (p.103). It is believed that the positive training/learning effects of mental simulation on physical task performance are explained by the activation of this common neural network. With respect to postural control, mental simulation of balance tasks has recently been shown to be effective in improving postural control [38] and to substantially activate motor centers responsible for postural control [39]. It therefore seems reasonable to assume that the activation patterns seen during mental simulation are, indeed, neural representations of postural tasks with a high functional relevance. Thus, the comparison of brain activation patterns in young and elderly adults seems a promising way to assess differences in cortical and subcortical representations of challenging dynamic postural tasks. Based on the results of dual-task studies indicating that processing of motor control shifts from automatic (more subcortical) processing to more consciously controlled (cortical) processing [33, 40], we hypothesized to find greater activation in cortical and lower activation in subcortical areas in old compared to young adults during mental simulation of postural tasks.

Moreover, this design allowed us to investigate age-related differences in the role of vision (or visual guidance)

during mental simulation in order to activate internal representations of balance tasks. It is known that elderly people depend more strongly on visual information for postural control than do young adults [41–43] and this dependency was argued to be mainly due to a deterioration of executive functions [44]. In addition, with respect to mental simulation techniques, the combination of AO and MI, the so-called AO + MI, has repeatedly been demonstrated to be more effective than AO or MI alone (for reviews, see [45, 46]). Thus, we speculated that AO + MI might be especially beneficial in the elderly to activate not only cortical but also subcortical brain areas that are important for balancing due to their stronger dependency on visual input with age.

To summarize, the current study aimed to investigate age-related differences in the internal representation of dynamic postural control. We assumed to observe (1) greater activation in cortical and deactivation in subcortical areas as well as (2) larger dependency on visual input to activate internal representations in elderly compared to young people during mental simulation of postural tasks.

2. Methods

2.1. Participants. Sixteen healthy elderly adults (seven females) aged between 65 and 80 years (mean ± SD = 72 ± 4.6) participated in this study. Their results were compared to the results of a group of sixteen healthy young adults (six females) aged between 20 and 37 years (27 ± 4.8) from a previous study [39]. All participants were free from neurological and orthopedic disorders. They had normal or corrected-to-normal vision. Participants were briefed on the experiments and provided written informed consent for the experimental procedure before testing. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

2.2. Experimental Procedure. The same protocol as in our previous study in young adults [39] was applied to the group of elderly adults. They were instructed to observe or mentally simulate two balance tasks in three different conditions while lying in the scanner. The three mental simulation conditions were (1) AO, (2) MI, and (3) the combination of the two (AO + MI). In the AO condition, the instruction was to merely watch the videos showing a person performing balance tasks. In the MI condition, the participants were asked to imagine themselves performing the respective task with their eyes closed. For the AO + MI condition, the participants were asked to combine the two by watching the video while imagining performing the task themselves at the same time. The MI was performed in a first-person perspective. Two different balance tasks were used in all three mental simulation conditions: (1) standing still on stable ground (Figure 1(a)) and (2) compensating a mediolateral perturbation while standing on a free-swinging platform (Figure 1(b)).

The three mental simulation conditions were tested in separate runs. In the scanner, written and verbal information was provided about which mental simulation condition and which balance task were about to be performed. Each experimental condition (mental simulation) consisted of eight segments (four times each balance task) presented in a random order. Each segment was composed of a 2 s video repeated 10 times, which resulted in video sequences of 20 s, followed by a rest period of 21 s, where a white cross was shown on a black screen. In the video showing the dynamic balance task, each of these 2 s iterations corresponded to one perturbation. In order to notify participants about the start of a new iteration, the start of each video was signaled by a tone. This was particularly important for the MI condition where participants had their eyes closed. All participants were carefully introduced to the tasks and familiarized with the videos by the experimenter before they were placed in the scanner. It was underlined that it was essential that they performed all the tasks only mentally, without any actual movements. The elderly's ability to imagine movements was assessed by a standardized questionnaire (short version of the Kinesthetic and Visual Imagery Questionnaire (KVIQ-10); [48]). In all elderly participants, the average rating of the clarity of the image and the intensity of the sensation was at least three (moderately clear image/moderately intense sensation) on a five-point scale.

(a) (b)

Figure 1: Balance tasks displayed during the experiment. (a) For the static balance task, a person was displayed standing on stable ground. (b) For the dynamic balance task, a person was shown compensating for a mediolateral perturbation while standing on a free-swinging platform (from [47]).

2.3. Material. Visual stimuli were displayed on an LCD screen (32″ LCD Monitor, NordicNeuroLab, Bergen, Norway) with E-Prime 2.0 software (Psychology Software Tools Inc., http://www.pstnet.com, PA, USA) at a refresh rate of 60 Hz. Participants looked at the screen through a mirror system. Auditory information was transmitted through MRI-compatible headphones (Starter f mkII+ MRI Audio System, MR confon, Magdeburg, Germany).

2.4. Image Acquisition. Participants were in a supine position in the scanner, and cushions were used to reduce head motion. Data were acquired with a 3T MRI scanner (Discovery MR750, GE Healthcare, Waukesha, Wisconsin, USA) at the Cantonal Hospital of Fribourg, Switzerland (http://www.h-fr.ch). A 32-channel standard head coil was employed for acquisition. High-resolution T1-weighted anatomical scans were collected in the coronal plane (FSPGR BRAVO sequence; voxel size = 0.86 × 0.86 × 1 mm, number of slices = 280, repetition time (TR) = 7300 ms, echo time (TE) = 2.8 ms, and flip angle = 9°; parallel imaging with an

acceleration factor of 1.5). Functional T2*-weighted images were recorded with a Gradient Echo-Echo Planar Imaging sequence. The blood oxygenation level-dependent (BOLD) contrast was used as an index of local increases in brain activity. For each experimental session, 150 dynamic volumes with axial acquisitions were collected over the whole brain (voxel size = $1.875 \times 1.875 \times 3$ mm, matrix size = 128×128, and number of slices = 40; interleaved acquisition from the bottom to the top of the head, inter-slice spacing = 0.3 mm, TR = 2500 ms, TE = 30 ms, and flip angle = 85°; parallel imaging with an acceleration factor of 2). To secure steady-state tissue magnetization, the first 7.5 s of each functional run was defined as dummy scans.

2.5. Data Processing and Analysis. MRI data were analyzed with the Statistical Parametric Mapping SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) running on MATLAB 2012b (The MathWorks Inc., http://www.mathworks.com, MA, USA). Functional volumes were preprocessed using standard methods implemented in SPM8: spatial realignment, coregistration with anatomical scan, normalization on MNI space ($2 \times 2 \times 2$ mm), and smoothing with an isotropic 6 mm full width at half maximum (FWHM) Gaussian kernel. Details have been described previously [39]. The preprocessed images were then subjected to a fixed effect analysis (first-level analysis) based on a general linear model to each voxel [49, 50] for each participant (block design) using an autoregressive [AR(1)] function to account for temporal correlations between voxels across the whole brain.

In a first step, a two-way random effect full factorial model (ANOVA 3×2) with the within-subject factor mental simulation condition (AO versus MI versus AO + MI) and balance task (static versus dynamic) was used to estimate brain activity in the elderly group. The pattern of brain activation in each experimental condition (the combination of mental simulation condition and postural task) was studied at the whole brain level by calculating simple effects (contrasts between task and baseline activities, $p < 0.05$ FWE corrected at the voxel level) and direct comparisons between conditions. Brain activation patterns in the young adults have been presented previously [39]. Commonalities as well as differences in brain activation patterns between groups were evaluated by comparing elderly with young people in a second-level analysis. For this purpose, a full factorial model with the age group as a between-subject factor was performed. On the full factorial model, a conjunction analysis [51] was used to determine the common activation of the two groups at the whole brain level ($p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level and with an extended cluster threshold of 5 contiguous voxels). The FWE-corrected p values of the significant clusters are presented in Results.

For the evaluation of age-related differences between groups, a region of interest (ROI) analysis was performed on the full factorial model ($p < 0.05$ FWE at the voxel level and with an extended cluster threshold of 5 contiguous voxels). The FWE-corrected p values of the significant voxels are displayed in Results.

Regions analyzed were based on sensorimotor regions that were previously shown to be activated during execution and mental simulation of balance and gait tasks in the literature [14, 15, 27, 52–55]: SMA, PMC, M1, cerebellum, PFC, and putamen.

The locations of ROI were defined with the anatomy toolbox [56], and the locations of the putamen and PFC were based on the automated anatomical labeling (AAL) atlas [57]. To assess the effect of task difficulty on age-related differences in cerebral activity, the interaction between balance task (dynamic versus static balance task) and age group was analyzed for each mental simulation condition (AO + MI, AO, and MI). Finally, to investigate the effect of aging on the type of mental simulation and the impact of visual guidance, the interaction between mental simulation condition (AO + MI versus AO versus MI) and age group was analyzed for both balance tasks.

3. Results

In the following, brain activation patterns in elderly adults are described first. Afterwards, common activity (revealed by the conjunction analysis) in young and elderly adults is displayed before describing differences in brain activation between the two groups. The results for the young participants have recently been presented elsewhere [39].

3.1. Brain Activity Pattern in Elderly Adults

3.1.1. Simple Effects. For elderly adults, activity in brain regions important for postural control was detected in all mental simulation conditions for the dynamic postural task. During MI of the dynamic balance task, activities in the bilateral SMA ($p < 0.001$), right PMC ($p = 0.006$), bilateral PFC ($p < 0.001$), and left putamen ($p < 0.001$) were observed. The AO + MI condition of the dynamic task involved the bilateral SMA ($p < 0.001$), bilateral M1 ($p < 0.001$), bilateral putamen ($p = 0.001$), right PMC ($p < 0.001$), bilateral PFC ($p < 0.001$), and left cerebellum ($p < 0.001$, lobules I–IV and lobule VI). Furthermore, during AO of the dynamic task, the right SMA ($p = 0.03$), right PFC ($p < 0.001$), and left cerebellum ($p = 0.03$; lobules VIIa and VIIb) were activated. The static balance task induced activation in the right PMC ($p = 0.01$) and right PFC ($p < 0.001$) during MI and in the right SMA ($p = 0.02$) during AO + MI. Interestingly, no significant activity was detected in brain areas associated with balance control during AO of the static balance task. We also found activity in areas processing visual and auditory information (results not illustrated).

3.1.2. Complexity of the Balance Task. In order to investigate whether the complexity of the balance task had an influence on the activation of brain centers in elderly adults, the dynamic balance task was compared to the static task. During AO + MI, this comparison displayed stronger activation in the bilateral SMA ($p < 0.001$), bilateral PMC ($p < 0.001$), bilateral PFC ($p = 0.001$), and left cerebellum ($p < 0.001$; lobules I–IV and V) for the dynamic task (results are presented in Table 1 of Supplementary Materials which provide the table of brain activities observed in the

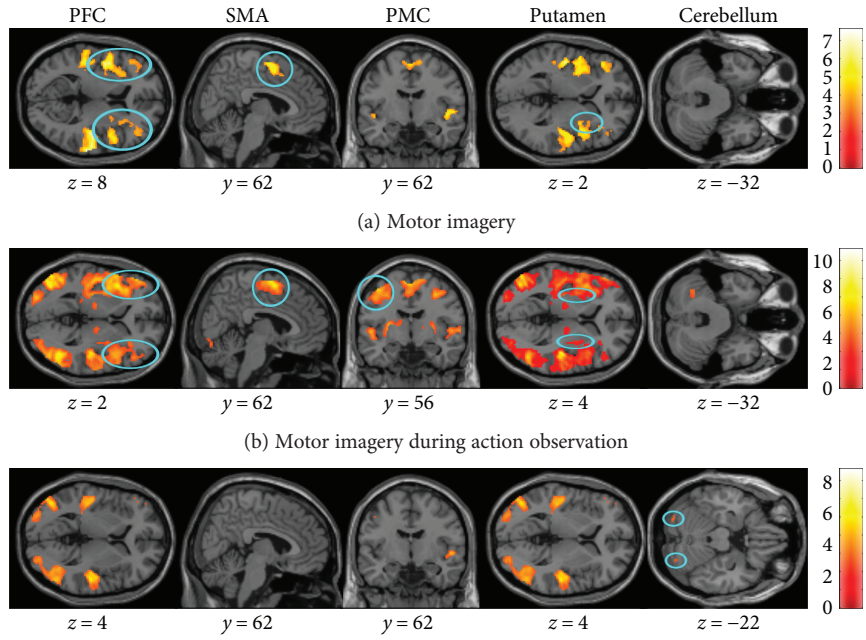

Figure 2: Common brain activity in young and elderly adults detected by a conjunction analysis. The three mental simulation conditions were contrasted with the baseline (mental simulation > baseline). The figure presents shared activities for the dynamic balance task during (a) motor imagery (MI), (b) motor imagery during action observation (AO + MI), and (c) action observation (AO). Colored circles underline significant common brain activity. Whole brain results are presented with $p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level. Colored bars display the significance level of the contrast. Spatial coordinates (x, y, and z) are provided in MNI space.

elderly when the dynamic balance is compared with the static task during action observation combined with motor imagery (AO+MI)). No significant differences between the dynamic and the static tasks were detected for the MI and AO conditions.

3.1.3. Effect of Mental Simulation Condition. There were no significant differences in brain activation in areas important for balance control between mental simulation conditions for the dynamic task when comparing AO + MI with MI and MI with AO. However, when AO + MI was compared with AO, higher activations were seen in the left putamen ($p < 0.001$), bilateral SMA ($p < 0.001$), and bilateral PMC ($p < 0.001$).

Motor imagery during action observation (AO + MI) of the dynamic task did not equal the sum of the AO and MI conditions. Indeed, the elderly presented significantly larger activation during AO + MI than the sum of brain activity during independent MI and independent AO in the bilateral M1 ($p < 0.001$), bilateral SMA ($p < 0.001$), left PMC ($p < 0.001$), bilateral cerebellum ($p < 0.005$), and left putamen ($p < 0.001$).

3.2. Common Activity in Young and Elderly Adults. In order to identify brain regions that were activated in both age groups, a conjunction analysis was conducted for each mental simulation condition (Figure 2). Common activation was observed in the bilateral SMA (dynamic: $p < 0.001$; static: $p = 0.05$) and bilateral PFC (dynamic: $p < 0.001$; static: $p < 0.001$) for MI of both balance tasks and in the right putamen ($p < 0.001$) only for the dynamic task. During AO + MI of both balance tasks, common activation was observed in the bilateral SMA (dynamic: $p < 0.001$; static $p = 0.009$), bilateral PMC (dynamic: $p < 0.001$; static: $p = 0.01$), the left putamen (dynamic: $p < 0.001$; static: $p < 0.001$), and PFC (dynamic: $p < 0.001$; static: $p < 0.001$). Common activity was further seen in the bilateral cerebellum (lobule VIIa Crus I, $p < 0.001$) during AO of the dynamic balance task, but no common cerebral activation was found for the static task. Not surprisingly, there was also common activity in areas processing visual and auditory information (results not illustrated).

3.3. Age-Related Differences in Brain Activity

3.3.1. Simple Effects. In order to detect differences in brain activity between elderly and young adults, comparisons of the simple effects (conditions compared to the baseline, Figure 3) were performed by means of an ROI analysis. The AO + MI of the dynamic task condition induced stronger activity in SMA ($p = 0.01$) and M1 ($p = 0.03$) in elderly compared to young people. No significant difference between groups was found for AO + MI of the static task. AO of the dynamic task induced larger activity in SMA ($p < 0.001$), PMC ($p = 0.05$), PFC ($p = 0.03$), and putamen ($p = 0.01$) in elderly compared to young participants. AO of the static task revealed increased brain activity only in the SMA ($p = 0.02$). During MI, larger brain activations were observed in older individuals compared to young adults in the PFC ($p = 0.04$) for the dynamic task and in the putamen ($p = 0.01$) for the static task. The younger adults did not present significantly

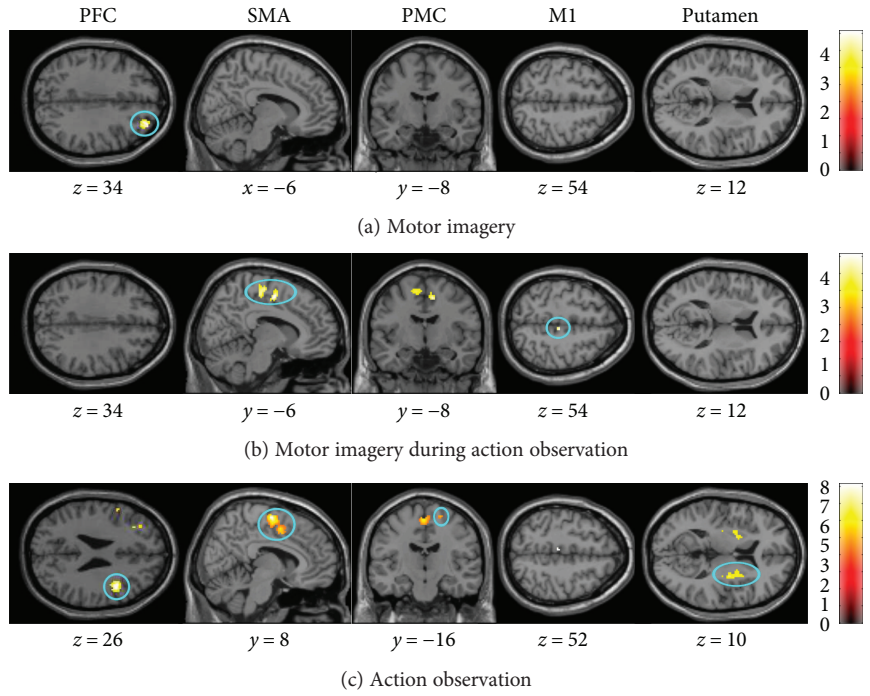

Figure 3: Age-related differences in brain activity. The three mental simulation conditions were contrasted between age group by means of an ROI analysis. Presented are significantly different activities for the dynamic balance task during (a) motor imagery (MI), (b) motor imagery during action observation (AO + MI), and (c) action observation (AO). Colored circles highlight significantly greater brain activity in elderly adults. Activations are presented with $p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level. Colored bars indicate the significance level of the contrasts. Spatial coordinates (x, y, and z) are provided in MNI space.

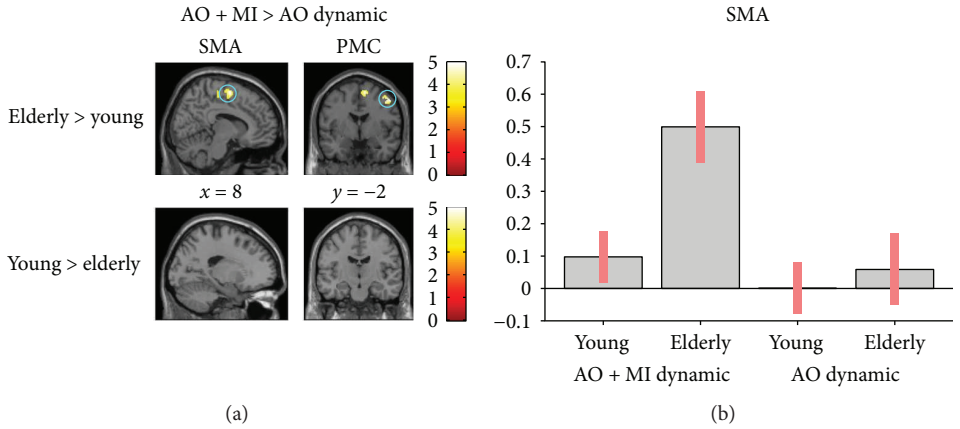

Figure 4: Age-related differences in brain activity when motor imagery during action observation (AO + MI) is contrasted with action observation (AO), revealed by an ROI analysis. (a) presents differences in activity in the SMA ($p = 0.02$) and PMC ($p = 0.02$) between groups. (b) shows the activation level of a representative voxel (8, −24, and 58) of the SMA. Colored circles highlight significantly stronger brain activity. Activations are presented with $p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level. Colored bars indicate the significance level of the contrasts. Spatial coordinates (x, y, and z) are provided in MNI space.

higher brain activity than the elderly individuals in any mental simulation condition.

3.3.2. Complexity of the Balance Task. To evaluate age-related differences in the effects of balance task type, task effects in the two groups were compared. During AO + MI, an ROI analysis revealed that the effect of task (dynamic task > static task) was greater in old individuals compared to the young adults in the SMA ($p = 0.04$) and PFC ($p = 0.001$). No significant age-related differences in task-specific effects were found for MI and AO.

3.3.3. Effect of Mental Simulation Condition

(1) AO + MI versus AO. An ROI analysis for this contrast indicated larger activation of the bilateral SMA ($p = 0.02$)

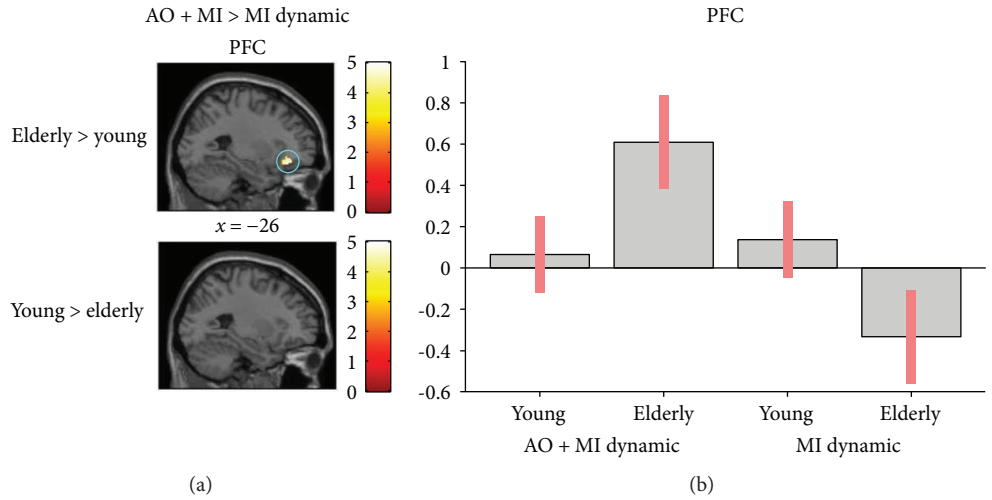

Figure 5: Age-related differences in brain activity when motor imagery during action observation (AO + MI) is contrasted with motor imagery alone (MI), revealed by an ROI analysis. (a) shows higher brain activity for the dynamic task in the PFC ($p = 0.05$) in older adults when compared to young adults. (b) shows the activation level of a representative voxel (−28, 34, and −14) of the PFC depending on the group and the mental simulation condition (AO + MI or MI). Colored circles highlight significantly stronger brain activity in elderly adults. Activations are displayed with $p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level. Colored bars indicate the significance level of the contrasts. Spatial coordinates (x, y, and z) are provided in MNI space.

and the right PMC ($p = 0.02$) in the elderly group for the dynamic task (see Figure 4). In contrast, young subjects did not show higher activation than elderly participants in any brain area for the dynamic task. For the static task, the young presented stronger activation in the cerebellum ($p = 0.01$; lobule VIIa Crus I, lobule VIIIb, and lobule VI).

(2) AO + MI versus MI. The comparison of AO + MI versus MI of the dynamic task revealed greater activation in the PFC ($p = 0.05$) in elderly individuals (see Figure 5).

(3) MI versus AO. When comparing the interaction between MI and AO (MI > AO) in the two age groups, an ROI analysis revealed that in the cerebellum ($p = 0.02$; lobule VIIa Crus I) and the putamen ($p = 0.05$), young adults had greater cerebral activity than the elderly for the dynamic task (see Figure 6). There was no difference between groups in the static task.

4. Discussion

This first study about different ways to mentally simulate dynamic postural tasks in old and young participants revealed a considerable amount of common brain activity between elderly and young adults. However, there were also marked differences in the activation patterns of elderly participants evidenced by greater cortical activation in PFC, SMA, PMC, M1, and putamen. Moreover, when MI (no visual input) was contrasted to AO (visual input), the elderly, relative to young participants, demonstrated deactivation of subcortical areas such as the cerebellum and the putamen in the condition with no visual input. Thus, elderly individuals appear to rely more on visual guidance to activate subcortical representations of balance tasks and it might therefore be even more important to combine AO with MI (AO + MI) in elderly than in young subjects.

4.1. Similarities in Cerebral Activity between Age Groups. The current results demonstrate that both young and elderly adults activated brain regions involved in postural control when they observed and/or imagined a postural task. In line with recent observations for nonpostural [26, 27, 58] and our previously reported results for postural tasks in young participants [39], elderly participants demonstrated greatest activity during AO + MI, followed by MI and AO. Moreover, brain activities observed in the M1, SMA, PMC, cerebellum, and putamen during AO + MI were not simply the addition of activity of independent AO and independent MI but were significantly larger than the sum of those two conditions. This finding supports previous studies reporting the phenomenon of supra-additive effects of AO + MI compared to AO or MI alone (e.g., Sakamoto et al. and Taube et al. [39]).

It was recently speculated that the combination of AO + MI may enable subjects to gain better physiological sensations and kinesthetic experiences of the imagined movement [45]. Importantly, the present study demonstrates that this supra-additive effect can also be seen in elderly subjects and therefore proposes that AO + MI is a very promising approach to activate internal movement representations of postural tasks in the elderly.

The importance of combining AO + MI in the elderly was also apparent, when combining the two different balance tasks. Only with AO + MI, the more demanding dynamic balance task induced significant greater activation in brain regions important for postural control than the simple balance task. This result is also in line with previous findings in young adults showing larger effects for the more demanding postural task [39]. Therefore, it is not surprising that

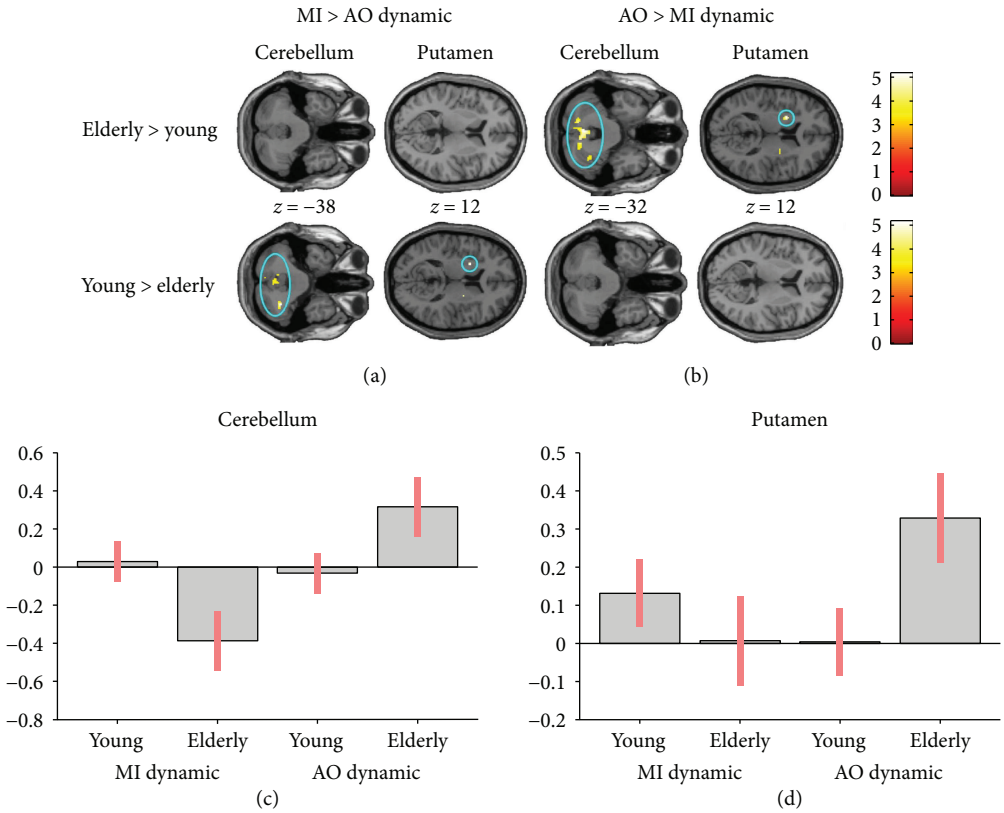

Figure 6: Age-related differences in the interactions between brain activity during motor imagery (MI) and action observation (AO), revealed by an ROI analysis. (a) shows higher brain activity in the cerebellum ($p = 0.02$) and putamen ($p = 0.05$) in young adults compared to older adults, when a condition with no visual support (MI) is contrasted with one with visual support (AO) for the dynamic task. Inversely, (b) presented greater cerebral activity in the cerebellum ($p = 0.02$) and putamen ($p = 0.008$) in elderly adults compared to young adults, when a condition with visual support (AO) is contrasted with one with no visual support (MI). (c) and (d) represent the activation of the cerebellum and the putamen depending on the group and the mental simulation condition. The plots for the cerebellum and the putamen are based on voxels (−2, −60, and −34 and 30, −18, and 2, resp.). Colored circles highlight significantly stronger brain activity in young adults. Activations are displayed with $p < 0.001$ at the voxel level, extended by a $p < 0.05$ FWE corrected at the cluster level. Colored bars indicate the significance level of the contrasts. Spatial coordinates (x, y, and z) are provided in MNI space.

when directly assessing common activity of brain centers in elderly and young people by means of a conjunction analysis, considerable overlap could be observed. However, despite these similarities there were also distinct differences between young and elderly participants.

4.2. Differences in Cerebral Activity between Age Groups. Compared to young adults, elderly participants displayed greater activity in the SMA, M1, PMC, and putamen during mental simulation of the dynamic balance tasks. For the upper extremity, most studies associated such an age-specific overactivation with better motor performance compared to age-matched subjects that did not show overactivation/disinhibition [18–20]. Therefore, it is generally believed that increased cortical activity and reduced cortical inhibition serve as compensatory mechanisms for structural degeneration ("compensation hypothesis"; for review, see [3]). Alternatively, it was suggested that elderly adults might present a more nonselective recruitment of brain regions ("dedifferentiation hypothesis"; [22]). However, this second hypothesis seems less likely, as elderly adults showed a very similar task-dependent pattern of activity as young adults (conjunction analysis) in the present study. In line with this, greater activations were seen in the cerebellum and SMA, when the dynamic task was contrasted with the static task during the AO + MI condition in both populations. However, comparison of elderly with young adults for this contrast revealed stronger activation of the SMA and PMC in the elderly. These results indicate that age-related changes were more prominent in the more complex dynamic postural task than in the static standing task. Furthermore, as these differences were only significant in the AO + MI condition, this finding supports the assumption of greater efficacy of AO + MI compared to AO or MI alone (for review, see [45]). From a motor control point of view, it can be argued that elderly people relied more strongly on cortical areas to active internal representations of the dynamic postural task. Alternatively, the age-related difference observed in this study could also indicate the decline of cognitive function in the elderly. However, we can only speculate regarding the latter, as the participants' cognitive abilities were not assessed, which is one limitation of this study. Nonetheless, as all our elderly participants were able to adequately perform MI, we do not think that cognitive abilities were substantially

different between groups. This is in line with previous studies on motor imagery reporting that the vividness is well preserved in the elderly [59, 60]. In addition, elderly individuals were shown to present similar temporal congruence between MI and movement execution to young adults [61–64]. Therefore, we reckon that the age-related changes detected in this study more likely indicate a decline of the mental ability to simulate challenging postural tasks than a general deterioration of the ability to perform mental simulation. This is further supported by the fact that there were no age-related differences when comparing the static postural task.

The age-related overactivation in cortical brain areas during mental simulation of the dynamic balance task confirms data from neurophysiological measurements during actual postural task execution. By means of TMS, several studies demonstrated increased corticospinal excitability in elderly compared to young people when performing balance tasks [25, 65]. In addition, intracortical inhibition was shown to be reduced in elderly compared to young participants in challenging postural conditions [23]. Thus, age-related overactivation of cortical areas seems to be apparent during both actual task execution and mental simulation of dynamic postural tasks. Unfortunately, measurements during balance activities are restricted to motor cortical areas accessible with TMS. Therefore, little is known about age-specific activity of subcortical brain regions during postural task execution. Furthermore, there exist no studies comparing young and elderly adults during mental simulation of dynamic postural tasks.

Allali et al. [27] investigated brain activation while subjects were asked to imagine walking over even ground or over cobblestones. In general, elderly adults demonstrated larger activation than did young adults in the left middle frontal gyrus (BA10), right SMA, and right superior orbitofrontal cortex (BA11). Furthermore, compared to young subjects, elderly participants displayed stronger activation in the left hippocampus when switching from walking over even ground to the more challenging task of walking over cobblestones [27]. However, although balance certainly plays a considerable role during walking, it may, nevertheless, not be entirely comparable to other postural tasks such as upright stance. For instance, when evaluating age-dependent alterations during imagined walking, running, and standing, Zwergal et al. [26] demonstrated the greatest multisensory activation during standing followed by walking and finally running in the elderly. The authors argued that gait relies strongly on subcortical locomotor centers that are evolutionarily old structures and, therefore, probably less susceptible to atrophy or dysfunction in advanced age. In contrast, unperturbed stance [8] and perturbed stance [7] were shown to rely on motor cortical areas, and cortical plasticity in these regions was correlated with behavioral adaptations after balance training [9, 55, 66]. Thus, the (cortical) control of dynamic upright stance may be more prone to aging. This may also explain the pronounced differences in cortical centers that were detected in the present study. Compared to young adults, elderly participants displayed greater activity in the SMA, M1, and PMC during mental simulation. However, there were also differences in subcortical brain activation patterns. However, these differences seemed to strongly depend on whether or not elderly subjects received "visual guidance" during mental simulation of postural tasks.

4.3. Impact of Visual Input for the Mental Simulation of Postural Tasks. In the current study, different types of mental simulation (AO + MI versus AO versus MI) were compared in terms of activating brain centers responsible for postural control in young and elderly subjects. In the elderly, stronger cortical activity was mainly found for the conditions with visual input (AO + MI and AO). In the condition without visual input (MI), elderly participants displayed solely facilitation in the PFC while reduced activity was found in subcortical areas such as the putamen and the cerebellum. Therefore, it seems that, in elderly adults, the activation of subcortical representations responsible for the control of (perturbed) stance strongly depended on visual input. Activation in these areas is considered important for automated (postural) task execution [67]. Based on mainly dual-task findings, the group around Stephan Swinnen stressed that elderly adults exhibit less automatic processing of upright posture, resulting in greater activation of cognitive resources [33]. Furthermore, dual-task studies investigating the influence of vision demonstrated that dual-task costs, that is, the reduction in performance due to the execution of a concurrent secondary task, were especially pronounced in elderly adults when secondary tasks that required substantial visual processing were chosen [42, 44]. Thus, the findings of the current study may provide a first indication that, for elderly people, visual input is important during mental simulation to better activate subcortical brain centers that enable more automatized movement control. When vision is removed (MI condition), elderly participants display a decrease of activation of these subcortical areas while, at the same time, activity in the PFC increases, indicating the greater involvement of cognitive resources.

4.4. Functional Considerations and Conclusion. Elderly and young adults demonstrated very similar brain activation patterns when mentally simulating postural tasks. Both age groups increased brain activity in the dynamic postural task and when combining AO with MI (AO + MI). Thus, for both age groups, interventions involving mental simulation should involve dynamic (complex) postural tasks and AO + MI. The comparison of brain activation in young and elderly participants between mental simulation conditions proposes that the combination of AO and MI might be even more important for elderly people. Indeed, in conditions with visual input (AO + MI and AO), the elderly demonstrated greater cortical activity whereas in the condition without visual input (MI), they showed solely facilitation in the PFC but a decrease in activity in subcortical areas such as the putamen and the cerebellum. Our results, therefore, indicate that the activation of internal representations of postural tasks by means of mental simulation in elderly people depends more strongly on visual input than that in young participants. This visual input seems especially important to activate subcortical brain centers, such as the cerebellum and the basal ganglia, which are probably important to enable automatized task execution. Consequently,

nonphysical balance training in elderly adults should use visual guidance to promote activity in these brain areas.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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Supplementary Materials

Table 1: brain activity observed in the elderly when the dynamic balance is compared with the static task during action observation combined with motor imagery (AO + MI). The table presents all significant brain activations observed in the condition. The spatial location (coordinates x, y, and z) of the voxel with the highest Z-score (Z-max) inside of each cluster is presented. *(Supplementary Materials)*

References

[1] B. E. Maki and W. E. McIlroy, "Postural control in the older adult," *Clinics in Geriatric Medicine*, vol. 12, no. 4, pp. 635–658, 1996.

[2] S. W. Muir, K. Berg, B. Chesworth, N. Klar, and M. Speechley, "Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis," *Journal of Clinical Epidemiology*, vol. 63, no. 4, pp. 389–406, 2010.

[3] S. Papegaaij, W. Taube, S. Baudry, E. Otten, and T. Hortobágyi, "Aging causes a reorganization of cortical and spinal control of posture," *Frontiers in Aging Neuroscience*, vol. 6, p. 28, 2014.

[4] P. Luccarini, Y. Gahery, and O. Pompeiano, "Injection of a cholinergic agonist in the dorsolateral pontine tegmentum of cats affects the posturokinetic responses to cortical stimulation," *Neuroscience Letters*, vol. 114, no. 1, pp. 75–81, 1990.

[5] C. S. Sherrington, "Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing," *The Journal of Physiology*, vol. 40, no. 1-2, pp. 28–121, 1910.

[6] J. V. Jacobs and F. B. Horak, "Cortical control of postural responses," *Journal of Neural Transmission*, vol. 114, no. 10, pp. 1339–1348, 2007.

[7] W. Taube, M. Schubert, M. Gruber, S. Beck, M. Faist, and A. Gollhofer, "Direct corticospinal pathways contribute to neuromuscular control of perturbed stance," *Journal of Applied Physiology*, vol. 101, no. 2, pp. 420–429, 2006.

[8] C. D. Tokuno, W. Taube, and A. G. Cresswell, "An enhanced level of motor cortical excitability during the control of human standing," *Acta Physiologica*, vol. 195, no. 3, pp. 385–395, 2009.

[9] W. Taube, M. Gruber, S. Beck, M. Faist, A. Gollhofer, and M. Schubert, "Cortical and spinal adaptations induced by balance training: correlation between stance stability and corticospinal activation," *Acta Physiologica*, vol. 189, no. 4, pp. 347–358, 2007.

[10] M. Taubert, B. Draganski, A. Anwander et al., "Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections," *The Journal of Neuroscience*, vol. 30, no. 35, pp. 11670–11677, 2010.

[11] H. C. Diener and J. Dichgans, "Pathophysiology of cerebellar ataxia," *Movement Disorders*, vol. 7, no. 2, pp. 95–109, 1992.

[12] L. Luciani, *Il cervelletto: nuovi studi di fisiologia normale e patologica*, Le Monnier, Florence, 1891.

[13] L. M. Nashner, "Adapting reflexes controlling the human posture," *Experimental Brain Research*, vol. 26, no. 1, pp. 59–72, 1976.

[14] J. E. Visser and B. R. Bloem, "Role of the basal ganglia in balance control," *Neural Plasticity*, vol. 12, no. 2-3, pp. 161–174, 2005.

[15] Y. Ouchi, H. Okada, E. Yoshikawa, S. Nobezawa, and M. Futatsubashi, "Brain activation during maintenance of standing postures in humans," *Brain*, vol. 122, no. 2, pp. 329–338, 1999.

[16] D. J. Goble, J. P. Coxon, A. Van Impe et al., "Brain activity during ankle proprioceptive stimulation predicts balance performance in young and older adults," *The Journal of Neuroscience*, vol. 31, no. 45, pp. 16344–16352, 2011.

[17] C. Calautti, C. Serrati, and J. C. Baron, "Effects of age on brain activation during auditory-cued thumb-to-index opposition: a positron emission tomography study," *Stroke*, vol. 32, no. 1, pp. 139–146, 2001.

[18] S. Heuninckx, N. Wenderoth, and S. P. Swinnen, "Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons," *The Journal of Neuroscience*, vol. 28, no. 1, pp. 91–99, 2008.

[19] V. S. Mattay, F. Fera, A. Tessitore et al., "Neurophysiological correlates of age-related changes in human motor function," *Neurology*, vol. 58, no. 4, pp. 630–635, 2002.

[20] T. Wu and M. Hallett, "The influence of normal human ageing on automatic movements," *The Journal of Physiology*, vol. 562, no. 2, pp. 605–615, 2005.

[21] J. A. Bernard and R. D. Seidler, "Evidence for motor cortex dedifferentiation in older adults," *Neurobiology of Aging*, vol. 33, no. 9, pp. 1890–1899, 2012.

[22] R. D. Seidler, J. A. Bernard, T. B. Burutolu et al., "Motor control and aging: links to age-related brain structural, functional, and biochemical effects," *Neuroscience and Biobehavioral Reviews*, vol. 34, no. 5, pp. 721–733, 2010.

[23] S. Papegaaij, W. Taube, M. Hogenhout, S. Baudry, and T. Hortobágyi, "Age-related decrease in motor cortical inhibition during standing under different sensory conditions," *Frontiers in Aging Neuroscience*, vol. 6, p. 126, 2014.

[24] S. Baudry, S. Collignon, and J. Duchateau, "Influence of age and posture on spinal and corticospinal excitability," *Experimental Gerontology*, vol. 69, pp. 62–69, 2015.

[25] S. Baudry, F. Penzer, and J. Duchateau, "Input-output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults," *Acta Physiologica*, vol. 210, no. 3, pp. 667–677, 2014.

[26] A. Zwergal, J. Linn, G. Xiong, T. Brandt, M. Strupp, and K. Jahn, "Aging of human supraspinal locomotor and postural control in fMRI," *Neurobiology of Aging*, vol. 33, no. 6, pp. 1073–1084, 2012.

[27] G. Allali, M. van der Meulen, O. Beauchet, S. W. Rieger, P. Vuilleumier, and F. Assal, "The neural basis of age-related changes in motor imagery of gait: an fMRI study," *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, vol. 69, no. 11, pp. 1389–1398, 2014.

[28] J. P. Coxon, D. J. Goble, A. Van Impe, J. De Vos, N. Wenderoth, and S. P. Swinnen, "Reduced basal ganglia function when elderly switch between coordinated movement patterns," *Cerebral Cortex*, vol. 20, no. 10, pp. 2368–2379, 2010.

[29] T. Taniwaki, A. Okayama, T. Yoshiura et al., "Age-related alterations of the functional interactions within the basal ganglia and cerebellar motor loops *in vivo*," *NeuroImage*, vol. 36, no. 4, pp. 1263–1276, 2007.

[30] A. Van Impe, J. P. Coxon, D. J. Goble, N. Wenderoth, and S. P. Swinnen, "Ipsilateral coordination at preferred rate: effects of age, body side and task complexity," *NeuroImage*, vol. 47, no. 4, pp. 1854–1862, 2009.

[31] S. Papegaaij, W. Taube, H. G. van Keeken, E. Otten, S. Baudry, and T. Hortobagyi, "Postural challenge affects motor cortical activity in young and old adults," *Experimental Gerontology*, vol. 73, pp. 78–85, 2016.

[32] S. Papegaaij, S. Baudry, J. Negyesi, W. Taube, and T. Hortobagyi, "Intracortical inhibition in the soleus muscle is reduced during the control of upright standing in both young and old adults," *European Journal of Applied Physiology*, vol. 116, no. 5, pp. 959–967, 2016.

[33] M. P. Boisgontier, I. A. M. Beets, J. Duysens, A. Nieuwboer, R. T. Krampe, and S. P. Swinnen, "Age-related differences in attentional cost associated with postural dual tasks: increased recruitment of generic cognitive resources in older adults," *Neuroscience and Biobehavioral Reviews*, vol. 37, no. 8, pp. 1824–1837, 2013.

[34] J. Grèzes, J. L. Armony, J. Rowe, and R. E. Passingham, "Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study," *NeuroImage*, vol. 18, no. 4, pp. 928–937, 2003.

[35] M. Jeannerod, "Mental imagery in the motor context," *Neuropsychologia*, vol. 33, no. 11, pp. 1419–1432, 1995.

[36] M. Jeannerod, "Neural simulation of action: a unifying mechanism for motor cognition," *NeuroImage*, vol. 14, no. 1, pp. S103–S109, 2001.

[37] C. J. Olsson, B. Jonsson, and L. Nyberg, "Learning by doing and learning by thinking: an FMRI study of combining motor and mental training," *Frontiers in Human Neuroscience*, vol. 2, p. 5, 2008.

[38] W. Taube, M. Lorch, S. Zeiter, and M. Keller, "Non-physical practice improves task performance in an unstable, perturbed environment: motor imagery and observational balance training," *Frontiers in Human Neuroscience*, vol. 8, p. 972, 2014.

[39] W. Taube, M. Mouthon, C. Leukel, H. M. Hoogewoud, J. M. Annoni, and M. Keller, "Brain activity during observation and motor imagery of different balance tasks: an fMRI study," *Cortex*, vol. 64, pp. 102–114, 2015.

[40] S. Heuninckx, N. Wenderoth, F. Debaere, R. Peeters, and S. P. Swinnen, "Neural basis of aging: the penetration of cognition into action control," *The Journal of Neuroscience*, vol. 25, no. 29, pp. 6787–6796, 2005.

[41] P. G. Anderson, B. Nienhuis, T. Mulder, and W. Hulstijn, "Are older adults more dependent on visual information in regulating self-motion than younger adults?," *Journal of Motor Behavior*, vol. 30, no. 2, pp. 104–113, 1998.

[42] R. Beurskens and O. Bock, "Does the walking task matter? Influence of different walking conditions on dual-task performances in young and older persons," *Human Movement Science*, vol. 32, no. 6, pp. 1456–1466, 2013.

[43] M. Jamet, D. Deviterne, G. C. Gauchard, G. Vancon, and P. P. Perrin, "Higher visual dependency increases balance control perturbation during cognitive task fulfilment in elderly people," *Neuroscience Letters*, vol. 359, no. 1-2, pp. 61–64, 2004.

[44] O. Bock and R. Beurskens, "Effects of a visual distracter task on the gait of elderly versus young persons," *Current Gerontology and Geriatrics Research*, vol. 2011, Article ID 651718, 7 pages, 2011.

[45] D. L. Eaves, M. Riach, P. S. Holmes, and D. J. Wright, "Motor imagery during action observation: a brief review of evidence, theory and future research opportunities," *Frontiers in Neuroscience*, vol. 10, p. 514, 2016.

[46] S. Vogt, F. Di Rienzo, C. Collet, A. Collins, and A. Guillot, "Multiple roles of motor imagery during action observation," *Frontiers in Human Neuroscience*, vol. 7, p. 807, 2013.

[47] A. Mouthon, J. Ruffieux, M. Walchli, M. Keller, and W. Taube, "Task-dependent changes of corticospinal excitability during observation and motor imagery of balance tasks," *Neuroscience*, vol. 303, pp. 535–543, 2015.

[48] F. Malouin, C. L. Richards, P. L. Jackson, M. F. Lafleur, A. Durand, and J. Doyon, "The kinesthetic and visual imagery questionnaire (KVIQ) for assessing motor imagery in persons with physical disabilities: a reliability and construct validity study," *Journal of Neurologic Physical Therapy*, vol. 31, no. 1, pp. 20–29, 2007.

[49] K. J. Friston, A. P. Holmes, K. J. Worsley, J. P. Poline, C. D. Frith, and R. S. J. Frackowiak, "Statistical parametric maps in functional imaging: a general linear approach," *Human Brain Mapping*, vol. 2, no. 4, pp. 189–210, 1994.

[50] K. J. Worsley and K. J. Friston, "Analysis of fMRI time-series revisited—again," *NeuroImage*, vol. 2, no. 3, pp. 173–181, 1995.

[51] C. J. Price and K. J. Friston, "Cognitive conjunction: a new approach to brain activation experiments," *NeuroImage*, vol. 5, no. 4, pp. 261–270, 1997.

[52] M. U. Ferraye, B. Debu, L. Heil, M. Carpenter, B. R. Bloem, and I. Toni, "Using motor imagery to study the neural substrates of dynamic balance," *PLoS One*, vol. 9, no. 3, article e91183, 2014.

[53] K. Jahn, A. Deutschlander, T. Stephan, M. Strupp, M. Wiesmann, and T. Brandt, "Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging," *NeuroImage*, vol. 22, no. 4, pp. 1722–1731, 2004.

[54] F. Malouin, C. L. Richards, P. L. Jackson, F. Dumas, and J. Doyon, "Brain activations during motor imagery of locomotor-related tasks: a PET study," *Human Brain Mapping*, vol. 19, no. 1, pp. 47–62, 2003.

[55] M. Taubert, G. Lohmann, D. S. Margulies, A. Villringer, and P. Ragert, "Long-term effects of motor training on resting-state networks and underlying brain structure," *NeuroImage*, vol. 57, no. 4, pp. 1492–1498, 2011.

[56] S. B. Eickhoff, K. E. Stephan, H. Mohlberg et al., "A new SPM toolbox for combining probabilistic cytoarchitectonic maps

and functional imaging data," *NeuroImage*, vol. 25, no. 4, pp. 1325–1335, 2005.

[57] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou et al., "Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain," *NeuroImage*, vol. 15, no. 1, pp. 273–289, 2002.

[58] V. Nedelko, T. Hassa, F. Hamzei et al., "Age-independent activation in areas of the mirror neuron system during action observation and action imagery. A fMRI study," *Restorative Neurology and Neuroscience*, vol. 28, no. 6, pp. 737–747, 2010.

[59] F. Malouin and C. L. Richards, "Mental practice for relearning locomotor skills," *Physical Therapy*, vol. 90, no. 2, pp. 240–251, 2010.

[60] T. Mulder, J. B. H. Hochstenbach, M. J. G. van Heuvelen, and A. R. den Otter, "Motor imagery: the relation between age and imagery capacity," *Human Movement Science*, vol. 26, no. 2, pp. 203–211, 2007.

[61] P. Personnier, C. Paizis, Y. Ballay, and C. Papaxanthis, "Mentally represented motor actions in normal aging II. The influence of the gravito-inertial context on the duration of overt and covert arm movements," *Behavioural Brain Research*, vol. 186, no. 2, pp. 273–283, 2008.

[62] N. Schott and J. Munzert, "Temporal accuracy of motor imagery in older women," *International Journal of Sport Psychology*, vol. 38, no. 3, pp. 304–320, 2007.

[63] X. Skoura, C. Papaxanthis, A. Vinter, and T. Pozzo, "Mentally represented motor actions in normal aging. I. Age effects on the temporal features of overt and covert execution of actions," *Behavioural Brain Research*, vol. 165, no. 2, pp. 229–239, 2005.

[64] X. Skoura, P. Personnier, A. Vinter, T. Pozzo, and C. Papaxanthis, "Decline in motor prediction in elderly subjects: right versus left arm differences in mentally simulated motor actions," *Cortex*, vol. 44, no. 9, pp. 1271–1278, 2008.

[65] S. Baudry and J. Duchateau, "Independent modulation of corticospinal and group I afferents pathways during upright standing," *Neuroscience*, vol. 275, pp. 162–169, 2014.

[66] M. Taubert, A. Villringer, and P. Ragert, "Learning-related gray and white matter changes in humans: an update," *The Neuroscientist*, vol. 18, no. 4, pp. 320–325, 2012.

[67] V. Puttemans, N. Wenderoth, and S. P. Swinnen, "Changes in brain activation during the acquisition of a multifrequency bimanual coordination task: from the cognitive stage to advanced levels of automaticity," *The Journal of Neuroscience*, vol. 25, no. 17, pp. 4270–4278, 2005.

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Review Article

How Visual Body Perception Influences Somatosensory Plasticity

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The study of somatosensory plasticity offers unique insights into the neuronal mechanisms that underlie human adaptive and maladaptive plasticity. So far, little attention has been paid on the specific influence of visual body perception on somatosensory plasticity and learning in humans. Here, we review evidence on how visual body perception induces changes in the functional architecture of the somatosensory system and discuss the specific influence the social environment has on tactile plasticity and learning. We focus on studies that have been published in the areas of human cognitive and clinical neuroscience and refer to animal studies when appropriate. We discuss the therapeutic potential of socially mediated modulations of somatosensory plasticity and introduce specific paradigms to induce plastic changes under controlled conditions. This review offers a contribution to understanding the complex interactions between social perception and somatosensory learning by focusing on a novel research field: socially mediated sensory plasticity.

1. Introduction

The tactile modality is the first to develop in a human embryo and has important implications for human sensation, action, and cognition. This review addresses the specific question how social cues influence the functional architecture and plasticity of the human somatosensory system. Social neuroscience is a rapidly developing field, but the specific influence of social cues on somatosensory perception is still an underinvestigated topic. Here, we first introduce basic mechanisms of tactile plasticity and learning, such as Hebbian plasticity, GABAergic learning mechanisms, and deprivation-related plasticity (Section 2). Then, we discuss the influence of social cues on human somatosensory cortex functioning and synthesize evidence on the neuronal pathways and experimental conditions that induce nonafferent (visually driven) activity in the human somatosensory system (Section 3). Before combining both research streams to answer the final question ("How do socially-induced 'resonance' responses in the somatosensory system influence tactile plasticity?"), we provide an overview over the role of touch in human cognition to broaden the scope in which the results can be discussed (Section 4). Finally, we use the introduced frameworks (tactile plasticity, Section 2; socially induced "resonance" responses in the somatosensory system, Section 3; and the role of touch in human cognition, Section 4) to discuss the influence of social cues on tactile plasticity and learning at multiple levels (both mechanistic and cognitive) and its consequences for human behavior in healthy participants, and in patients (Section 5). Whereas the first three sections therefore provide relevant background information, the final section combines the introduced research streams to focus on socially mediated tactile plasticity. We focus on the literature offered by human cognitive and clinical neuroscience, while sometimes referring to animal studies when specific plasticity mechanisms are introduced. This review offers a contribution towards the development of a better understanding of the complex interactions between social perception and somatosensory learning by focusing on a novel and rapidly developing research field: socially mediated sensory plasticity.

2. Plasticity Mechanisms in the Somatosensory System

Perceptual learning is the specific modification of perception following sensory experience. This, in turn, involves structural and functional changes in primary sensory cortices [1]. In tactile learning, most of our knowledge about brain plasticity is derived from primary somatosensory cortex (S-I). Larger representations of certain body parts, such as the fingers or lips, are partly due to higher receptor densities reflecting higher demands for cortical processing. These cortical body maps in animals and humans, however, are dynamic constructs that are constantly remodeled by changes in the sensory input statistics throughout life. Structural myelin borders between major body part representations such as the hand and the face in human S-I [2, 3] may to a certain extent limit such plastic changes [4]. Despite the traditional view that perceptual learning requires attention or reinforcement, there is also evidence that only the timing of input statistics can mediate cortical plasticity [5–11]. In fact, since Hebb [12] and even since James [13], the aspect of simultaneity has become a metaphor in neuronal plasticity.

An important feature of the Hebbian metaphor is the coincident pre- and postsynaptic firing of synapses that evokes long-lasting changes in synaptic efficacy. First evidences that temporally correlated activity is required for input-dependent modification in synapses come from the hippocampus in rats [14] and Aplysia ganglia [15]. Although pairing of synaptic inputs and outputs has been hypothesized to play a key role in mediating plastic changes [16–18], more recent evidences suggest that Hebbian plasticity also occurs at dendritic spines without simultaneous pre- and postsynaptic activation [19].

In vitro and computational studies suggested that beyond a simultaneous activation of pre- and postsynaptic cells, there is a "critical time window" of spiking for synaptic modification that is highly specific to certain brain regions [20–26]. These activity-induced changes can occur in vitro at a precision of down to a few milliseconds thus influencing the strength and sign of synaptic plasticity. A critical window for the induction of long-term potentiation (LTP) and long-term depression (LTD) has been characterized in rat hippocampal neurons. This window is about 40 ms long and is temporally asymmetric. Bi and Poo found that repetitive postsynaptic spiking that precedes presynaptic activation in a time window of 20 ms (60 pulses at 1 Hz) resulted in LTP, whereas postsynaptic spiking 20 ms before repetitive presynaptic activation led to LTD. Apart from a critical window for modification of synaptic excitability, synaptic strength and specific postsynaptic cell types (NMDA and GABAergic receptors) are crucial factors for the induction of LTP and LTD [21]. In line with these findings, an almost identical time dependence was described in developing *Xenopus* retinotectal synapses [27]. In contrast, neurons in cortical layer 4 of somatosensory cortex seem to have only a symmetric time window for LTD within ±10 ms, whereas no long-term potentiation in synaptic response was observed [28].

Also, the deprivation of sensory input leads to changes in the functional architecture of S-I representations. In limb amputees, where afferent input to the limb is absent, the cortical representation of the face shifts towards the territory of the hand [29, 30]. Recent findings indicate, however, that these shifts are smaller than originally suggested and that the representation of the absent hand is still preserved [30–32]. Also, altered hand use in amputees induces somatomotor plasticity in amputees. Makin et al. [33] showed that deprived sensorimotor cortex is employed by whichever limb individuals are overusing.

Perceptual learning occurs continuously throughout life and involves either transient or persistent changes in central nervous perceptual systems, which in turn improves the ability to respond to the environment [34–36]. To obtain information about the role of input statistics alone in mediating plasticity in perceptual systems, several protocols, in which neuronal activity was generated by associative pairing, have been developed [37]. In adult rats, for instance, it has been shown that "whisker pairing," which involves trimming of whiskers except two neighboring vibrissae, resulted in changes in sensory neural activity [37].

Based on the same idea of paired sensory inputs, several studies in animals and humans demonstrate that a variation of input statistics using passive stimulation protocols results in cortical plasticity [5–11]. Godde and coworkers developed a stimulation protocol, called "tactile coactivation," to receptive fields on the hindpaw of adult rats. The basic idea behind this stimulation protocol was to coactivate a large number of receptive fields in a Hebbian manner in order to strengthen their mutual interconnectedness. Coactivation consists of tactile stimuli that were presented at different interstimulus intervals from 100 to 3000 ms in pseudorandomized order with a mean stimulation frequency of 1 Hz. Coactivation of the hindpaw for 3 hours revealed a selective enlargement of corresponding cortical maps and receptive fields [38]. To investigate the perceptual relevance of the coactivation effect, tactile spatial discrimination performance was tested in humans. Coactivation of receptive field on the fingertip resulted in an improved tactile spatial discrimination ability that lasted for 24 hours. Perceptual changes were highly selective because no transfer of improved performance to nonstimulated fingers was found [5].

Pleger et al. studied the relation between those coactivation-induced perceptual changes and parallel plasticity in human S-I. Using somatosensory-evoked potential (SSEP) mapping [6] and functional magnetic resonance imaging (fMRI) [7], they found that coactivation-induced changes in tactile acuity were reflected in the degree of cortical reorganization. The cortical representation of the coactivated finger in S-I post- versus precoactivation was considerably larger on the coactivated side than on the control side [6, 7]. Using fMRI, Pleger et al. extended the focus on cortical plasticity in the secondary somatosensory cortex (S-II). Contralateral to the coactivated finger, S-II presented with enhanced BOLD signal change comparable to the effects observed in S-I. In line with previous findings [5], tactile discrimination thresholds recovered to baseline 24 hours after coactivation. Furthermore, the relation

between cortical plasticity in S-I and perceptual changes was linearly correlated, indicating a close link between the magnitude of plastic changes and coactivation-induced spatial discrimination improvements [6, 7]. In S-II, no such brain-behavior relationship was observed, which might be due to the less fine-grained representational organization of S-II as compared to S-I [39]. Coactivation-induced cortical plasticity together with perceptual improvements was found not only in the young brain but also in older adults suggesting that coactivation-induced effects occur continuously throughout life [40].

To shed light on the underlying cellular mechanisms mediating this specific type of perceptual learning and associated cortical plasticity, Dinse et al. manipulated coactivation-induced perceptual learning with different drugs that specifically block or stimulate central nervous receptors assumed to play a key role in mediating brain plasticity [8, 9]. Under memantine, a NMDA receptor blocker [41], they found that both perceptual improvements and associated cortical plasticity were blocked [8]. Under a single dose of amphetamine, which is known to modify long-term changes in synaptic function [42], perceptual improvements and cortical plasticity were boosted [8]. These results emphasize the prominent role of the NMDA receptor in mediating coactivation-induced perceptual improvements and cortical plasticity. Monoaminergic substances such as amphetamine instead seem to facilitate this specific type of perceptual learning. In line with these experimental findings, perceptual learning after the application of coactivation was shown to be dependent on GABAergic mechanisms. Tactile discrimination improvement was completely abolished by lorazepam, indicating that this $GABA_A$ receptor agonist acts to suppress the coactivation-induced effect [9]. Positive correlations between levels of GABA in primary brain regions and sensory discriminative abilities stress the importance of GABA in increasing the perceived contrast of sensory percepts [43].

3. The Influence of Social Cues on the Somatosensory System

A dominant theory holds that similar motor areas in the brain are activated when a specific action is either observed or executed [44–46]. This reactivation during observation is often referred to as "neuronal resonance" response [47] and has been investigated quite extensively in recent years [48–51]. Neuronal resonance responses in the motor system are supposed to allow an understanding of others' goals, intentions, and motor plans [44, 46, 52–55] and can lead to interference effects between one's own actions and observed actions [55]. The concept of neuronal resonance was subsequently transferred to other domains, such as the domain of pain, emotion, and touch [52, 56–60], but also to the domain of touch [60–65]. Neuronal resonance responses in the pain matrix or sensory cortices are assumed to trigger shared affective or sensory states, respectively, between observed person and observer.

S-I holds dense connections to S-II, the parvocellular area (PV), the primary motor cortex (M-I), the premotor cortex (PM), and the frontal cortices [66, 67]. Particularly, the posterior end of S-I is strongly connected to the superior parietal cortex (SPC) and, even more densely, to the anterior bank of the inferior parietal sulcus (aIPS) [68–70]. The aIPS connections themselves are also widespread and include the motor and premotor cortices, the supplementary motor cortex, S-II, PV, other areas of the posterior parietal cortex (PPC), the cingulate cortex, and the extrastriate visual cortex [67]. Although most of these connections are stronger in the outward direction than in the inward direction, anatomical evidence shows that many connections between S-I and other brain areas are bidirectional and allow an influence of S-I activity not only on other parts of the brain but also on the reverse direction [71–75].

S-I and S-II are typically activated when people observe another person receiving tactile stimulation [61, 63–65, 76]. The S-I activation is topographic, and the activation of single-finger receptive areas in S-I can be triggered purely by observing touches to different fingers [64, 77]. The degree of S-I activity during touch observation seems to be particularly strong in vision-touch synaesthetes who actually feel touch on their own body when they merely observe touch to another person's body [62]. Somatosensory cortices also respond to observing actions [51, 65, 78] and to observing haptic explorations [79] not only in humans but also in monkeys [80].

S-I is composed of altogether four subunits, three of which are mainly responsible for tactile perception (area 3b, area 1, and area 2). Whereas activation of area 1 and area 2 during touch observation is established ([63, 64, 76], but see [81]), there has been a long debate about the social response properties of area 3b, which is the homologue of S-I in other mammals [82]. Whereas some studies reported the activation of area 3b during the observation of touch [76], most studies found this area to be silent during touch observation [63, 64]. A recent study shed light on this issue. Kuehn et al. invited 16 healthy participants to a series of fMRI measurements using a 7-Tesla MRI system. Participants viewed individual touches to four fingers (index finger, middle finger, ring finger, and small finger) or received physical touches to the same four fingers in a separate scanning session [77]. Weak but fine-grained finger maps in contralateral area 3b were activated both when participants physically perceived touches at their own fingers and when they merely observed touches at another person's hand. This effect was robust across viewing perspectives but did not occur when the observed hand was not touched. The tactile-driven finger maps and the visually driven finger maps in fact overlapped in area 3b in most participants. For the first time, this study provides empirical evidence that area 3b has mirror-like response properties and that plasticity mechanisms mediated by this area should in principle be influenced by vision of touch.

Also, a number of behavioral studies showed an influence of viewing the body on somatosensory processing. Taylor-Clarke et al. showed that perceived distances between objects touching the skin are altered when participants looked at a distorted version of their body [83, 84]. Because this perceptual shift was induced by viewing the body, not by viewing

the object touching the body, the effect was assumed to be driven by visual body perception. The ability to spatially discriminate two small needles applied to the skin surface ([85] but see [86]) and the ability to judge the spatial orientation of gratings touching the skin [84, 87, 88] also increased specifically when looking at one's own body compared to looking at an object. Finally, the ability to detect and discriminate the amplitude of electrical stimuli when presented to the skin clearly above threshold improved when viewing the body [89, 90].

An effect of visual body perception on tactile abilities, however, is not restricted to seeing one's own life body. They also seem to occur when participants look at a video image of a body [88, 91], at another person's body [63, 77, 92–94], or at a rubber hand [95, 96], although the effect is often stronger the more the viewed body part can be assigned to the observer's own body ([90, 95–97] but see [63]).

Evidence for a causal role of S-I in mediating tactile improvements when viewing the body was provided by a transcranial magnetic stimulation (TMS) study [98]. Here, repetitive TMS pulses were delivered to S-I or to S-II shortly after the body was visible but before the tactile stimulus arrived. TMS pulses applied to S-I, but not to S-II, diminished the effect of body vision on tactile abilities.

4. The Role of Touch in Human Cognition

S-I is known to be involved in the detection [99], perception [100], discrimination [101–103], and categorization [104] of touch. However, touch plays manifold roles in human cognition that go beyond the mere perception of object qualities [63, 105–107]. For example, tactile stimulation triggers emotions. Pleasant touch applied in a social context is assumed to build the basis for affiliative behavior, to contribute to the formation and maintenance of social bonds, and to build a means for communicating emotions [108, 109]. Tactile C fiber afferents particularly respond to pleasant, caress-like touch applied to hairy parts of the skin [109–111]. They terminate at the posterior insula and are assumed to elicit positive, rewarding emotions [112, 113]. Patients lacking C fiber afferents therefore perceive caress-like stroking as less pleasant than normal controls [111]. S-I may also play a role in processing affective aspects of touch [114], and it may aid in conveying socially elicited emotions to the perceiver [112].

Touch also influences human spatial perception. The incoming information in S-I is spatially ordered and represents the contralateral side of the human body in a mediolateral sequence. This body map in S-I offers a body-centered reference frame for sensory perception [115–120]. The body-centered reference frame is seen in some contrast to an external (spatial) reference frame mediated by the PPC (see [118] for a review) or the temporoparietal junction (TPJ) [121]. The body-centered reference frame may convey more self-centered information to the perceiver because information about the body as stored in S-I is assumed to be little influenced by spatial variables such as body posture [116–118, 122, 123], whereas information about the body that is stored in the PPC changes more dynamically with spatial variables (for reviews see [118, 124]).

Touch may also provide structural information about the body and its parts [125, 126]. In one experiment, participants were better in a tactile task when different tactile stimuli touched the same body part, compared to when they touched different (but adjacent) body parts [127]. Tactile processing in S-I may therefore take anatomical borders between body parts into account (see also [2]). Beauchamp et al. used multivariate pattern analyses (MVPA) to ask which aspects of body part-specific tactile processing are stored in S-I and which are stored in S-II [128]. They showed that touch applied to digits of one hand can be decoded on the basis of activity pattern in S-I, whereas gross anatomical distinctions are better decoded in S-II. Also, deafferented patients, who are deprived of somatosensory and proprioceptive input, have particular difficulties to distinctly control body parts that are nearby [129]. Finally, anaesthetizing a body part leads to an enlargement of the cortical area in S-I representing this body part [130], which presumably leads to the illusory feeling that this part of the body is larger than it actually is [131].

Touch also influences action and motor control. For example, when deprived of vision, humans have problems maintaining a stable body position. When allowed to touch an object, this supports balance, helps to control body sway [132–135], and prevents recovery falls [136]. Other examples of how tactile input influences action are haptic exploration [137, 138] or precision grips [126, 139].

5. The Influence of Visual Body Perception on Somatosensory Plasticity

Above, we have introduced basic mechanisms of somatosensory plasticity and learning (Section 2), discussed possible input pathways and experimental conditions that trigger nonafferent (visually driven) activations of human somatosensory cortices (Section 3), and provided an overview over the role of touch in human cognition (Section 4). Next, we will combine these research streams to target the final question, that is, "How do socially-induced 'resonance' responses in the somatosensory system influence tactile plasticity?"

Hebbian tactile plasticity in S-I is mediated by NMDA receptors (see Section 2) that mostly reside in superficial cortical layers of the coactivated receptive field [140, 141]. So far, it is not clear whether visual signals that reach human S-I during touch observation are integrated into deeper or more superficial cortical layers in S-I. This question is relevant, because only if signals integrated into superficial cortical layers and activated similar neurons, an influence of vision of touch on S-I-mediated Hebbian learning would be expected. To target this question, Kuehn et al. [11] used the established coactivation protocol as introduced above (see Section 2) to induce S-I-mediated Hebbian plasticity in three groups of healthy participants by applying weak tactile stimulation to the tip of the index finger for the duration of three hours. Whereas one group only received tactile stimulation, two other groups were additionally presented with temporally congruent visual signals during the learning phase. One group observed object-to-hand touch; the other group observed object-to-object touch. Whereas all three

groups but not the control group showed the expected tactile learning effect as measured by decreased tactile spatial discrimination thresholds after the stimulation compared to before the stimulation, there were no significant learning differences between the tactile and the two visual groups. The additional visual inputs therefore did not influence tactile plasticity to a measurable (i.e., significant) extent. Whereas different reasons can explain this finding, for example, the specific training protocol used, or different cell types that were activated by vision of touch compared to touch [142], one possibility is that visual signals integrate into deeper cortical layers in S-I. Because Hebbian learning takes place primarily in superficial cortical layers as outlined above, this would explain weak or absent effects of touch observation on Hebbian-mediated plasticity in S-I.

GABAergic inhibitory interactions are an important driving force of S-I-mediated tactile plasticity (see Section 2). Inhibitory interactions in S-I are classically characterized by measuring the relative shrinkage of index- and middle-finger receptive areas in S-I when both are activated simultaneously, compared to when they are activated alone [143, 144]. Kuehn et al. [64] replicated this effect using 7-Tesla fMRI and additionally showed that such inhibitory interactions between index-finger and middle-finger receptive areas in S-I also occur when touch to the fingers is only observed but not physically perceived. Also, a prior study has indicated an influence of vision of a body part on inhibitory interactions in somatosensory cortex during physical touch perception [87], and there is evidence that vision triggers particularly the activation of interneurons in S-I [142]. Positive correlations between levels of GABA in primary brain regions and sensory discriminative abilities stress the importance of GABA in increasing the perceived contrast of sensory percepts [43]. Weakened cortical inhibition is also a main contributor to age-related changes in somatosensation [40]. Suppressive interactions in S-I triggered by touch observation may therefore sharpen S-I receptive fields even without any afferent tactile input [64].

A single-neuron recording study in monkeys showed that there are not only (mirror) neurons that respond positively (i.e., with an increase in firing rates) to action observation but also neurons which respond negatively (i.e., with a decrease in their firing rates [145]). Although this study recorded mirror neurons in the vPM during action observation and not neurons in the somatosensory system during action or touch observation, this finding indicates that neuronal resonance responses can in principle also be inhibitory. And indeed, BOLD signals recorded in S-I during touch observation were mostly negative for the observation of noncongruent finger touches [77]. In line with this, viewing the body typically increases tactile detection thresholds [89, 90].

To study the influence of environmental conditions on somatosensory plasticity, rats were in one experimental series either reared in groups of 12 rats in spacious cages that offered multiple possibilities for object manipulation and social interaction or they were reared alone in small cages that offered fewer possibilities for object manipulation and social interaction. Rats that were reared in groups and in spacious cages showed an expansion of the forepaw maps in S-I compared to those who were reared alone and in an impoverished environment [146]. This effect occurred both for young and older rats [147]. However, it cannot be derived from these studies whether the effects were driven by increased rates of object manipulation (i.e., sensorimotor experience) and/or the presence of social interaction partners (i.e., social touch). Dissociating both influences on somatosensory plasticity would be an important goal for future research.

Rubber hands are an often-used tool to study the influence of visuotactile stimulation on bodily awareness. Press et al. [148] used a similar paradigm to study the influence of vision on somatosensory plasticity. They applied touches to a rubber hand or to a rubber object when participants perceived either synchronous or asynchronous touches at their own hand. After the bimodal (synchronous or asynchronous) training, ERPs over somatosensory cortex were measured in response to unimodal tactile stimulation to the hand. The temporal contingency of visuotactile stimulation delivered during the training phase influenced the ERPs in response to pure tactile stimulation: those participants who trained with synchronous visuotactile stimulation showed an enhanced somatosensory N140 component compared to those who trained with asynchronous visuotactile stimulation. The N140 component is assumed to be elicited in S-II, which contains bilateral receptive fields. This may explain why the effect was not side specific but occurred for both hands. The enhanced N140 after the learning was found both after participants observed touch to a hand and after they observed touch to an object. Classical mirror mechanisms were likely not at play but perhaps bottom-up effects mediated by multisensory integration.

As introduced above (Section 4), touch plays a significant role in emotion perception. Disrupting S-I activity impairs the ability to recognize emotional facial expressions in peers [149–151], and S-I plays a role in recognizing emotional voices [152]. Somatosensory plasticity may therefore also influence emotion perception, such as those elicited by social stimuli. To study this, Friedrich et al. [153] conducted a training study on children with autism spectrum disorder (ASD). For the duration of 6 to 10 weeks, children were trained to either increase mu power (group 1) as measured with EEG over somatosensory cortex or decrease mu power (group 2) when performing a social interaction video game. Suppression of mu power is assumed to reflect neuronal resonance responses in the somatosensory cortex. When comparing pretraining with posttraining mu suppression during an independent task that was not used during training and where children observed emotional facial expressions, only group 2 showed more mu suppression after the training compared to before the training and also showed more mu suppression than group 1 after the training. It is worth noting that other outcome measures did not differ between groups. Training the responsivity of the somatosensory cortex during social perception may therefore enhance empathic responses towards emotional conspecifics also in situations that were not part of the training data set. Further work will have to confirm this finding.

As outlined above (see Section 4), touch contributes to a body-centered reference frame. S-I activity during touch observation may therefore trigger the ability to "put yourself into the shoes of others" [78]. The positive correlation between S-I activity during touch observation and perspective taking abilities as assessed by questionnaires ([154], see similar results in [78]) may be interpreted in this direction. Physical touch perception, on the other hand, could prevent undertaking such a shift in reference frames. This is indicated by a study of Palluel et al. [155]. Here, a virtual reality setup was chosen that allowed showing participants their own back in front. They saw their own back being stroked by brushes, either synchronously or asynchronously to the stroking they felt on their real back. This situation typically triggers participants to feel that the virtual back is their own back, which induces a strong visuotactile interference effect (see also [156]). When participants were stimulated by vibration stimuli on their leg, however, they did not feel the illusion anymore, and they also did not show the visuotactile interference effect [155]. One may argue that the perceived leg vibration caused an activation of their own body-centered reference frame, which prevented them from taking over the other person's reference frame. To the best of our knowledge, so far, no study has specifically studied the effect of tactile training on social perspective taking. The above-outlined studies would indicate a reverse relationship.

Touch observation has also been used to study clinical populations, such as limb amputees, and extinction patients. Hand amputees are an often used model system to study somatosensory plasticity in humans. As outlined above (see Section 2), in spite of an absent hand, limb amputees show an astonishingly intact and only slightly shifted representation of the missing hand in the sensorimotor cortex. It has been argued that both the degree of distortion [29] and the degree of preservation [31] of somatotopic maps in limb amputees contribute to the perception of phantom limb pain. To induce activation and/or to modify the representation of the S-I missing-hand territory in amputees therefore seems to be a goal worth pursuing. Again, the rubber hand illusion may be a suitable tool. Ehrsson et al. [157] showed that observing a rubber hand that is touched synchronously to the stump evokes the illusion in upper limb amputees that the observed hand is their own hand, even though in fact their hand is missing. This effect was present using different psychophysical markers and was also seen in self-report questionnaires. Also, Goller et al. [158] showed that when limb amputees observe another person being touched at different body sites, some of them start feeling touch on their own phantom limb (see also [159]). This did not only occur in patients who frequently experienced phantom limb sensations but also in patients who reported experiencing phantom limb sensations only occasionally, or not at all. Similar to the mirror-box illusion where the moving intact hand creates the illusion of a moving missing hand, also the rubber hand illusion may serve as a therapeutic tool for influencing somatosensory plasticity in limb amputees. However, congenital limb amputees do not show S-I activity when observing another person in pain [160], which indicates possible functional differences between S-I responsivity to touch and pain in limb amputees.

Extinction impairs the ability to perceive multiple stimuli of the same type simultaneously and occurs usually after damage to the contralateral hemisphere. One study investigated whether also the visual presentation of a rubber hand can cause tactile extinction in patients with right brain damage [161]. In patients with left tactile extinction, a visual stimulus was presented near a right rubber hand and near the real right hand. The rubber hand condition induced visuotactile extinction similar to the real hand, indicating that tactile extinction is not specific for perceiving one's own body, but it can also be induced by observing another person's body.

Finally, as outlined above (see Section 3), besides mirroring observed touches, S-I also responds to the observation of human movements, and S-I influences different aspects of human action and motor control (see Section 4). In this last paragraph, we therefore concern with the interaction between action observation, motor resonance, and somatosensory plasticity. TMS is an often-used tool to induce or modulate cortical plasticity. Avenanti et al. [162] investigated the specific influence of virtual lesions in S-I as induced by repetitive TMS (rTMS) over S-I on motor-evoked potentials (MEPs) measured at the hand during observed hand movements. The authors found rTMS to specifically disrupt the ability to resonate with extreme joint-stretching finger movements that induced, by subjective report, strong tactile/proprioceptive sensations during observation. In a different study, TMS pulses delivered over S-I disrupted the ability to correctly judge the weight of a box lifted by a hand but not the ability to correctly judge the weight of a bouncing ball [163]. A contribution of S-I to proprioceptively driven weight judgments has also been indicated by a patient study. Here, deafferented patients were shown to be impaired in their ability to correctly estimate the weight of a box lifted by a person [164]. On the other hand, TMS-adaptation (TMS-A) over S-I can be used for behavioral enhancement [165]. Jacquet and Avenanti showed that TMS-A over S-I leads to a reduction in reaction times when participants were asked to recognize the goal (but not the movement) of an observed hand movement. Somatosensory plasticity can therefore potentially be used to enhance empathic abilities during action observation. There also seems to be the potential to use action observation to induce somatosensory plasticity.

6. Summary

Converging evidences from human and monkey research support the notion that S-I is not only involved in the detection, perception, discrimination, and categorization of touch but also linked to more complex cognitive and emotional functions. More recent work even proposes S-I as a reference frame for social "resonance" that involves those subareas formally assumed to only respond to "real" physical tactile inputs arising from the thalamus [77]. This raises the fundamental question of whether social tactile cues may induce or boost tactile processing, perception, and even plasticity [11] and whether this may offer new treatment options, for instance, in phantom limb pain, stroke rehabilitation, or

even social distortions. Future research is needed to understand the functional role of cortical social "resonance" in primary and further downstream sensory regions and their specific contribution to perception and plasticity.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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References

[1] M. Fahle and T. Poggio, *Perceptual Learning*, MIT Press, Boston, 2002.

[2] E. Kuehn, J. Dinse, E. Jakobsen et al., "Body topography parcellates human sensory and motor cortex," *Cerebral Cortex*, vol. 27, no. 7, pp. 3790–3805, 2017.

[3] M. F. Glasser, T. S. Coalson, E. C. Robinson et al., "A multi-modal parcellation of human cerebral cortex," *Nature*, vol. 536, no. 7615, pp. 171–178, 2016.

[4] M. Sereno, "Plasticity and its limits," *Nature*, vol. 435, no. 7040, pp. 288-289, 2005.

[5] B. Godde, B. Stauffenberg, F. Spengler, and H. R. Dinse, "Tactile coactivation-induced changes in spatial discrimination performance," *The Journal of Neuroscience*, vol. 20, no. 4, pp. 1617–1624, 2000.

[6] B. Pleger, H. R. Dinse, P. Ragert, P. Schwenkreis, J. P. Malin, and M. Tegenthoff, "Shifts in cortical representations predict human discrimination improvement," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 21, pp. 12255–12260, 2001.

[7] B. Pleger, A. F. Foerster, P. Ragert et al., "Functional imaging of perceptual learning in human primary and secondary somatosensory cortex," *Neuron*, vol. 40, no. 3, pp. 643–653, 2003.

[8] H. R. Dinse, P. Ragert, B. Pleger, P. Schwenkreis, and M. Tegenthoff, "Pharmacological modulation of perceptual learning and associated cortical reorganization," *Science*, vol. 301, no. 5629, pp. 91–94, 2003.

[9] H. R. Dinse, P. Ragert, B. Pleger, P. Schwenkreis, and M. Tegenthoff, "GABAergic mechanisms gate tactile discrimination learning," *Neuroreport*, vol. 14, no. 13, pp. 1747–1751, 2003.

[10] D. Muret, H. R. Dinse, S. Macchione, C. Urquizar, A. Farnè, and K. T. Reilly, "Touch improvement at the hand transfers to the face," *Current Biology*, vol. 24, no. 16, pp. R736–R737, 2014.

[11] E. Kuehn, J. Doehler, and B. Pleger, "The influence of vision on tactile Hebbian learning," *Scientific Reports*, vol. 7, no. 1, p. 9069, 2017.

[12] D. Hebb, *The Organization of Behavior*, Wiley, New York, New York, NY, USA, 1949.

[13] W. James, *Psychology: Brief Course*, Harvard Univ Press, Cambridge, MA, USA, 1890.

[14] W. B. Levy and O. Steward, "Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus," *Neuroscience*, vol. 8, no. 4, pp. 791–797, 1983.

[15] R. D. Hawkins, T. W. Abrams, T. J. Carew, and E. R. Kandel, "A cellular mechanism of classical conditioning in Aplysia: activity-dependent amplification of presynaptic facilitation," *Science*, vol. 219, no. 4583, pp. 400–405, 1983.

[16] B. Gustafsson, H. Wigström, W. C. Abraham, and Y. Y. Huang, "Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials," *The Journal of Neuroscience*, vol. 7, no. 3, pp. 774–780, 1987.

[17] J. C. Magee and D. Johnston, "A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons," *Science*, vol. 275, no. 5297, pp. 209–213, 1997.

[18] H. Markram, J. Lubke, M. Frotscher, and B. Sakmann, "Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs," *Science*, vol. 275, no. 5297, pp. 213–215, 1997.

[19] N. L. Golding, Staff NP, and N. Spruston, "Dendritic spikes as a mechanism for cooperative long-term potentiation," *Nature*, vol. 418, no. 6895, pp. 326–331, 2002.

[20] D. Debanne, B. H. Gähwiler, and S. M. Thompson, "Asynchronous pre- and postsynaptic activity induces associative long-term depression in area CA1 of the rat hippocampus in vitro," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 3, pp. 1148–1152, 1994.

[21] G. Q. Bi and M. M. Poo, "Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type," *The Journal of Neuroscience*, vol. 18, no. 24, pp. 10464–10472, 1998.

[22] G. Q. Bi and M. M. Poo, "Synaptic modification by correlated activity: Hebb's postulate revisited," *Annual Review of Neuroscience*, vol. 24, no. 1, pp. 139–166, 2001.

[23] R. Kempter, W. Gerstner, and J. L. van Hemmen, "Intrinsic stabilization of output rates by spike-based Hebbian learning," *Neural Computation*, vol. 13, no. 12, pp. 2709–2741, 2001.

[24] S. Song and L. F. Abbott, "Cortical development and remapping through spike timing-dependent plasticity," *Neuron*, vol. 32, no. 2, pp. 339–350, 2001.

[25] G. Q. Bi and H. X. Wang, "Temporal asymmetry in spike timing-dependent synaptic plasticity," *Physiology & Behavior*, vol. 77, no. 4-5, pp. 551–555, 2002.

[26] L. F. Abbott and S. B. Nelson, "Synaptic plasticity: taming the beast," *Nature Neuroscience*, vol. 3, pp. 1178–1183, 2000.

[27] L. I. Zhang, H. W. Tao, C. E. Holt, W. A. Harris, and M. M. Poo, "A critical window for cooperation and competition among developing retinotectal synapses," *Nature*, vol. 395, no. 6697, pp. 37–44, 1998.

[28] V. Egger, D. Feldmeyer, and B. Sakman, "Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex," *Nature Neuroscience*, vol. 2, no. 12, pp. 1098–1105, 1999.

[29] H. Flor, T. Elbert, S. Knecht et al., "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, no. 6531, pp. 482–484, 1995.

[30] T. R. Makin, J. Scholz, D. Henderson Slater, H. Johansen-Berg, and I. Tracey, "Reassessing cortical reorganization in

the primary sensorimotor cortex following arm amputation," *Brain*, vol. 138, no. 8, pp. 2140–2146, 2015.

[31] T. R. Makin, J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey, and H. Johansen-Berg, "Phantom pain is associated with preserved structure and function in the former hand area," *Nature Communications*, vol. 4, p. 1570, 2013.

[32] S. Kikkert, J. Kolasinski, S. Jbabdi et al., "Revealing the neural fingerprints of a missing hand," *eLife*, vol. 5, article e15492, 2016.

[33] T. R. Makin, A. O. Cramer, J. Scholz et al., "Deprivation-related and use-dependent plasticity go hand in hand," *eLife*, vol. 2, article e01273, 2013.

[34] L. G. Cohen, J. P. Brasil-Neto, A. Pascual-Leone, and M. Hallett, "Plasticity of cortical motor output organization following deafferentation, cerebral lesions, and skill acquisition," *Advances in Neurology*, vol. 63, pp. 187–200, 1993.

[35] A. Sterr, M. M. Müller, T. Elbert, B. Rockstroh, C. Pantev, and E. Taub, "Perceptual correlates of changes in cortical representation of fingers in blind multifinger Braille readers," *The Journal of Neuroscience*, vol. 18, no. 11, pp. 4417–4423, 1998.

[36] C. Braun, R. Schweizer, T. Elbert, N. Birbaumer, and E. Taub, "Differential activation in somatosensory cortex for different discrimination tasks," *The Journal of Neuroscience*, vol. 20, no. 1, pp. 446–450, 2000.

[37] M. E. Diamond, M. Armstrong-James, and F. F. Ebner, "Experience-dependent plasticity in adult rat barrel cortex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 5, pp. 2082–2086, 1993.

[38] B. Godde, F. Spengler, and H. R. Dinse, "Associative pairing of tactile stimulation induces somatosensory cortical reorganization in rats and humans," *Neuroreport*, vol. 8, no. 1, pp. 281–285, 1996.

[39] J. Ruben, J. Schwiemann, M. Deuschert et al., "Somatotopic organization of human secondary somatosensory cortex," *Cerebral Cortex*, vol. 11, no. 5, pp. 463–473, 2001.

[40] B. Pleger, C. Wilimzig, V. Nicolas et al., "A complementary role of intracortical inhibition in age-related tactile degradation and its remodelling in humans," *Scientific Reports*, vol. 6, no. 1, article 27388, 2016.

[41] C. G. Parsons, W. Danysz, and G. Quack, "Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data," *Neuropharmacology*, vol. 38, no. 6, pp. 735–767, 1999.

[42] R. L. Delanoy, D. L. Tucci, and P. E. Gold, "Amphetamine effects on long term potentiation in dentate granule cells," *Pharmacology, Biochemistry and Behavior*, vol. 18, no. 1, pp. 137–139, 1983.

[43] N. A. Puts, R. A. Edden, C. J. Evans, F. McGlone, and D. J. McGonigle, "Regionally specific human GABA concentration correlates with tactile discrimination thresholds," *Journal of Neuroscience*, vol. 31, no. 46, pp. 16556–16560, 2011.

[44] M. Iacoboni, "Imitation, empathy, and mirror neurons," *Annual Review of Psychology*, vol. 60, no. 1, pp. 653–670, 2009.

[45] G. Rizzolatti and L. Craighero, "The mirror-neuron system," *Annual Review of Neuroscience*, vol. 27, no. 1, pp. 169–192, 2004.

[46] G. Rizzolatti, L. Fogassi, and V. Gallese, "Neurophysiological mechanisms underlying the understanding and imitation of action," *Nature Reviews. Neuroscience*, vol. 2, no. 9, pp. 661–670, 2001.

[47] J. Zaki and K. Ochsner, "The neuroscience of empathy: progress, pitfalls and promise," *Nature Neuroscience*, vol. 15, no. 5, pp. 675–680, 2012.

[48] G. Buccino, F. Binkofski, G. R. Fink et al., "Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study," *The European Journal of Neuroscience*, vol. 13, no. 2, pp. 400–404, 2001.

[49] G. Buccino, F. Binkofski, and L. Riggio, "The mirror neuron system and action recognition," *Brain and Language*, vol. 89, no. 2, pp. 370–376, 2004.

[50] B. Calvo-Merino, D. E. Glaser, J. Grèzes, R. E. Passingham, and P. Haggard, "Action observation and acquired motor skills: an FMRI study with expert dancers," *Cerebral Cortex*, vol. 15, no. 8, pp. 1243–1249, 2005.

[51] S. Caspers, K. Zilles, A. R. Laird, and S. B. Eickhoff, "ALE meta-analysis of action observation and imitation in the human brain," *NeuroImage*, vol. 50, no. 3, pp. 1148–1167, 2010.

[52] E. C. Brown and M. Brüne, "The role of prediction in social neuroscience," *Frontiers in Human Neuroscience*, vol. 6, p. 148, 2012.

[53] K. Friston, J. Mattout, and J. Kilner, "Action understanding and active inference," *Biological Cybernetics*, vol. 104, no. 1-2, pp. 137–160, 2011.

[54] V. Gallese, "Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition," *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, vol. 362, no. 1480, pp. 659–669, 2007.

[55] M. Brass, H. Bekkering, A. Wohlschläger, and W. Prinz, "Compatibility between observed and executed finger movements: comparing symbolic, spatial, and imitative cues," *Brain and Cognition*, vol. 44, no. 2, pp. 124–143, 2000.

[56] T. Singer, B. Seymour, J. O'Doherty, H. Kaube, R. J. Dolan, and C. D. Frith, "Empathy for pain involves the affective but not sensory components of pain," *Science*, vol. 303, no. 5661, pp. 1157–1162, 2004.

[57] T. Singer, B. Seymour, J. P. O'Doherty, K. E. Stephan, R. J. Dolan, and C. D. Frith, "Empathic neural responses are modulated by the perceived fairness of others," *Nature*, vol. 439, no. 7075, pp. 466–469, 2006.

[58] T. Singer, "The past, present and future of social neuroscience: a European perspective," *NeuroImage*, vol. 61, no. 2, pp. 437–449, 2012.

[59] B. C. Bernhardt and T. Singer, "The neural basis of empathy," *Annual Review of Neuroscience*, vol. 35, no. 1, pp. 1–23, 2012.

[60] I. Bufalari, T. Aprile, A. Avenanti, F. Di Russo, and S. M. Aglioti, "Empathy for pain and touch in the human somatosensory cortex," *Cerebral Cortex*, vol. 17, no. 11, pp. 2553–2561, 2007.

[61] C. Keysers, B. Wicker, V. Gazzola, J. L. Anton, L. Fogassi, and V. Gallese, "A touching sight: SII/PV activation during the observation and experience of touch," *Neuron*, vol. 42, no. 2, pp. 335–346, 2004.

[62] S. J. Blakemore, D. Bristow, G. Bird, C. Frith, and J. Ward, "Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia," *Brain*, vol. 128, no. 7, pp. 1571–1583, 2005.

[63] E. Kuehn, R. Trampel, K. Mueller, R. Turner, and S. Schütz-Bosbach, "Judging roughness by sight - a 7 Tesla fMRI study on responsivity of the primary somatosensory cortex during observed touch of self and others," *Human Brain Mapping*, vol. 34, no. 8, pp. 1882–1895, 2013.

[64] E. Kuehn, K. Mueller, R. Turner, and S. Schütz-Bosbach, "The functional architecture of S1 during touch observation described with 7 T fMRI," *Brain Structure & Function*, vol. 219, no. 1, pp. 119–140, 2014.

[65] C. Keysers, J. H. Kaas, and V. Gazzola, "Somatosensation in social perception," *Nature Reviews Neuroscience*, vol. 11, no. 6, pp. 417–428, 2010.

[66] E. G. Jones and T. P. Powell, "Connexions of the somatic sensory cortex of the rhesus monkey. II. Contralateral cortical connexions," *Brain*, vol. 92, no. 4, pp. 717–730, 1969.

[67] L. Krubitzer and E. DisbrowE. Kaas JHG, "The evolution of parietal areas involved in hand use in primates," in *The Senses - Somatosensation, Vol 6*, pp. 183–214, Elsevier, Amsterdam, 2008.

[68] T. P. Pons, P. E. Garraghty, C. G. Cusick, and J. H. Kaas, "The somatotopic organization of area 2 in macaque monkeys," *The Journal of Comparative Neurology*, vol. 241, no. 4, pp. 445–466, 1985.

[69] Y. Iwamura, "Bilateral receptive field neurons and callosal connections in the somatosensory cortex," *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, vol. 355, no. 1394, pp. 267–273, 2000.

[70] Y. Iwamura, A. Iriki, M. Tanaka, M. Taoka, and T. Toda, "Processing of higher order somatosensory and visual information in the intraparietal region of the postcentral gyrus," in *Somatosensory Processing - from Single Neuron to Brain Imaging*, Y. Rowe MJI, Ed., pp. 101–112, Harwood Academic Publishers, Amsterdam, 2001.

[71] D. P. Friedman, E. G. Jones, and H. Burton, "Representation pattern in the second somatic sensory area of the monkey cerebral cortex," *The Journal of Comparative Neurology*, vol. 192, no. 1, pp. 21–41, 1980.

[72] T. P. Pons and J. H. Kaas, "Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study," *The Journal of Comparative Neurology*, vol. 248, no. 3, pp. 313–335, 1986.

[73] T. P. Pons, P. E. Garraghty, D. P. Friedman, and M. Mishkin, "Physiological evidence for serial processing in somatosensory cortex," *Science*, vol. 237, no. 4813, pp. 417–420, 1987.

[74] P. Barbaresi, A. Minelli, and T. Manzoni, "Topographical relations between ipsilateral cortical afferents and callosal neurons in the second somatic sensory area of cats," *The Journal of Comparative Neurology*, vol. 343, no. 4, pp. 582–596, 1994.

[75] E. Disbrow, E. Litinas, G. H. Recanzone, J. Padberg, and L. Krubitzer, "Cortical connections of the second somatosensory area and the parietal ventral area in macaque monkeys," *The Journal of Comparative Neurology*, vol. 462, no. 4, pp. 382–399, 2003.

[76] M. Schaefer, B. Xu, H. Flor, and L. G. Cohen, "Effects of different viewing perspectives on somatosensory activations during observation of touch," *Human Brain Mapping*, vol. 30, no. 9, pp. 2722–2730, 2009.

[77] E. Kuehn, P. Haggard, A. Villringer, B. Pleger, and M. Sereno, "Visually-driven maps in area 3b," *The Journal of Neuroscience*, vol. 38, no. 5, pp. 1295–1310, 2018.

[78] V. Gazzola and C. Keysers, "The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data," *Cerebral Cortex*, vol. 19, no. 6, pp. 1239–1255, 2009.

[79] J. T. Kaplan and K. Meyer, "Multivariate pattern analysis reveals common neural patterns across individuals during touch observation," *NeuroImage*, vol. 60, no. 1, pp. 204–212, 2012.

[80] S. Hihara, M. Taoka, M. Tanaka, and A. Iriki, "Visual responsiveness of neurons in the secondary somatosensory area and its surrounding parietal operculum regions in awake macaque monkeys," *Cerebral Cortex*, vol. 25, no. 11, pp. 4535–4550, 2015.

[81] A. W. Chan and C. I. Baker, "Seeing is not feeling: posterior parietal but not somatosensory cortex engagement during touch observation," *The Journal of Neuroscience*, vol. 35, no. 4, pp. 1468–1480, 2015.

[82] J. H. Kaas, "What, if anything, is SI? Organization of first somatosensory area of cortex," *Physiological Reviews*, vol. 63, no. 1, pp. 206–231, 1983.

[83] M. Taylor-Clarke, P. Jacobsen, and P. Haggard, "Keeping the world a constant size: object constancy in human touch," *Nature Neuroscience*, vol. 7, no. 3, pp. 219-220, 2004.

[84] M. Taylor-Clarke, S. Kennett, and P. Haggard, "Persistence of visual-tactile enhancement in humans," *Neuroscience Letters*, vol. 354, no. 1, pp. 22–25, 2004.

[85] S. Kennett, M. Taylor-Clarke, and P. Haggard, "Noninformative vision improves the spatial resolution of touch in humans," *Current Biology*, vol. 11, no. 15, pp. 1188–1191, 2001.

[86] A. Serino, A. Farne, M. L. Rinaldesi, P. Haggard, and E. Làdavas, "Can vision of the body ameliorate impaired somatosensory function?," *Neuropsychologia*, vol. 45, no. 5, pp. 1101–1107, 2007.

[87] F. Cardini, M. R. Longo, and P. Haggard, "Vision of the body modulates somatosensory intracortical inhibition," *Cerebral Cortex*, vol. 21, no. 9, pp. 2014–2022, 2011.

[88] F. Cardini, M. R. Longo, J. Driver, and P. Haggard, "Rapid enhancement of touch from non-informative vision of the hand," *Neuropsychologia*, vol. 50, no. 8, pp. 1954–1960, 2012.

[89] J. A. Harris, E. Arabzadeh, C. A. Moore, and C. W. Clifford, "Noninformative vision causes adaptive changes in tactile sensitivity," *Journal of Neuroscience*, vol. 27, no. 27, pp. 7136–7140, 2007.

[90] R. Zopf, J. A. Harris, and M. A. Williams, "The influence of body-ownership cues on tactile sensitivity," *Cognitive Neuroscience*, vol. 2, no. 3-4, pp. 147–154, 2011.

[91] S. P. Tipper, D. Lloyd, B. Shorland, C. Dancer, L. A. Howard, and F. McGlone, "Vision influences tactile perception without proprioceptive orienting," *Neuroreport*, vol. 9, no. 8, pp. 1741–1744, 1998.

[92] P. Haggard, "Just seeing you makes me feel better: interpersonal enhancement of touch," *Social Neuroscience*, vol. 1, no. 2, pp. 104–110, 2006.

[93] R. Thomas, C. Press, and P. Haggard, "Shared representations in body perception," *Acta Psychologica*, vol. 121, no. 3, pp. 317–330, 2006.

[94] A. Maravita, C. Spence, C. Sergent, and J. Driver, "Seeing your own touched hands in a mirror modulates cross-modal interactions," *Psychological Science*, vol. 13, no. 4, pp. 350–355, 2002.

[95] M. R. Longo, S. Cardozo, and P. Haggard, "Visual enhancement of touch and the bodily self," *Consciousness and Cognition*, vol. 17, no. 4, pp. 1181–1191, 2008.

[96] F. Pavani, C. Spence, and J. Driver, "Visual capture of touch: out-of-the-body experiences with rubber gloves," *Psychological Science*, vol. 11, no. 5, pp. 353–359, 2000.

[97] E. L. Austen, S. Soto-Faraco, J. T. Enns, and A. Kingstone, "Mislocalizations of touch to a fake hand," *Cognitive, Affective, & Behavioral Neuroscience*, vol. 4, no. 2, pp. 170–181, 2004.

[98] M. Fiorio and P. Haggard, "Viewing the body prepares the brain for touch: effects of TMS over somatosensory cortex," *The European Journal of Neuroscience*, vol. 22, no. 3, pp. 773–777, 2005.

[99] B. Pleger and A. Villringer, "The human somatosensory system: from perception to decision making," *Progress in Neurobiology*, vol. 103, pp. 76–97, 2013.

[100] R. Auksztulewicz, B. Spitzer, and F. Blankenburg, "Recurrent neural processing and somatosensory awareness," *The Journal of Neuroscience*, vol. 32, no. 3, pp. 799–805, 2012.

[101] A. Hernández, A. Zainos, and R. Romo, "Neuronal correlates of sensory discrimination in the somatosensory cortex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 11, pp. 6191–6196, 2000.

[102] R. Luna, A. Hernández, C. D. Brody, and R. Romo, "Neural codes for perceptual discrimination in primary somatosensory cortex," *Nature Neuroscience*, vol. 8, no. 9, pp. 1210–1219, 2005.

[103] R. Rossi-Pool, E. Salinas, A. Zainos et al., "Emergence of an abstract categorical code enabling the discrimination of temporally structured tactile stimuli," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 49, pp. E7966–E7975, 2016.

[104] M. Alvarez, A. Zainos, and R. Romo, "Decoding stimulus features in primate somatosensory cortex during perceptual categorization," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 15, pp. 4773–4778, 2015.

[105] E. Azañón and P. Haggard, "Somatosensory processing and body representation," *Cortex*, vol. 45, no. 9, pp. 1078–1084, 2009.

[106] A. Serino and P. Haggard, "Touch and the body," *Neuroscience and Biobehavioral Reviews*, vol. 34, no. 2, pp. 224–236, 2010.

[107] E. Kuehn, *Open Body Maps - Primary Somatosensory Cortex Activity during Touch Observation Described with 7 Tesla fMRI. Dissertation*, University of Leipzig, Leipzig, Germany, 2013.

[108] I. Morrison, L. S. Löken, and H. Olausson, "The skin as a social organ," *Experimental Brain Research*, vol. 204, no. 3, pp. 305–314, 2010.

[109] I. Morrison, M. Björnsdotter, and H. Olausson, "Vicarious responses to social touch in posterior insular cortex are tuned to pleasant caressing speeds," *The Journal of Neuroscience*, vol. 31, no. 26, pp. 9554–9562, 2011.

[110] I. Morrison, L. S. Löken, J. Minde et al., "Reduced C-afferent fibre density affects perceived pleasantness and empathy for touch," *Brain*, vol. 134, no. 4, pp. 1116–1126, 2011.

[111] I. Morrison, "CT afferents," *Current Biology*, vol. 22, no. 3, pp. R77–R78, 2012.

[112] I. U. Kress, L. Minati, S. Ferraro, and H. D. Critchley, "Direct skin-to-skin versus indirect touch modulates neural responses to stroking versus tapping," *Neuroreport*, vol. 22, no. 13, pp. 646–651, 2011.

[113] A. Gentsch, E. Panagiotopoulou, and A. Fotopoulou, "Active interpersonal touch gives rise to the social softness illusion," *Current Biology*, vol. 25, no. 18, pp. 2392–2397, 2015.

[114] V. Gazzola, M. L. Spezio, J. A. Etzel, F. Castelli, R. Adolphs, and C. Keysers, "Primary somatosensory cortex discriminates affective significance in social touch," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 25, pp. E1657–E1666, 2012.

[115] S. Aglioti, N. Smania, and A. Peru, "Frames of reference for mapping tactile stimuli in brain-damaged patients," *Journal of Cognitive Neuroscience*, vol. 11, no. 1, pp. 67–79, 1999.

[116] E. Azañón and S. Soto-Faraco, "Alleviating the 'crossed-hands' deficit by seeing uncrossed rubber hands," *Experimental Brain Research*, vol. 182, no. 4, pp. 537–548, 2007.

[117] E. Azañón and S. Soto-Faraco, "Changing reference frames during the encoding of tactile events," *Current Biology*, vol. 18, no. 16, pp. 1267–1049, 2008.

[118] E. Macaluso and A. Maravita, "The representation of space near the body through touch and vision," *Neuropsychologia*, vol. 48, no. 3, pp. 782–795, 2010.

[119] D. I. Shore, K. Gray, E. Spry, and C. Spence, "Spatial modulation of tactile temporal order judgments," *Perception*, vol. 34, no. 10, pp. 1251–1262, 2005.

[120] S. Soto-Faraco, A. Ronald, and C. Spence, "Tactile selective attention and body posture: assessing the multisensory contributions of vision and proprioception," *Perception & Psychophysics*, vol. 66, no. 7, pp. 1077–1094, 2004.

[121] S. Ionta, L. Heydrich, B. Lenggenhager et al., "Multisensory mechanisms in temporo-parietal cortex support self-location and first-person perspective," *Neuron*, vol. 70, no. 2, pp. 363–374, 2011.

[122] K. E. Overvliet, H. A. Anema, E. Brenner, H. C. Dijkerman, and J. B. Smeets, "Relative finger position influences whether you can localize tactile stimuli," *Experimental Brain Research*, vol. 208, no. 2, pp. 245–255, 2011.

[123] P. Haggard, K. Kitadono, C. Press, and M. Taylor-Clarke, "The brain's fingers and hands," *Experimental Brain Research*, vol. 172, no. 1, pp. 94–102, 2006.

[124] A. Gallace and C. Spence, "The cognitive and neural correlates of "tactile consciousness": a multisensory perspective," *Consciousness and Cognition*, vol. 17, no. 1, pp. 370–407, 2008.

[125] F. T. de Vignemont, M. Tsakiris, and P. Haggard, "Body mereology," in *The Body from Inside Out*, G. T. Knoblich, M. Grosjean, and M. Shiffrar, Eds., pp. 148–170, Oxford University Press, New York, NY, USA, 2005.

[126] H. C. Dijkerman and E. H. de Haan, "Somatosensory processes subserving perception and action," *The Behavioral and Brain Sciences*, vol. 30, no. 2, pp. 189–201, 2007.

[127] P. Haggard and G. Giovagnoli, "Spatial patterns in tactile perception: is there a tactile field?," *Acta Psychologica*, vol. 137, no. 1, pp. 65–75, 2011.

[128] M. S. Beauchamp, S. Laconte, and N. Yasar, "Distributed representation of single touches in somatosensory and visual

cortex," *Human Brain Mapping*, vol. 30, no. 10, pp. 3163–3171, 2009.

[129] P. Cole and J. Paillard, "Living without touch and peripheral information about body position and movement: studies with deafferented subjects," in *The Body and the Self*, L. M. Bermudez and N. Eilan, Eds., pp. 245–266, MIT Press, Cambridge, MA USA, 1995.

[130] H. Buchner, C. Kauert, and I. Radermacher, "Short-term changes of finger representation at the somatosensory cortex in humans," *Neuroscience Letters*, vol. 198, no. 1, pp. 57–59, 1995.

[131] S. C. Gandevia and C. M. Phegan, "Perceptual distortions of the human body image produced by local anaesthesia, pain and cutaneous stimulation," *The Journal of Physiology*, vol. 514, no. 2, pp. 609–616, 1999.

[132] M. Holden, J. Ventura, and J. R. Lackner, "Stabilization of posture by precision contact of the index finger," *Journal of Vestibular Research*, vol. 4, no. 4, pp. 285–301, 1994.

[133] J. J. Jeka and J. R. Lackner, "Fingertip contact influences human postural control," *Experimental Brain Research*, vol. 100, no. 3, pp. 495–502, 1994.

[134] J. R. Lackner, P. DiZio, J. Jeka, F. Horak, D. Krebs, and E. Rabin, "Precision contact of the fingertip reduces postural sway of individuals with bilateral vestibular loss," *Experimental Brain Research*, vol. 126, no. 4, pp. 459–466, 1999.

[135] J. R. Lackner, E. Rabin, and P. DiZio, "Stabilization of posture by precision touch of the index finger with rigid and flexible filaments," *Experimental Brain Research*, vol. 139, no. 4, pp. 454–464, 2001.

[136] S. B. Bortolami, P. DiZio, E. Rabin, and J. R. Lackner, "Analysis of human postural responses to recoverable falls," *Experimental Brain Research*, vol. 151, no. 3, pp. 387–404, 2003.

[137] S. J. Lederman and R. L. Klatzky, "Hand movements: a window into haptic object recognition," *Cognitive Psychology*, vol. 19, no. 3, pp. 342–368, 1987.

[138] S. J. Lederman and R. L. Klatzky, "Extracting object properties through haptic exploration," *Acta Psychologica*, vol. 84, no. 1, pp. 29–40, 1993.

[139] B. B. Edin, G. Westling, and R. S. Johansson, "Independent control of human finger-tip forces at individual digits during precision lifting," *The Journal of Physiology*, vol. 450, no. 1, pp. 547–564, 1992.

[140] E. Foeller and D. E. Feldman, "Synaptic basis for developmental plasticity in somatosensory cortex," *Current Opinion in Neurobiology*, vol. 14, no. 1, pp. 89–95, 2004.

[141] D. T. Monaghan and C. W. Cotman, "Distribution of N-methyl-D-aspartate-sensitive L-[3H]glutamate-binding sites in rat brain," *Journal of Neuroscience*, vol. 5, no. 11, pp. 2909–2919, 1985.

[142] M. Bieler, K. Sieben, N. Cichon, S. Schildt, B. Röder, and I. Hanganu-Opatz, "Rate and temporal coding convey multisensory information in primary sensory cortices," *eNeuro*, vol. 4, no. 2, pp. ENEURO.0037–ENEU17.2017, 2017.

[143] S. C. Gandevia, D. Burke, and B. B. McKeon, "Convergence in the somatosensory pathway between cutaneous afferents from the index and middle fingers in man," *Experimental Brain Research*, vol. 50, no. 2-3, pp. 415–425, 1983.

[144] J. Ruben, T. Krause, B. Taskin, F. Blankenburg, M. Moosmann, and A. Villringer, "Subarea-specific suppressive interaction in the BOLD responses to simultaneous finger stimulation in human primary somatosensory cortex: evidence for increasing rostral to-caudal convergence," *Cerebral Cortex*, vol. 16, no. 6, pp. 819–826, 2006.

[145] A. Kraskov, N. Dancause, M. M. Quallo, S. Shepherd, and R. N. Lemon, "Corticospinal neurons in macaque ventral premotor cortex with mirror properties: a potential mechanism for action suppression?," *Neuron*, vol. 64, no. 6, pp. 922–930, 2009.

[146] J.-O. Coq and C. Xerri, "Environmental enrichment alters organizational features of the forepaw representation in the primary somatosensory cortex of adult rats," *Experimental Brain Research*, vol. 121, no. 2, pp. 191–204, 1998.

[147] J.-O. Coq and C. Xerri, "Sensorimotor experience modulates age-dependent alterations of the forepaw representation in the rat primary somatosensory cortex," *Neuroscience*, vol. 104, no. 3, pp. 705–715, 2001.

[148] C. Press, C. Heyes, P. Haggard, and M. Eimer, "Visuotactile learning and body representation: an ERP study with rubber hands and rubber objects," *Journal of Cognitive Neuroscience*, vol. 20, no. 2, pp. 312–323, 2008.

[149] R. Adolphs, H. Damasio, D. Tranel, G. Cooper, and A. R. Damasio, "A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping," *The Journal of Neuroscience*, vol. 20, no. 7, pp. 2683–2690, 2000.

[150] D. Pitcher, L. Garrido, V. Walsh, and B. C. Duchaine, "Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions," *The Journal of Neuroscience*, vol. 28, no. 36, pp. 8929–8933, 2008.

[151] R. Paracampo, E. Tidoni, S. Borgomaneri, G. di Pellegrino, and A. Avenanti, "Sensorimotor network crucial for inferring amusement from smiles," *Cerebral Cortex*, vol. 27, no. 11, pp. 5116–5129, 2017.

[152] M. J. Banissy, D. A. Sauter, J. Ward, J. E. Warren, V. Walsh, and S. K. Scott, "Suppressing sensorimotor activity modulates the discrimination of auditory emotions but not speaker identity," *Journal of Neuroscience*, vol. 30, no. 41, pp. 13552–13557, 2010.

[153] E. V. Friedrich, A. Sivanathan, T. Lim et al., "An effective neurofeedback intervention to improve social interactions in children with autism spectrum disorder," *Journal of Autism and Developmental Disorders*, vol. 45, no. 12, pp. 4084–4100, 2015.

[154] M. Schaefer, H. J. Heinze, and M. Rotte, "Embodied empathy for tactile events: interindividual differences and vicarious somatosensory responses during touch observation," *Neuroimage*, vol. 60, no. 2, pp. 952–957, 2012.

[155] E. Palluel, J. E. Aspell, and O. Blanke, "Leg muscle vibration modulates bodily self-consciousness: integration of proprioceptive, visual, and tactile signals," *Journal of Neurophysiology*, vol. 105, no. 5, pp. 2239–2247, 2011.

[156] J. E. Aspell, B. Lenggenhager, and O. Blanke, "Keeping in touch with one's self: multisensory mechanisms of self-consciousness," *PLoS One*, vol. 4, no. 8, article e6488, 2009.

[157] H. H. Ehrsson, B. Rosén, A. Stockselius, C. Ragnö, P. Köhler, and G. Lundborg, "Upper limb amputees can be induced to experience a rubber hand as their own," *Brain*, vol. 131, no. 12, pp. 3443–3452, 2008.

[158] A. I. Goller, K. Richards, S. Novak, and J. Ward, "Mirror-touch synaesthesia in the phantom limbs of amputees," *Cortex*, vol. 49, no. 1, pp. 243–251, 2013.

[159] V. S. Ramachandran and D. Brang, "Sensations evoked in patients with amputation from watching an individual whose corresponding intact limb is being touched," *Archives of Neurology*, vol. 66, no. 10, pp. 1281–1284, 2009.

[160] L. Aziz-Zadeh, T. Sheng, S. L. Liew, and H. Damasio, "Understanding otherness: the neural bases of action comprehension and pain empathy in a congenital amputee," *Cerebral Cortex*, vol. 22, no. 4, pp. 811–819, 2012.

[161] A. Farnè, F. Pavani, F. Meneghello, and E. Làdavas, "Left tactile extinction following visual stimulation of a rubber hand," *Brain*, vol. 123, no. 11, pp. 2350–2360, 2000.

[162] A. Avenanti, N. Bolognini, A. Maravita, and S. M. Aglioti, "Somatic and motor components of action simulation," *Current Biology*, vol. 17, no. 24, pp. 2129–2135, 2007.

[163] N. Valchev, E. Tidoni, A. F. C. Hamilton, V. Gazzola, and A. Avenanti, "Primary somatosensory cortex necessary for the perception of weight from other people's action: a continous theta-burst TMS experiment," *Neuroimage*, vol. 152, pp. 195–206, 2017.

[164] S. Bosbach, J. Cole, W. Prinz, and G. Knoblich, "Inferring another's expectation from action: the role of peripheral sensation," *Nature Neuroscience*, vol. 8, no. 10, pp. 1295–1297, 2005.

[165] P. O. Jacquet and A. Avenanti, "Perturbing the action observation network during perception and categorization of actions' goals and grips: state-dependency and virtual lesion TMS effects," *Cerebral Cortex*, vol. 25, no. 3, pp. 598–608, 2015.