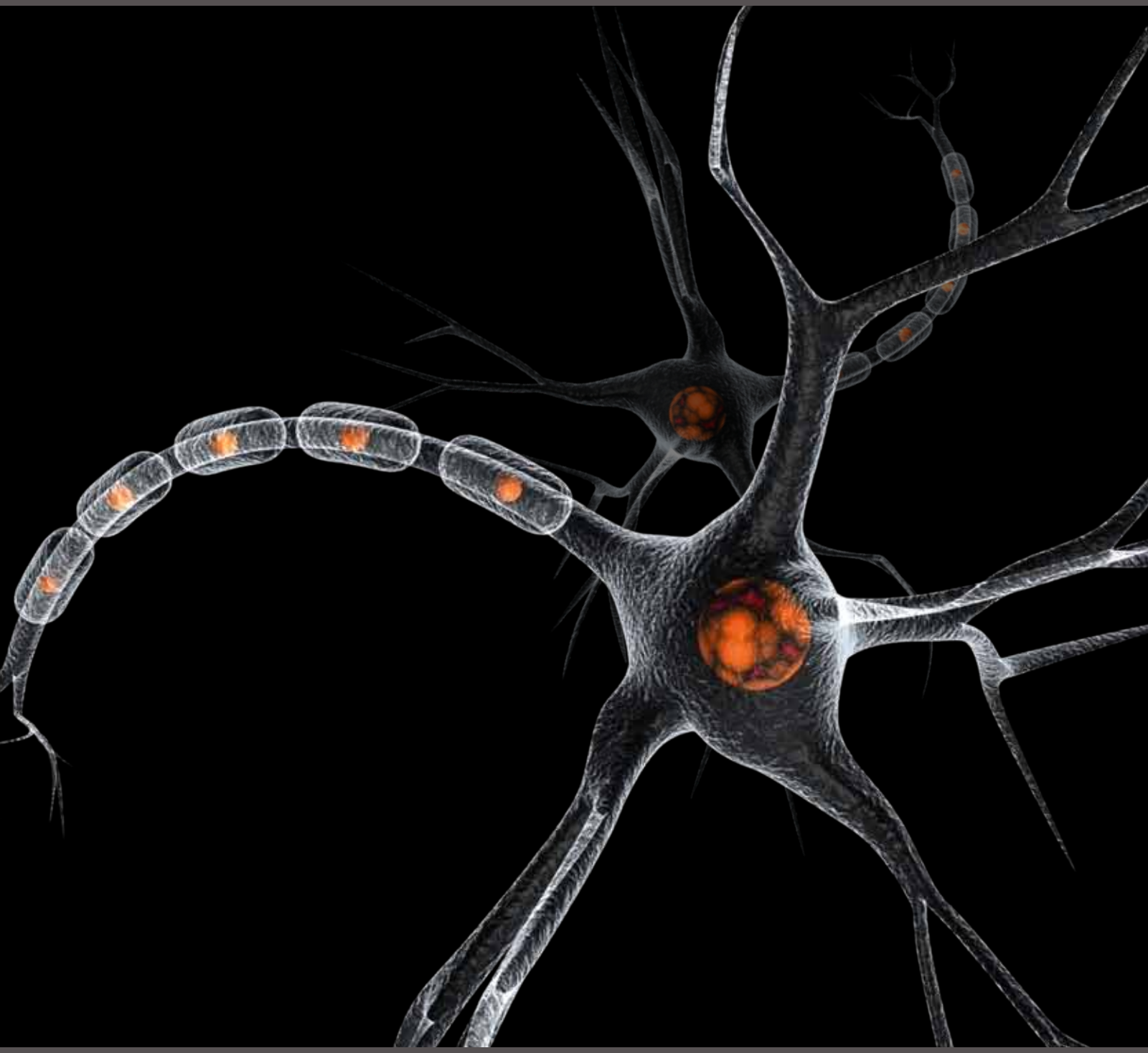
Neural Plasticity

Plasticity of Adult Sensorimotor System

Guest Editors: Marie-Hélène Canu, Jacques-Olivier Coq,
Mary F. Barbe, and Hubert Dinse



Plasticity of Adult Sensorimotor System

Neural Plasticity

Plasticity of Adult Sensorimotor System

Guest Editors: Marie-Hélène Canu, Jacques-Olivier Coq, Mary F. Barbe, and Hubert R. Dinse

Editorial Board

Contents

Plasticity of Adult Sensorimotor System, Marie-Hélène Canu, Jacques-Olivier Coq, Mary F. Barbe, and Hubert R. Dinse
Volume 2012, Article ID 768259, 2 pages

Left-Deviating Prism Adaptation in Left Neglect Patient: Reflexions on a Negative Result, Jacques Luauté, Sophie Jacquin-Courtois, Jacinta O'Shea, Laure Christophe, Gilles Rode, Dominique Boisson, and Yves Rossetti
Volume 2012, Article ID 718604, 10 pages

Activity-Dependent Plasticity of Spinal Circuits in the Developing and Mature Spinal Cord, Behdad Tahayori and David M. Koceja
Volume 2012, Article ID 964843, 12 pages

Plasticity of Corticospinal Neural Control after Locomotor Training in Human Spinal Cord Injury, Maria Knikou
Volume 2012, Article ID 254948, 13 pages

Plasticity-Inducing TMS Protocols to Investigate Somatosensory Control of Hand Function, M. Jacobs, A. Premji, and A. J. Nelson
Volume 2012, Article ID 350574, 12 pages

Plasticity of Adult Sensorimotor System in Severe Brain Infarcts: Challenges and Opportunities, Annette Sterr and Adriana Bastos Conforto
Volume 2012, Article ID 970136, 10 pages

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 768259, 2 pages
doi:10.1155/2012/768259

Editorial

Plasticity of Adult Sensorimotor System

Marie-Hélène Canu,[1,2] Jacques-Olivier Coq,[3] Mary F. Barbe,[4] and Hubert R. Dinse[5]

[1] *Université Lille Nord de France, 59000 Lille, France*
[2] *Laboratoire "Activité Physique, Muscle et Santé," EA 4488, IFR 114, Université Lille 1, Sciences et Technologies, 59650 Villeneuve d'Ascq, France*
[3] *Faculté de Médecine-Secteur Nord, UMR1072 UNIS Inserm/Aix-Marseille Université, Bat C, Bd Pierre Dramard, 13344 Marseille Cedex 15, France*
[4] *Comprehensive NeuroAIDS Center, Animal Models and Behavioral Testing Core, Temple University School of Medicine, 3500 North Broad Street, Philadelphia, PA 19140, USA*
[5] *Neural Plasticity Lab, Institut fur Neuroinformatik, Ruhr University Bochum, Building NB 3, 44780 Bochum, Germany*

Correspondence should be addressed to Marie-Hélène Canu, marie-helene.canu@univ-lille1.fr

Received 26 November 2012; Accepted 26 November 2012

The central nervous system is a highly plastic structure that can adapt throughout the lifespan of higher mammals to changes in environment. The establishment of neural connectivity, during embryonic period and during early postnatal stages, is under genetic and epigenetic control. Environmental factors, in particular during the critical period, can heavily influence the organization of the brain, both in the short and long term. In the 1980s, Kaas, Merzenich, and collaborators have reported that the adult central nervous system of mammals was also capable of a remarkable reorganization following traumatic lesions (amputation, nerve section, etc.). Since these pioneering works, the concept of neural plasticity stirs up a growing interest in the scientific community. Many works have been focused on the extensive reorganization of cortical and subcortical structures in relation to individual experience (*activity-dependent plasticity*). Within the sensorimotor system, plastic mechanisms can occur spontaneously after an injury, such as stroke or spinal cord injury (*injury-induced plasticity*). These changes can sometimes be considered as adaptative or compensatory, but in some cases, they may lead to a maladaptative process. More recently, it has been demonstrated that in addition to training, practicing, and use, mere exposure to repetitive sensory or central stimulation, significant changes of behavior and neural processing can be evoked. In patients, one can take advantage of both the activity-dependent plastic properties of the CNS to develop efficient therapeutic methods, in particular through repetitive sensory or direct current/magnetic stimulation. Increasing the basic knowledge of activity-dependent plasticity throughout the lifespan of humans can substantially influence the treatment and rehabilitation methods used for a variety of movement disorders.

Four contributions to this special issue provide an overview of data in the field of activity-dependent plasticity of adult sensorimotor system. They are accompanied by a research paper addressing the question of adaptation to prisms. All papers pay a particular attention to rehabilitation strategies.

The research paper is entitled "*Left-deviating prism adaptation in left neglect patient: reflexions on a negative result*" by J. Luauté et al. In healthy subjects, optical prisms are used to induce experimentally a sensorimotor plasticity. Prism adaptation is also used in patients with left spatial neglect, where it appears as a promising therapeutic intervention for rehabilitation. The authors demonstrate that there is a directional specificity of the prisms: patients with left spatial neglect are not affected by prism adaptation to a leftward optical shift whereas right-deviating prisms are known to have beneficial effects. The paper also raises the question about the conditions necessary to produce cognitive aftereffects. Very interestingly, it shows that no cognitive effects are found in the absence of adaptation, playing against the hypothesis that active exposure to a simple modification of sensorimotor coordinates by simple visuomanual pointing is sufficient to reduce left spatial neglect.

This paper is followed by four reviews. The contribution by A. Sterr and A. B. Conforto "*Plasticity of adult sensorimotor system in severe brain infarcts: challenges and*

opportunities" is a very integrative overview of the sensorimotor system. Interestingly, it highlights that the execution of movement should be considered from anticipatory processes within cortical areas to motor performance and that treatment strategies should consider all these aspects. In addition, it points out that use-dependent reorganization of neural representations is a complex process, which is modulated by various factors, such as attention, motivation, tiredness and fatigue, and engagement of the patient with the therapy process.

The other reviews are focused on several levels of the motor control: cortical, spinal, or corticospinal drive. Although reflexes had been thought to be very stereotyped for a long time, it is now well established that spinal reflex characteristics can change in response to an operant conditioning task, providing evidence for activity-induced plastic changes within the spinal cord. In consequence, the stretch reflex or the H-reflex has been extensively studied to evaluate spinal plasticity in the mature nervous system. The paper by B. Tahayori and D. M. Koceja "*Activity-dependent plasticity of spinal circuits in the developing and mature spinal cord*" compares plasticity of spinal circuits during development and in adulthood. In childhood, the authors point out the role of input from both large-diameter primary afferents and from supraspinal afferents. The paper also explains how changes in the reflex pathway occur and how they become permanent and highlights the role of presynaptic inhibition of afferent fibers.

In her review "*Plasticity of corticospinal neural control after locomotor training in human spinal cord injury*" M. Knikou provides an overview of cortical control of spinal cord after training. The author demonstrates that the spinal cord circuitries have the capacity to alter their structure and function with motor training, in particular in spinal cord-injured patients. Rehabilitation protocols should take advantage of the plastic capabilities of corticospinal drive and spinal interneuronal circuits for restoration of locomotion after an injury.

An effective motor rehabilitation in humans requires a better knowledge of somatosensory physiology and its influence on primary motor cortex (M1) activity. Primary somatosensory cortex (S1) and M1 have anatomical and functional connections. In humans as in animals, there is substantial evidence that direct manipulation of S1 activity alters motor behavior. M. Jacobs et al. "*Plasticity-inducing TMS protocols to investigate somatosensory control of hand function*" provide a critical review showing that plasticity-inducing TMS protocols are a powerful tool to modulate S1 physiology, tactile perception, and neural activity within both S1 and M1 and suggest that these protocols might be used to improve hand function in patients.

We hope that this special issue will have brought new insights into the underlying mechanisms of neural plasticity that occurs in response to changes in sensorimotor experience and will help to elaborate efficient rehabilitation strategies and/or to optimize the currently available strategies.

Marie-Hélène Canu
Jacques-Olivier Coq

Mary F. Barbe
Hubert R. Dinse

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 718604, 10 pages
doi:10.1155/2012/718604

Research Article

Left-Deviating Prism Adaptation in Left Neglect Patient: Reflexions on a Negative Result

Jacques Luauté,[1,2,3] Sophie Jacquin-Courtois,[1,2,3] Jacinta O'Shea,[4] Laure Christophe,[1,2,3] Gilles Rode,[1,2,3] Dominique Boisson,[1,2,3] and Yves Rossetti[1,2,3]

[1] *Pole de rééducation et réadaptation, Plateforme mouvement et handicap, Hôpital Henry Gabrielle, Hospices Civils de Lyon, 69000 Lyon, France*
[2] *ImpAct, INSERM (U1028), CNRS (UMR5292), Lyon Neuroscience Research Center, 69000 Lyon, France*
[3] *Université de Lyon, Université Lyon 1, F-69100, Villeurbanne, France*
[4] *Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK*

Correspondence should be addressed to Jacques Luauté, jacques.luaute@chu-lyon.fr

Received 2 April 2012; Accepted 8 August 2012

Academic Editor: Hubert Dinse

Adaptation to right-deviating prisms is a promising intervention for the rehabilitation of patients with left spatial neglect. In order to test the lateral specificity of prism adaptation on left neglect, the present study evaluated the effect of left-deviating prism on straight-ahead pointing movements and on several classical neuropsychological tests in a group of five right brain-damaged patients with left spatial neglect. A group of healthy subjects was also included for comparison purposes. After a single session of exposing simple manual pointing to left-deviating prisms, contrary to healthy controls, none of the patients showed a reliable change of the straight-ahead pointing movement in the dark. No significant modification of attentional paper-and-pencil tasks was either observed immediately or 2 hours after prism adaptation. These results suggest that the therapeutic effect of prism adaptation on left spatial neglect relies on a specific lateralized mechanism. Evidence for a directional effect for prism adaptation both in terms of the side of the visuomanual adaptation and therefore possibly in terms of the side of brain affected by the stimulation is discussed.

1. Introduction

Patients with right cerebral hemisphere lesions often show a reduced tendency to respond to stimuli and to search actively for them in the contralateral part of space [1]. This condition described as left spatial neglect is typically demonstrated by clinical observation and simple perceptual motor tests such as a line bisection or cancellation test [2]. Left spatial neglect occurs in about 25–30% of all stroke patients [3], and although some degrees of spontaneous recovery occurs [4], the disorder persists chronically in many cases [5]. Frequently associated with contralesional motor or somatosensory deficit, left spatial neglect is recognized as one of the main factors associated with poor functional outcome [6–8]. For these reasons, the improvement of left spatial neglect over and above spontaneous recovery represents a challenge in the area of neurological rehabilitation. Over the past 60 years, many different attempts to alleviate this impairment have been developed (for a review see [9]).

Among these, prism adaptation is one of the most promising therapeutic interventions [10]. Prism adaptation has been widely used since the end of the nineteenth century as a paradigm to demonstrate visuomotor short-term plasticity [11]. Exposure to prisms produces a lateral shift of the visual field so that the visual target appears at a displaced position. Adaptation to such an optical induced shift critically requires a set of successive perceptual-motor pointing movements. While the initial movements tend to

approximate to the virtual position of the target, subsequent pointing movements ensure that the pointing error rapidly decreases so that subjects can readily point towards the real target position [12]. This initial error reduction comprises a "strategic component" of the reaction to prisms and does not necessarily produce adaptation at this stage [13]. To obtain robust compensatory after-effects following removal of prisms, further pointing movements are required. These reinforce the sensory-motor adaptation and are considered characteristic of the "real" or "true" adaptive component of the adaptation (e.g., [14]). After-effects result from a compensatory shift in manual straightahead pointing in a direction opposite to the original visual shift produced by prisms. Rossetti et al. [15] proposed that the adaptation to right-deviating prisms with leftward compensatory after-effects (using the intact right hand) improved left neglect symptoms. In this study, a significant improvement was demonstrated across a variety of different standard paper and pencil tests (line bisection, line cancellation, copying a scene, and reading a simple text). Subsequent studies have shown that these clinical effects could extend to numerous neglect-related processes (for a review see [16]) such as straightahead pointing [17], visual exploration toward the left hemispace [18], postural control [19], contralesional somatosensory perception [20–22], temporal order judgment [23], and mental representation [24–26]. From a rehabilitation perspective, the long-term beneficial effect on several functional measures set this intervention apart from the other attempts. (i) Farné et al. [27] found a reduction of spatial dyslexia still present one day after a single session of prism adaptation in a group of 6 patients with left spatial neglect. (ii) Rode et al. [28] reported a positive effect of prism adaptation on spatial dysgraphia. The improvement concerned the right-page preference and was maintained up to 4 days after a single session of prism adaptation. (iii) Jacquin-Courtois et al. [29] and Watanabe and Amimoto [30] reported an improvement of wheelchair navigation after a single session of prism adaptation in two single-case studies. (iv) A long-lasting amelioration, up to five weeks, was reported on several functional tasks following a twice-daily adaptation program during a period of two weeks [31, 32] or one-daily prism-adaptation session during two weeks [33, 34].

This impressive generalization and long-standing effects of prism adaptation have revived interest in the neuro-cognitive mechanisms by which it has been achieved. The most two basic questions about the mechanisms of action of prism adaptation are (i) whether adaptation per se is necessary to produce cognitive after-effects or whether simple visuomanual pointing could produce similar effects, and (ii) whether this adaptation is specific in terms of its direction. As a matter of facts, such specificity has been demonstrated in healthy individuals (see for review [35]), in patients with complex regional pain syndrome [36], but no data is available on neglect patients. The purpose of the present study was to evaluate the directional specificity of prism adaptation in neglect patients. Given that the effect of right-deviating prisms on left spatial neglect is already well documented (cf. supra), this work was designed to evaluate the effect of left-deviating prisms on left spatial neglect. Since it has been shown that adaptation to right-deviating prism may affect differently straightahead pointing movements and attentional tasks [17], the effect of left-deviating prism was measured both on straightahead pointing movements and several attentional tasks classically used to assess left spatial neglect.

2. Methods

2.1. Participants. Patients were selected from the Neuro-rehabilitation Department of the Hospices Civils de Lyon, France. Inclusion criteria were right-handed patients with left spatial neglect after right hemispheric ischemic or hemorrhagic stroke. Patients with previous history of stroke, psychiatric diseases, global cognitive deterioration, or any impairment that could compromise comprehension and compliance with the tasks were excluded.

For all patients screened, hand preference was assessed by the Edinburgh inventory [37]. Left spatial neglect was assessed using a battery of six paper and pencil tests: line cancellation, balloon test, line bisection, copy of a scene, drawing from memory, simple text reading (cf. Section 2.2.2. for description). The presence of hemianopia was assessed by means of Goldman perimetry. A cerebral computerized tomography (CT) or MRI scan was performed for each patient in order to specify the type of lesion (ischemic or hemorrhagic), to rule out any other relevant prestroke lesions and to determine the anatomic location of the lesion.

A group of healthy subjects was included for comparison purposes.

This study was conducted with the informed consent of the participants, in agreement with the French law (March 2002) and the Helsinki declaration relative to patient's rights.

The sample comprised six healthy subjects and five patients aged between 67 and 80 years old (see Table 1 for clinical profiles of each patient). The mean time period between stroke onset and inclusion was 1.5 months (range: 1 to 2.5 months). One patient had a hemorrhagic stroke (patient 2); the four others had an ischemic stroke: two in the posterior part of the superficial middle cerebral artery territory (patients 1 and 3), one in the anterior part of the superficial middle cerebral artery territory (patient 5), and one in the deep part of the middle cerebral artery territory (patient 4).

Lesion analysis showed the involvement of the inferior, middle, and superior temporal gyri in three patients (patient 1, patient 3, and patient 5); the temporoparietooccipital junction was damaged in two patients (patient 1 and patient 3). Lesions of other brain structures involved the somatosensory parietal cortex (patient 1 and patient 5), the primary motor cortex (patient 1 and patient 5), the occipital cortex (patient 1 and patient 3), the prefrontal and the orbito-frontal cortex (patient 5), the insula (patient 1, patient 2, patient 4, and patient 5), the thalamus (patient 2 and patient 4), the putamen and pallidum (patient 2, patient 4, and patient 5), the internal capsule (patient 2 and patient 4), the caudate nucleus, the hippocampus,

Table 1: Clinical profiles of each patient.

Patients number	1	2	3	4	5
Sex	M	F	F	F	F
Age	80	75	73	67	74
Time after onset (mt)	2	1.5	2.5	1	1
Motor deficit	L hemiparesis	L hemiplegia	L hemiplegia (transient)	L hemiplegia	L hemiparesis
Somatosensory deficit	+	+	−	+	+
Hemianopia	+	−	+	−	−
Constructive apraxia	−	+	−	−	+
Type of lesion	I (MCA)	H	I (MCA)	I (MCA)	I (MCA)

Motor and somato-sensory deficits were assessed by a classical clinical examination. Presence of hemianopia was assessed by means of the Goldman perimetry. Constructive apraxia was assessed on copying geometrical drawings.
Abbreviations—+: present; −: absent; mt: month; F: female; M: male; L: left, H: hemorrhagic; I: ischemic; MCA: middle cerebral artery.

and parahippocampus (patient 4). Figure 1 shows selected horizontal sections of the lesions for each patient.

2.2. Experimental Procedure. Patients' performance was investigated in sessions that took place before prism adaptation (referred to as "pre"), immediately after (post), and 2 hours after (late). Healthy subjects performed the same tasks as patients before (pre) and immediately after (post) prism adaptation. During each session, left spatial neglect was assessed using line cancellation, balloon test, line bisection, copy of a scene, drawing from memory, and a simple text reading (cf. Section 2.2.2. for description). In order to check whether healthy subjects and patients correctly adapted to prisms, a measure of straightahead pointing was performed before adaptation (pre) and after participants had completed the immediate neuropsychological tests (post) as in Rossetti et al. [15].

2.2.1. Straight-Ahead Pointing. The participant was seated blindfolded in front of a horizontal box that allowed for an electronic measurement of the finger movement endpoints with an accuracy of 1 deg. Participants were required to point straightahead while their head was kept aligned with the body's sagittal axis. Seven pointing trials were performed during each of the two assessments.

2.2.2. Assessment of Left Spatial Neglect. Test Details

Line Cancellation [38]. This test consists of an A4 page containing 40 lines arranged in different direction. The page is placed at body midline. Participants were instructed to cross out all the lines on the page. The score was the total number of lines crossed.

The Balloon Test [39]. This test consists of two subtests, carried out on two A3 landscape-orientated stimulus sheets, each containing 202 items (circles or balloons). In the first subtest "pop-out", 22 target balloons are interspersed between 180 circles which play the role of distractor. Subjects were asked to cross out as many balloons as they could find. This test is based on the phenomenon of perceptual "popout," that is, the time taken to detect target of this kind does not increase significantly as the number of distractors increase [40]. In the second subtest "search," the number and position of the balloons and circles are exactly the reverse; thus 22 of the 202 items are circles to be cancelled and the other 180 items are balloons. In this test, subjects were required to cancel out as many circles as they could find. In this test, the targets do not "pop out." Rather they have to be searched, and therefore, this test requires a greater demand on attention. In both subtests, the score represents the number of targets correctly cancelled.

Line Bisection [41]. Participants were presented with an A4 page, in front of their body midline, containing twenty lines of different length ranging from 100 mm to 200 mm. Participants were instructed to cut each line in half by placing a small pencil mark through each line as close to its center as possible. The score was the mean percentage of deviation from the true center of the line (the score is positive when the deviation is in the right direction and negative when the deviation is in the left direction).

Copy of a Scene [42]. Participants were required to reproduce a picture made up of five items (4 trees and a house) in the space bellow it. Performances were assessed by two scores: (i) the number of items reproduced and (ii) the number of items symmetrically depicted.

Drawing from Memory. Participants were simply asked to draw a daisy without any model. A score of 1 was given when the daisy was highly asymmetrical, 2 when the drawing was moderately asymmetrical, and 3 when the drawing was symmetrical.

Simple Text Reading. Patients were required to read a simple text. The score on this test represented the number of words omitted or modified.

2.2.3. Prism Adaptation (See Figure 2). The adaptation procedure involved the participants having to wear prismatic goggles that produced a 10° leftward shift of the visual wide-field that is in the opposite direction to Rossetti et al. (1998) [15]. While wearing prisms, the participant was required

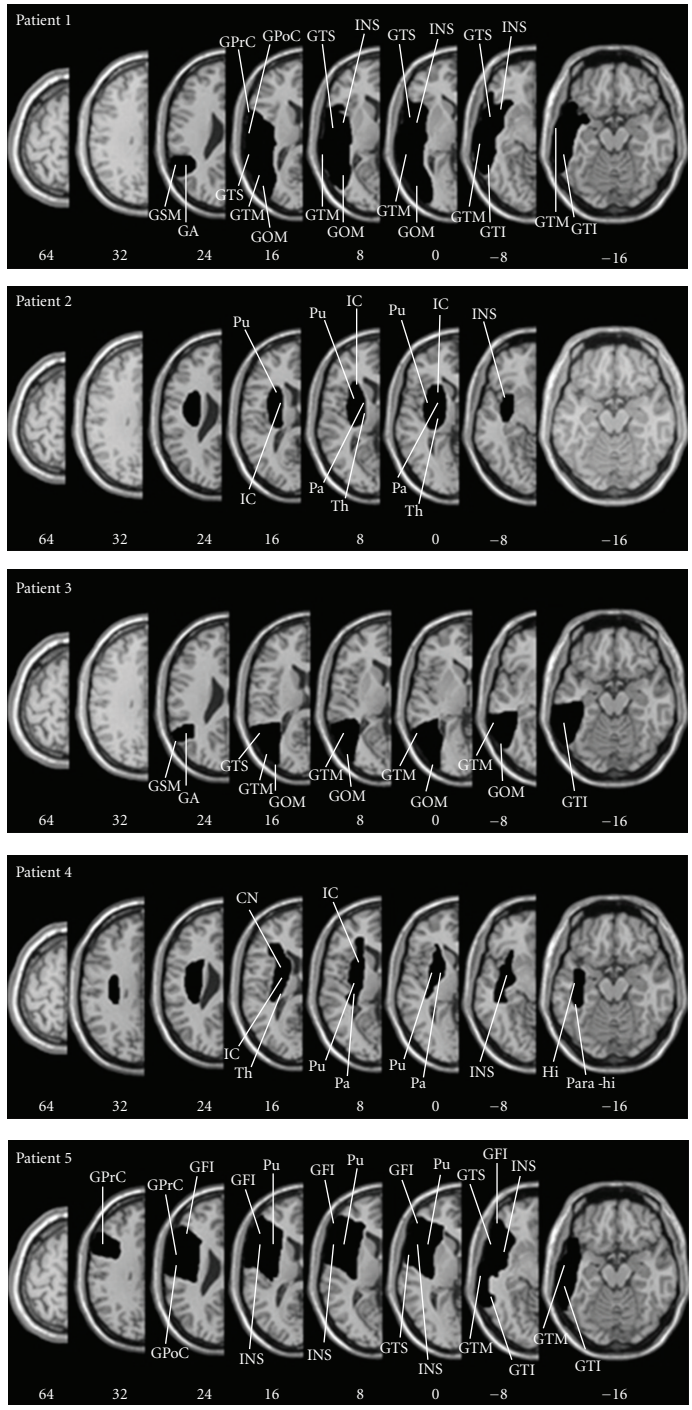
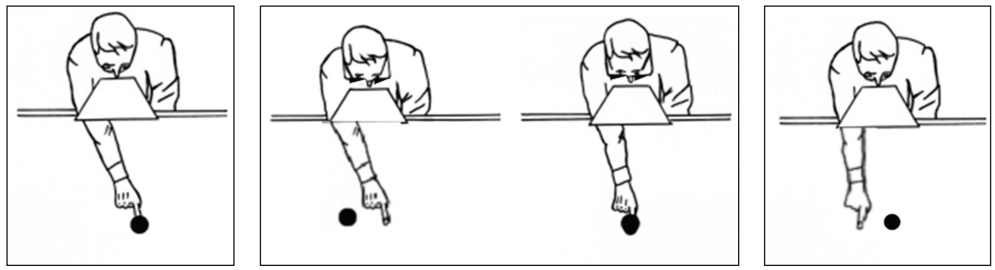


Figure 1: Lesion anatomy. For each patient, all lesions were mapped using the free MRIcro software and were drawn manually on slices of the high-resolution 3D T1-weighted template MRI scan. This template is oriented to match the Talairach space. Lesions were mapped onto the horizontal slices that correspond to Z-coordinates −16, −8, 0, 8, 16, 24, 32, 64 in the Talairach space by using the identical or the closest matching horizontal slices of each individual. Following radiological convention, the right cerebral hemisphere is displayed on the left side. *Abbreviations*: CN, caudate nucleus; GFI, gyrus frontalis inferior; GOM, gyrus occipitalis medius; GPrC, gyrus precentralis; GPoC, gyrus postcentralis; GTM, Gyrus temporalis medius; GTI, gyrus temporalis inferior, GTS, gyrus temporalis superior; Hi, hippocampus; IC, internal capsule; INS, insula; Pa, pallidum; Para-hi, parahippocampus; Pu, putamen; Th, thalamus; GSM, gyrus supra-marginalis; GA, gyrus angular.



(a) Baseline (open-loop pointing) (b) Exposition to left-deviating prisms (manuel pointing) (c) After-effects (open loop pointing)

Figure 2: Left-deviating prism adaptation schematic procedure.

to make—as fast as possible—a series of approximately 50 pointing responses, with his/her right hand, to visual targets located to the left and right side of midline. The procedure lasted approximately five minutes. In order to ensure optimal adaptation, visual feedback of the starting point of the hand was always occluded and the pointing trajectories were visible.

2.2.4. Statistical Analysis. The first analysis was to test whether healthy subjects and patients correctly adapted to left-deviating prisms. We carried out t-tests to compare the average end-position before (pre) and after (post) prism adaptation.

In order to evaluate the presence of an amelioration of left neglect symptoms after prism adaptation, an analysis of variance with repeated measure (ANOVA) was performed on each neuropsychological test, using sessions (pre, post, late) as factor. Hence, for a specified test, the null hypothesis (P value >0.05) is the absence of difference between sessions of the mean score across patients. The alternative hypothesis (P value <0.05) can be written as follow: at least one of the mean score differs between sessions. In this latter case, a post hoc Sheffé test was carried out in order to compare the mean scores across sessions: "pre versus post," "pre versus late," and "post versus late."

3. Results

For the healthy controls, a significant displacement of the straightahead pointings to the right was observed after exposure to left deviating prisms without significant modification of the performances on the attentional paper and pencil tests.

For the neglect patients, no significant effect of prism exposure was observed neither on the straight-ahead pointing task nor on the neuropsychological tests.

3.1. Straight-Ahead Pointing. Controls. Before left-deviating prism adaptation (pre), the group analysis showed that the mean end-position of 7 straightahead pointing trials was shifted 1.3 degrees to the right of the body midline (range: -2.3° to 5.1°). After prism adaptation (post), the mean deviation was significantly displaced to the right (mean position after prism adaptation: 5.8 degrees to the right of the body midline; range: 0.7° to 9.0°). Comparison between trials performed before and after prism adaptation was significant ($t = 3.15$; $P = 0.026$). (cf. Figure 3(a) left graph).

Patients. Before left-deviating prism adaptation (pre), the group analysis showed that the mean end-position of 7 straightahead pointing trials was shifted 3.7 degrees to the right of the body midline (range: 2.0° to 4.9°). After prism adaptation (post), the mean end-position was unchanged (mean: 3.7 degrees to the right; range: 2.4° to 4°). Comparison between trials performed before and after prism adaptation was not significant ($t = 0.74$; $P = 0.48$). Individually, the difference of end-position before and after prism adaptation was always less than 1 degree of angle (cf. Figure 3(a) right graph).

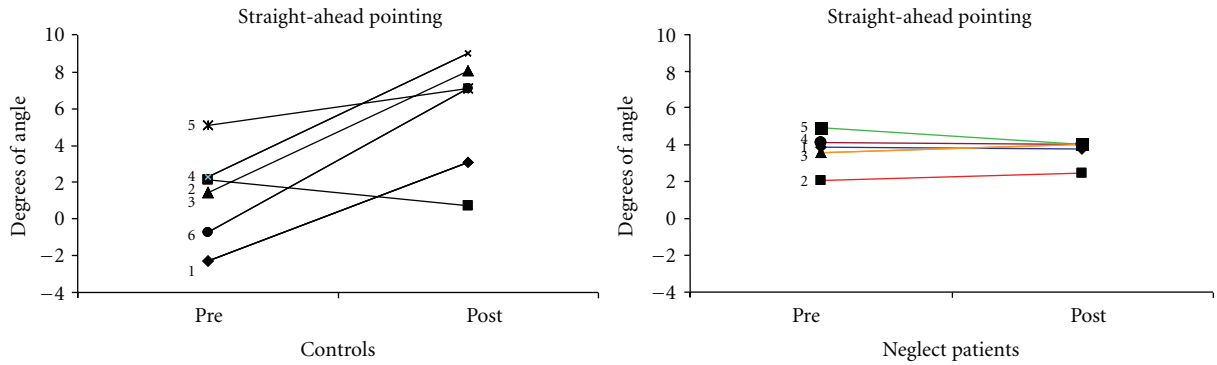
3.2. Effect of Adaptation to Left-Deviating Prism on Left Spatial Neglect (Figure 3). None of the paper and pencil attentional tests have been significantly modified by left-deviating prisms in the control group. The 95% confident interval of healthy subjects' performances is displayed on Figure 3(b) for each test.

For the neglect group, numerical results are reported for each test in the following section and in Figure 3(b).

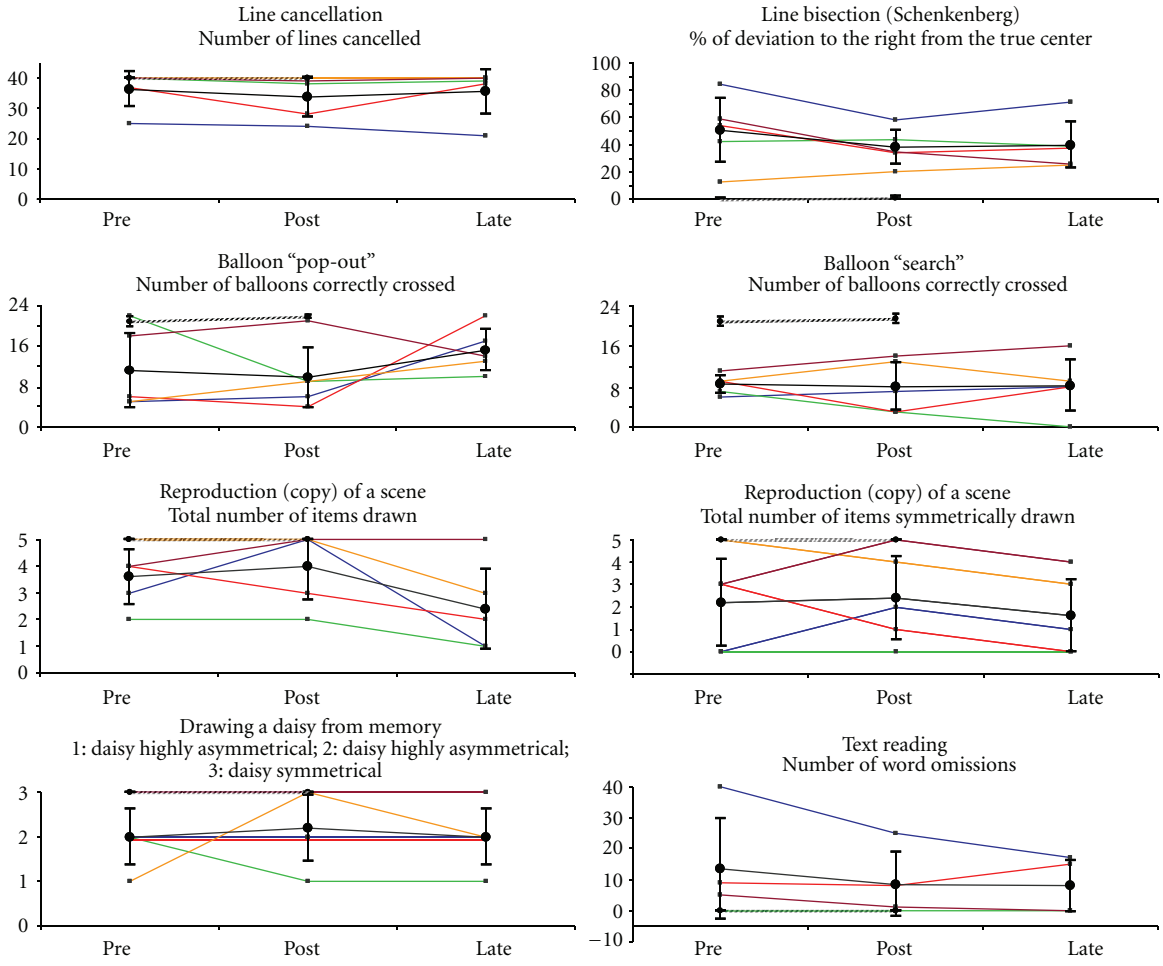
3.2.1. Line Cancellation. An average of 36.4 lines were cancelled before prism adaptation, 33.8 immediately after prism adaptation, and 35.6 two hours later (standard error of mean = 3.3). Analysis of variance showed no significant difference between sessions, $F(2, 8) = 1.31$; $P = 0.32$.

3.2.2. The Balloon Test. In the "pop-out" subtest, a mean of 11.2 targets balloons were crossed before prism adaptation, 9.8 immediately after, and 15.2 two hours later (standard error of mean = 3.0). Analysis of variance showed no significant difference between sessions $F(2, 8) = 0.86$; $P = 0.46$.

In the "search" subtest, a mean of 8.4 circles were crossed before prism adaptation, 8.0 immediately after prism adaptation, and 8.2 two hours later (standard error of mean = 2.1). Analysis of variance showed no significant difference between sessions $F(2, 8) = 0.02$; $P = 0.98$.



(a)



(b)

Figure 3: Straighthead pointing movements before and after prism adaptation for healthy controls (left) and neglect patients (right). (a) For each subject, the average end-position of straightahead pointing movements is represented before (pre) and after (post) left-deviating prism adaptation. Deviation from body midline is displayed in degrees of angle in positive value for right deviation and negative value for left deviation. Numbers refer to patient's identification (cf. Table 1) with the following color code: patient 1 (blue); patient 2 (red); patient 3 (orange); patient 4 (purple); patient 5 (green). (b) Left spatial neglect assessment before (pre), immediately after (post), and 2 hours after (late) prism adaptation. For each test, the graph represents the mean score ±95% confident interval for the group of five patients at each session. Individual curves are represented using the same color code as in Figure 3(a). Moreover, performances of the healthy controls (95% confident interval) are displayed in cross-hatching. For tests and scores description see Section 2.2.2.

3.2.3. Line Bisection. Before prism adaptation, patients bisected lines with a mean deviation calculated at 50.3 percent on the right of the true centre; this deviation was 35.8 immediately after prism adaptation and 39.5 two hours later (standard error of mean = 9.0). Analysis of variance showed no significant difference between sessions F (2, 8) = 2.27; $P = 0.17$.

3.2.4. Copy of a Scene. Before prism adaptation, an average of 3.6 of the five items was copied and an average of 2.2 items was symmetrically copied. Immediately after prism adaptation, an average of 4 items was copied and an average of 2.4 items was symmetrically copied. Two hours after prism adaptation, an average of 2.4 items was copied and an average of 1.6 items was symmetrically copied. Standard error of mean was 0.64 for the total number of items copied and 0.91 for items symmetrically copied. Analysis of variance showed no significant difference between sessions both for the total number of items copied F (2, 8) = 3.92; $P = 0.06$ and for the number of items symmetrically copied F (2, 8) = 0.78; $P = 0.49$.

3.2.5. Drawing from Memory. The daisy was moderately asymmetrical before prism adaptation (mean = 2), immediately after (mean = 2.2), and two hours later (mean = 2). Standard error of mean for this test was 0.34. Analysis of variance showed no significant difference between sessions F (2, 8) = 2.21; $P = 0.81$.

3.2.6. Simple Text Reading. Before prism adaptation, an average of 13.5 words were omitted, 8.5 immediately after prism adaptation, and 8.0 two hours later (standard error of mean = 6.7). Analysis of variance showed no significant difference between sessions F (2, 8) = 0.92; $P = 0.45$.

4. Discussion

The present study showed that patients with left spatial neglect are not affected by prism adaptation to a leftward optical shift. Indeed, neither the rightward deviation of straightahead pointing nor left spatial neglect, as assessed by a battery of classical paper and pencil tests, has been significantly improved or modified after a single session of visuomotor adaptation to left-deviating prisms. Not only do these results suggest that there is a directional specificity of the prisms, but they also show that no cognitive effects are found in the absence of adaptation. The present results play against the hypothesis that active exposure to a simple modification of sensori-motor coordinates is sufficient to reduce left spatial neglect. The short duration of the adaptation procedure cannot explain independently the absence of sensorimotor after-effects given that healthy controls adapt to prisms with the same procedure and neglect patients show sensori-motor after-effects, even larger than controls, when exposed to right-deviating prisms during the same amount of time [15].

4.1. Specific Directional Effects of Prism Adaptation in Neglect Patients

4.1.1. Adaptability to Wedge Prisms. In our experiment, none of the 5 neglect patients showed a consistent sensori-motor adaptation to left-deviating prisms. A similar result was already reported in experiment 1 of the original research performed by Rossetti et al. [15]. In this latter study, eight patients with left spatial neglect were randomly assigned to a session of left- or right-deviating prism adaptation. Adaptability was assessed by measuring body-midline demonstration (i.e. straightahead pointing in the dark). In contrast to normal subjects, results showed that patients with left neglect adapted only to right-deviating prism and not to left-deviating prism. The effect of left-deviating prism adaptation on left spatial neglect symptoms was not specifically assessed in this latter work.

These results suggest that patients with left spatial neglect after right-brain damage are not able to adapt to left-deviating prisms whereas they are able to adapt to right-deviating prisms. This result contrasts with the finding of Weiner et al. [14] that the only lesion site that impaired prism adaptation was within the cerebellum (see [43]). Although Weiner et al. [14] tested groups of patients with left versus right hemisphere lesion, no information is provided concerning the assessment of left spatial neglect. In their study it was stated that only patients with occipital lesion exhibited reduced negative after-effects. However in our group, the lesion overlapped the occipital cortex in only two out of the five patients. One explanation to this intriguing negative result could be related to the absence of detection of the visual errors by left neglect patients in the case of left-deviating prisms. Indeed, the first pointing movements with left-deviating prisms are shifted to the left side of the visual target, and considering that patients focus their vision on the target position, the visual error lies in the left visual field. Hence, it is not surprising that this visual error, which represents the first necessary signal for prism adaptation, is not even implicitly detected in patients with left spatial neglect.

Alternatively, it is possible that visual realignment after leftward-deviating prisms critically requires the integrity of the right hemisphere in contrast to visual realignment after rightward deviating prisms. As regard to this hypothesis, it is interesting to consider the directional asymmetry for visual after-effects observed in healthy subjects after a visual adaptation to leftward versus rightward prism displacement [44]. This could explain why right-brain-lesioned patients are only able to adapt to rightward deviating prisms. The larger amplitude of sensori-motor after-effects observed in right brain damaged neglect patients compared to healthy controls [15] is another interesting issue which could be related to the asymmetrical integration of the prism adaptation process.

4.1.2. Effect on Left Spatial Neglect and Related Symptoms. Our results showed for the first time that left-deviating prisms had no effect on various symptoms of left spatial

neglect. Previous studies have reported a similar lateralized specificity of prism adaptation on several neglect-related symptoms. Tilikete et al. [19] investigated the effect of prism adaptation on postural imbalance in a group of 15 left hemiparetic patients, randomly exposed to right-deviating prism, left-deviating prism, or neutral goggles. The lateral displacement of the centre of pressure observed in the pretest was significantly reduced specifically following right-deviating prisms. Finally, for one of the neglect patients (patient 4) included in the experiment performed by Maravita et al. [21], contralesional tactile perception and visual extinction were improved only after adaptation to right-deviating prism and not after adaptation to left-deviating prism.

Hence, these results favour a specificity of prism adaptation in terms of the direction of optical shift: only adaptation to right-deviating prisms can improve left spatial neglect. The most obvious explanation to account for these results is related to the absence of adaptability to left-deviating prism for patients with left spatial neglect (cf. Section 4.1.1). These results support the hypothesis that the presence of sensori-motor after-effect is a necessary condition to influence the highest cognitive levels of space and action representation subserving neglect recovery. However, as pointed out by Rode et al. [16], several studies have shown that the quantitative relationship between the amplitude of after-effect and neglect amelioration is not obvious (e.g., [45]).

4.2. Specific Directional Cognitive Effects of Prism Adaptation in Healthy Subjects. Interestingly, the cognitive effects of prism, in non-brain-damaged subjects, are also supported by an asymmetrical pattern of performance. Colent et al. [46] examined the possibility that visuomotor adaptation to left- or right-deviating prisms could generate a bias on a line bisection task. Only adaptation to left-deviating prisms induced a rightward bias on the perceptual version of the line bisection task. This result was then confirmed by Berberovic et al. [47]. Michel et al. [48] investigated the effect of prism adaptation on postural control in healthy subjects. Fourteen participants were either adapted to a leftward or rightward visual shift and it was found again that only adaptation to a leftward visual shift induced significant rightward postural bias. (For a review see [35]. In another experiment, Michel et al. [49] showed asymmetric effects after manual or locomotor adaptation (walking along a rectangle drawn on the floor with prismatic google) to a leftward or ritghtward optical deviation on a goal-oriented locomotor task (estimation of the spatial location of a visual target with body displacement). On the goal-oriented locomotor task which comprises a spatial dimension, the rightward after-effects generated by left-deviating prisms were greater than the leftward after-effects generated by right-deviating prisms. This result suggests that in contrast to rightward-deviating prisms generating only sensori-motor adaptation, leftward-deviating prisms may induce both sensori-motor and an additional cognitive after-effect.

Striemer et al. [50] investigated whether prism adaptation could influence visual attention, as assessed by a visual attention cueing paradigm. Two versions of the task were employed depending on the delay separating cue onset and target onset. In the reflexive version, the delay was short (50 to 300 ms), whereas it was longer in the voluntary version (300 to 500 ms). Healthy participants were divided in three groups: left-deviating prisms, right-deviating prisms, and neutral goggles. The main result was an increase of voluntary attention efficiency for both left and right visual space after adaptation to left-deviating prisms. In contrast, right-deviating prisms decreased the efficiency of voluntary attention in both left and right space. The experiment performed by Morris et al. [51] was less conclusive in the sense that neither adaptation to left-deviating prism nor adaptation to right-deviating prism significantly modified a visual search task. However, results presented in this latter article showed a clear decrease of reaction time and percentage of error in the left visual space (not present in the right visual space) after left-deviating prism. Altogether, the data available in the literature suggest that the cognitive effects of prism adaptation in healthy subjects depend on the direction of the optical shift. The present results suggest that the same is true for unilateral neglect patients, but in the opposite direction. Spatial neglect is improved only by adaptation to rightward optical shifts and spatial cognitive functions tested on healthy subjects are affected mainly after adaptation to a left-ward shift. This coherence allows proposing an integrated model of the effects of prism adaptation on spatial cognition, whereby the lateralized effects of adaptation on the cerebellum would affect the controlateral hemisphere [52].

4.3. Neural Mechanisms Underlying Prism Adaptation Beneficial Effect on Left Spatial Neglect. The neural substrate underlying the therapeutic effect of this method remains to be fully elucidated. Our study was not specifically designed to deal with this issue but argues at least for an initial lateralized bottom-up activation implicated in the detection of the right visual error during the first pointing movements through prisms. In a recent functional imaging study performed on healthy subjects, we used event-related fMRI to analyze dynamic changes in brain activity during a prolonged exposure to visual prisms [53]. Results suggest that during exposure to a leftward prismatic deviation, error-detection was processed in the left intraparietal sulcus, errorcorrection involved the left parietooccipital sulcus, and visuomotor realignment implicated the right cerebellum. Furthermore, the activation observed bilaterally in the superior temporal cortex during the late phase of prism exposure was thought to mediate the effects of prism adaptation on cognitive spatial representations.

The mechanism by which such lateralized sensori-motor plasticity induced by prism adaptation can improve spatial neglect remains unclear. Moreover, the gap might be important between what we know about sensori-motor plasticity in normal subjects and what happens in brain-damaged neglect patients.

In a functional imaging PET study, we investigated the anatomical substrates underlying the beneficial effect of

prism adaptation in five patients with left spatial neglect following right stroke [54]. We used a covariation analysis to examine linear changes over sessions as a function of neglect improvement. This study confirmed that a low-level sensori-motor adaptation can modulate several cortical areas involved in spatial cognition and gives further support to a bottom-up mechanism. Altogether, the following model is proposed: error signals induced by prisms are initially processed by the left occipitoparietal cortex, then forwarded to the right cerebellum where visuomotor realignment takes place. The clinical benefit would result from the modulation of left-hemisphere areas via a bottom-up signal produced by the cerebellum. These areas would partially match those involved in spatial cognition in the right hemisphere, and their modulation would improve interhemispheric rebalancing. The basic idea proposed here is that the activation of the right cerebellum by prism adaptation would play a negative influence on the activation of the left cerebral hemisphere. A recent support for such interaction was provided by Pope and Miall [55] who explored the effect of cerebellar activity modulation on cognitive tasks. One classic idea about the contribution of the cerebellum to cognitive function has been that the processing capacities developed in the cerebellum for sensorimotor control could also turn out to be useful for cognitive operations. Accordingly, the expectation is that reducing cerebellar activity on one side would impair contralateral hemispheric functions. However Pope and Miall revealed that cathodal tDCS on the right cerebellum resulted in an improvement of several cognitive tasks known to rely on the left cerebral hemisphere functions. The reciprocal arguments that enhancing right cerebellum activity by prism adaptation may inhibit left cerebral cortex function and that downregulating right cerebellum activity by cathodal tDCS may enhance left cerebral cortex function provide a general coherence to the idea that cerebellocortical interactions contribute to the expansion of prism adaptation effects to cognitive functions.

References

[1] E. Bisiach, "Mental representation in unilateral neglect and related disorders: the twentieth Bartlett Memorial Lecture," *Quarterly Journal of Experimental Psychology A*, vol. 46, no. 3, pp. 435–461, 1993.

[2] I. H. Robertson and P. W. Halligan, *Spatial Neglect: A Clinical Handbook for Diagnosis and Treatment*, 1999.

[3] P. Appelros, G. M. Karlsson, A. Seiger, and I. Nydevik, "Neglect and anosognosia after first-ever stroke: incidence and relationship to disability," *Journal of Rehabilitation Medicine*, vol. 34, no. 5, pp. 215–220, 2002.

[4] A. Farnè, L. J. Buxbaum, M. Ferraro et al., "Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 75, no. 10, pp. 1401–1410, 2004.

[5] H. Samuelsson, C. Jensen, S. Ekholm, H. Naver, and C. Blomstrand, "Anatomical and neurological correlates of acute and chronic visuospatial neglect following right hemisphere stroke," *Cortex*, vol. 33, no. 2, pp. 271–285, 1997.

[6] D. Boisson and A. Vighetto, "La négligence spatiale. De l'évaluation clinique aux possibilités thérapeutiques," *Annales de Réadaptation et de Médecine Physique*, vol. 32, no. 5, pp. 539–562, 1989.

[7] G. Denes, C. Semenza, E. Stoppa, and A. Lis, "Unilateral spatial neglect and recovery from hemiplegia. A follow-up study," *Brain*, vol. 105, no. 3, pp. 543–552, 1982.

[8] M. Jehkonen, J. P. Ahonen, P. Dastidar et al., "Visual neglect as a predictor of functional outcome one year after stroke," *Acta Neurologica Scandinavica*, vol. 101, no. 3, pp. 195–201, 2000.

[9] J. Luauté, P. Halligan, G. Rode, Y. Rossetti, and D. Boisson, "Visuo-spatial neglect: a systematic review of current interventions and their effectiveness," *Neuroscience and Biobehavioral Reviews*, vol. 30, no. 7, pp. 961–982, 2006.

[10] J. Luauté, P. Halligan, G. Rode, S. Jacquin-Courtois, and D. Boisson, "Prism adaptation first among equals in alleviating left neglect: a review," *Restorative Neurology and Neuroscience*, vol. 24, no. 4–6, pp. 409–418, 2006.

[11] G. M. Redding, Y. Rossetti, and B. Wallace, "Applications of prism adaptation: a tutorial in theory and method," *Neuroscience and Biobehavioral Reviews*, vol. 29, no. 3, pp. 431–444, 2005.

[12] Y. Rossetti, K. Koga, and T. Mano, "Prismatic displacement of vision induces transient changes in the timing of eye-hand coordination.," *Perception and Psychophysics*, vol. 54, no. 3, pp. 355–364, 1993.

[13] G. M. Redding and B. Wallace, "Adaptive spatial alignment and strategic perceptual-motor control," *Journal of Experimental Psychology*, vol. 22, no. 2, pp. 379–394, 1996.

[14] M. J. Weiner, M. Hallett, and H. H. Funkenstein, "Adaptation to lateral displacement of vision in patients with lesions of the central nervous system," *Neurology*, vol. 33, no. 6, pp. 766–772, 1983.

[15] Y. Rossetti, G. Rode, L. Pisella et al., "Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect," *Nature*, vol. 395, no. 6698, pp. 166–169, 1998.

[16] G. Rode, T. Klos, S. Courtois-Jacquin, Y. Rossetti, and L. Pisella, "Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders," *Restorative Neurology and Neuroscience*, vol. 24, no. 4–6, pp. 347–356, 2006.

[17] L. Pisella, G. Rode, A. Famè, D. Boisson, and Y. Rossetti, "Dissociated long lasting improvements of straight-ahead pointing and line bisection tasks in two hemineglect patients," *Neuropsychologia*, vol. 40, no. 3, pp. 327–334, 2002.

[18] S. Ferber, J. Danckert, M. Joanisse, H. C. Goltz, and M. A. Goodale, "Eye movements tell only half the story," *Neurology*, vol. 60, no. 11, pp. 1826–1829, 2003.

[19] C. Tilikete, G. Rode, Y. Rossetti, J. Pichon, L. Li, and D. Boisson, "Prism adaptation to rightward optical deviation improves postural imbalance in left-hemiparetic patients," *Current Biology*, vol. 11, no. 7, pp. 524–528, 2001.

[20] R. D. McIntosh, Y. Rossetti, and A. D. Milner, "Prism adaptation improves chronic visual and haptic neglect: a single case study," *Cortex*, vol. 38, no. 3, pp. 309–320, 2002.

[21] A. Maravita, J. McNeil, P. Malhotra, R. Greenwood, M. Husain, and J. Driver, "Prism adaptation can improve contralesional tactile perception in neglect," *Neurology*, vol. 60, no. 11, pp. 1829–1831, 2003.

[22] H. C. Dijkerman, M. Webeling, J. M. Ter Wal, E. Groet, and M. J. E. Van Zandvoort, "A long-lasting improvement of somatosensory function after prism adaptation, a case study," *Neuropsychologia*, vol. 42, no. 12, pp. 1697–1702, 2004.

[23] N. Berberovic, L. Pisella, A. P. Morris, and J. B. Mattingley, "Prismatic adaptation reduces biased temporal order judgements in spatial neglect," *NeuroReport*, vol. 15, no. 7, pp. 1199–1204, 2004.

[24] G. Rode, Y. Rossetti, L. Li, and D. Boisson, "Improvement of mental imagery after prism exposure in neglect: a case study," *Behavioural Neurology*, vol. 11, no. 4, pp. 251–258, 1998.

[25] G. Rode, Y. Rossetti, and D. Boisson, "Prism adaptation improves representational neglect," *Neuropsychologia*, vol. 39, no. 11, pp. 1250–1254, 2001.

[26] Y. Rossetti, S. Jacquin-Courtois, G. Rode, H. Ota, G. Michel, and D. Boisson, "Does action make the link between number and space representation? Visuo-manual adaptation improves number bisection in unilateral neglect," *Psychological Science*, vol. 15, no. 6, pp. 426–430, 2004.

[27] A. Farnè, Y. Rossetti, S. Toniolo, and E. Làdavas, "Ameliorating neglect with prism adaptation: visuo-manual and visuo-verbal measures," *Neuropsychologia*, vol. 40, no. 7, pp. 718–729, 2002.

[28] G. Rode, L. Pisella, L. Marsal, S. Mercier, Y. Rossetti, and D. Boisson, "Prism adaptation improves spatial dysgraphia following right brain damage," *Neuropsychologia*, vol. 44, no. 12, pp. 2487–2493, 2006.

[29] S. Jacquin-Courtois, G. Rode, L. Pisella, D. Boisson, and Y. Rossetti, "Wheel-chair driving improvement following visuo-manual prism adaptation," *Cortex*, vol. 44, no. 1, pp. 90–96, 2008.

[30] S. Watanabe and K. Amimoto, "Generalization of prism adaptation for wheelchair driving task in patients with unilateral spatial neglect," *Archives of Physical Medicine and Rehabilitation*, vol. 91, no. 3, pp. 443–447, 2010.

[31] F. Frassinetti, V. Angeli, F. Meneghello, S. Avanzi, and E. Làdavas, "Long-lasting amelioration of visuospatial neglect by prism adaptation," *Brain*, vol. 125, no. 3, pp. 608–623, 2002.

[32] S. Vangkilde and T. Habekost, "Finding Wally: prism adaptation improves visual search in chronic neglect," *Neuropsychologia*, vol. 48, no. 7, pp. 1994–2004, 2010.

[33] A. Serino, M. Barbiani, M. L. Rinaldesi, and E. Ladavas, "Effectiveness of prism adaptation in neglect rehabilitation: a controlled trial study," *Stroke*, vol. 40, no. 4, pp. 1392–1398, 2009.

[34] A. J. Turton, K. O'Leary, J. Gabb, R. Woodward, and I. D. Gilchrist, "A single blinded randomised controlled pilot trial of prism adaptation for improving self-care in stroke patients with neglect," *Neuropsychological Rehabilitation*, vol. 20, no. 2, pp. 180–196, 2010.

[35] C. Michel, "Simulating unilateral neglect in normals: myth or reality?" *Restorative Neurology and Neuroscience*, vol. 24, no. 4–6, pp. 419–430, 2006.

[36] M. Sumitani, Y. Rossetti, M. Shibata et al., "Prism adaptation to optical deviation alleviates pathologic pain," *Neurology*, vol. 68, no. 2, pp. 128–133, 2007.

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

[38] M. L. Alberti, "A simple test of visual neglect," *Neurology*, vol. 23, no. 6, pp. 658–664, 1973.

[39] J. Edgeworth, I. Robertson, and T. M. Mac Millan, *The Balloons Test*, Thames Valley Test Company, London, UK, 1998.

[40] M. Eglin, L. C. Robertson, and R. T. Knight, "Visual search performance in the neglect syndrome," *Journal of Cognitive Neuroscience*, vol. 1, no. 4, pp. 372–385, 1989.

[41] T. Schenkenberg, D. C. Bradford, and E. T. Ajax, "Line bisection and unilateral visual neglect in patients with neurologic impairment," *Neurology*, vol. 30, no. 5, pp. 509–517, 1980.

[42] G. Gainotti, P. Messerli, and R. Tissot, "Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions.," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 35, no. 4, pp. 545–550, 1972.

[43] L. Pisella, Y. Rossetti, C. Michel et al., "Ipsidirectional impairment of prism adaptation after unilateral lesion of anterior cerebellum," *Neurology*, vol. 65, no. 1, pp. 150–152, 2005.

[44] G. M. Redding and B. Wallace, "Implications of prism adaptation asymmetry for unilateral visual neglect: theoretical note," *Cortex*, vol. 46, no. 3, pp. 390–396, 2010.

[45] M. Girardi, R. D. McIntosh, C. Michel, G. Vallar, and Y. Rossetti, "Sensorimotor effects on central space representation: prism adaptation influences haptic and visual representations in normal subjects," *Neuropsychologia*, vol. 42, no. 11, pp. 1477–1487, 2004.

[46] C. Colent, L. Pisella, C. Bernieri, G. Rode, and Y. Rossetti, "Cognitive bias induced by visuo-motor adaptation to prisms: a simulation of unilateral neglect in normal individuals?" *NeuroReport*, vol. 11, no. 9, pp. 1899–1902, 2000.

[47] N. Berberovic and J. B. Mattingley, "Effects of prismatic adaptation on judgements of spatial extent in peripersonal and extrapersonal space," *Neuropsychologia*, vol. 41, no. 4, pp. 493–503, 2003.

[48] C. Michel, Y. Rossetti, G. Rode, and C. Tilikete, "After-effects of visuo-manual adaptation to prisms on body posture in normal subjects," *Experimental Brain Research*, vol. 148, no. 2, pp. 219–226, 2003.

[49] C. Michel, P. Vernet, G. Courtine, Y. Ballay, and T. Pozzo, "Asymmetrical after-effects of prism adaptation during goal oriented locomotion," *Experimental Brain Research*, vol. 185, no. 2, pp. 259–268, 2008.

[50] C. Striemer, J. Sablatnig, and J. Danckert, "Differential influences of prism adaptation on reflexive and voluntary covert attention," *Journal of the International Neuropsychological Society*, vol. 12, no. 3, pp. 337–349, 2006.

[51] A. P. Morris, A. Kritikos, N. Berberovic, L. Pisella, C. D. Chambers, and J. B. Mattingley, "Prism adaptation and spatial attention: a study of visual search in normals and patients with unilateral neglect," *Cortex*, vol. 40, no. 4-5, pp. 703–721, 2004.

[52] L. Pisella, G. Rode, A. Farnè, C. Tilikete, and Y. Rossetti, "Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders," *Current Opinion in Neurology*, vol. 19, no. 6, pp. 534–542, 2006.

[53] J. Luauté, S. Schwartz, Y. Rossetti et al., "Dynamic changes in brain activity during prism adaptation," *Journal of Neuroscience*, vol. 29, no. 1, pp. 169–178, 2009.

[54] J. Luauté, C. Michel, G. Rode et al., "Functional anatomy of the therapeutic effects of prism adaptation on left neglect," *Neurology*, vol. 66, no. 12, pp. 1859–1867, 2006.

[55] P. A. Pope and R. C. Miall, "Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum," *Brain Stimulation*, vol. 5, no. 2, pp. 84–94, 2012.

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 964843, 12 pages
doi:10.1155/2012/964843

Review Article

Activity-Dependent Plasticity of Spinal Circuits in the Developing and Mature Spinal Cord

Behdad Tahayori and David M. Koceja

Department of Kinesiology and Program in Neuroscience, Indiana University Bloomington, Bloomington, IN 47405-7109, USA

Correspondence should be addressed to David M. Koceja, koceja@indiana.edu

Received 2 March 2012; Accepted 12 June 2012

Academic Editor: Mary F. Barbe

Part of the development and maturation of the central nervous system (CNS) occurs through interactions with the environment. Through physical activities and interactions with the world, an animal receives considerable sensory information from various sources. These sources can be internally (proprioceptive) or externally (such as touch and pressure) generated senses. Ample evidence exists to demonstrate that the sensory information originating from large diameter afferents (Ia fibers) have an important role in inducing essential functional and morphological changes for the maturation of both the brain and the spinal cord. The Ia fibers transmit sensory information generated by muscle activity and movement. Such use or activity-dependent plastic changes occur throughout life and are one reason for the ability to acquire new skills and learn new movements. However, the extent and particularly the mechanisms of activity-dependent changes are markedly different between a developing nervous system and a mature nervous system. Understanding these mechanisms is an important step to develop strategies for regaining motor function after different injuries to the CNS. Plastic changes induced by activity occur both in the brain and spinal cord. This paper reviews the activity-dependent changes in the spinal cord neural circuits during both the developmental stages of the CNS and in adulthood.

1. Introduction

Deprivation of sensory information during certain periods of an animal's life span causes substantial impairment in the normal development and function of the central nervous system (CNS). Hence, this period is referred to as a critical period. The pioneering works of Hubel and Wiesel [1–5], which culminated in the Nobel Prize in Medicine, showed that during a critical period, depriving kittens' visual information for as few as three to four days resulted in a substantial decline in the number of striatal neurons [1]. Other studies have shown that during normal development the acquisition of motor abilities such as standing [6] and walking [7] are extensively dependent on various sensory inputs generated by movement. The term *activity-dependent plasticity* is used to describe the changes induced in the CNS associated with movement activity. These activity-dependent changes occur ubiquitously in the CNS; connections between the brain and spinal neurons and connections between sensory neurons and motoneurons of the spinal cord also show extensive reorganization in response to movement and activity.

However, activity-dependent changes in the nervous system are not solely limited to the developing period but also exist throughout the life span for both the spinal cord [8] and the brain [9]. The adult CNS also undergoes plastic changes during the learning of new motor skills which persists for extended periods of time. Conversely, the loss of plasticity of the nervous system with aging has been shown to be related to the decline in specific motor capacities of the individual. For example, a decline in the flexibility or adaptability of spinal reflexes has been shown in different and independent studies to be meaningfully correlated with fall risk or abnormal postural control strategies [10–14]. In this instance, regaining the adaptive capacity of the nervous system is, therefore, a promising strategy for neurological rehabilitation.

The purpose of this paper is to review and compare activity-dependent plasticity of spinal circuits during development and in adulthood, focusing on the fundamental differences in the mechanisms of spinal plasticity between development and adulthood. Understanding the underlying mechanisms involved in the activity-dependent induction of plasticity is potentially meaningful for modern treatments of a variety of movement disorders.

2. Activity-Dependent Plasticity during Development

A variety of mechanisms ranging from intrinsic cellular and morphological properties to genetic and epigenetic factors [17, 18] have been identified which participate in the transition of an immature nervous system into its final shape and function. The maturation process partly depends on the activity of the neonate during the movement development critical period [19]. For example, the ability of kittens to acquire standing, walking, and running skills has been shown to be related to the maturation of motor units and the central connectivity between the motoneurons and their various sensory inputs [20]. Studies of the past two decades have shown that during maturation, extensive morphological, molecular, and structural changes occur in motoneurons [21, 22]. In this part, we will review the effect of sensory input, receptor activity, and descending drive on the plastic changes of the spinal circuits during development.

2.1. The Importance of Sensory Input for Proper Development. Experimental studies have found molecular correlates with activity, which are predominantly observed during maturation and the developmental progression of motoneurons. One of the well-studied molecules is a monoclonal antibody which recognizes a certain proteoglycan known as Cat-301 proteoglycan. Expression of Cat-301 substantially increases in association with movement [26, 27]. This proteoglycan does not exist in immediate postnatal cells but its expression increases as development proceeds, and it has a substantial role in the morphological and physiological maturation of the motoneurons. There is evidence to show that this movement-associated increase in Cat-301 expression is actually related to the sensory input from large diameter fibers and not the generation of the movement per se. Studies with animal models have shown that crushing the sciatic nerve in neonatal hamsters seriously affects the expression of Cat-301 proteoglycan on the cell body of motoneurons [27] whereas in adulthood, a sciatic nerve crush injury does not cause a substantial change in the expression of Cat-301, emphasizing its importance during development. Severing the sensory afferents via dorsal rhizotomy during development also produces the same pattern of results in the expression of Cat-301, suggesting the importance of sensory input to the motoneuron. Interestingly, destruction of the smaller-diameter unmyelinated afferents (C-fibers) which are involved in the transmission of pain information, does not affect the expression of the antibody [26]. Taken together, it seems that the proprioceptive sensory information from muscle spindles, whose firing rates are related to the movement of body parts, has a significant role for the induction of change in the spinal circuits of developing animals.

2.2. NMDA Receptors Have an Important Role in the Induction of Plasticity. It is well known that sensory Ia fibers make both monosynaptic and oligosynaptic connections to alpha motoneurons in the ventral horn and comprise the reflex arc, using glutamine as the excitatory neurotransmitter. In the spinal cord, glutamine activates two major types of ionotropic receptors: NMDA and AMPA receptors. It was initially thought that these two types of glutamatergic ionotropic receptors have differential roles in synaptic transmission of the reflexes. Initial studies suggested that NMDA receptors were involved in the transmission of polysynaptic reflexes and AMPA receptors were involved in the transmission of the monosynaptic reflexes; however subsequent studies have shown this not to be the case [28]. Rather, numerous studies have shown that the NMDA receptor function is crucial for the induction of plasticity [29]. For example, in an *in vitro* experimental setup, Fields and colleagues cultured the spinal motoneurons of 13-d mouse fetuses in a 3-chambered cell-culture system and electrically stimulated the sensory afferents of the motoneurons of one of the chambers. It was shown that the motoneurons which were subject to chronic stimulation developed stronger synaptic connections with the afferent fibers in terms of yielding larger excitatory postsynaptic potentials (EPSP) compared to the untreated chambers of the sensory afferents. Therefore, this experimental model suggested that an increase in sensory input to spinal motoneurons could increase the efficacy of this synaptic connection. These stimulation-induced changes in sensory afferent efficacy were suppressed by the application of the selective NMDAR antagonist APV [30], suggesting that sensory input to motoneurons induced morphological changes through the activation of the NMDA receptors. Cell bodies and dendrites initially grow in size and number but after this initial growth, they show a regression until they reach their final mature configuration. NMDA receptors have a role in this dendritic growth and retraction. The application of an NMDA antagonist during the first three weeks after birth substantially abolishes motoneuron and dendritic growth in neonate hamsters; whereas in adulthood, NMDAR blockade has not been shown to affect motoneuron morphology [31]. In conclusion, although NMDA glutamatergic receptors do not have a significant role in signal transmission of the reflexes, NMDARs do have an important role in inducing plastic changes in spinal motoneurons.

Interestingly, NMDA receptors can be found throughout the spinal cord gray matter (ventral and dorsal horn) at very early stages of development [32], but during maturation they are essentially eliminated from all parts of the spinal cord except from the substantia gelatinosa [33]. NMDA receptors of the substantia gelatinosa have roles in modifying the input from sensory fibers such as A-delta. Experimental studies on rat spinal cord has shown that low-frequency stimulation of A-delta fibers can induce NMDA-dependent long-term depression (LTD) in substantia gelatinosa [34]. In pathologic

conditions such as excitotoxicity, activation of these receptors in the CNS is a contributing part of the process of neuronal destruction [35]. Likewise, NMDA receptors might be involved in the development of neuropathic pain [36]. Although these receptors are eliminated from the ventral horn in the mature spinal cord, this does not rule out the ability for change at later stages of life.

2.3. Descending Inputs Are Essential for the Induction of Plasticity. The induction of temporary or permanent plastic change is, logically, also contingent on descending drive. For example, severing the spinal cord during the developmental stages substantially reduces the expression of Cat-301 on the motoneuron soma in neonatal hamsters [27]. At birth, the corticospinal tract makes synapses with both the dorsal and ventral regions of the spinal cord. However, during the course of development, the connections between the corticospinal tract and the ventral neurons are pruned. The pattern of synapse elimination seems to be complex and dependent on activation in both the contralateral and ipsilateral tracts. In human [37, 38], as well as monkeys [39] and mice [40], the corticospinal tract makes synaptic connections with both contralateral as well as ipsilateral spinal motoneurons, and during normal development of the CNS, the majority of the connections to the ipsilateral side are eliminated. Ablation of the cortex in subprimate mammals during the early stages of postnatal life has been shown to prevent the elimination of the corticospinal tract connections to the ipsilateral motoneurons [37]. This injury-induced maintenance of ipsilateral projections from the corticospinal tract is accompanied by a hypertrophy of the cortex of the undamaged side [40]. In line with animal studies, the same findings have been indirectly shown in human subjects. In newborns, the application of transcranial magnetic stimulation (TMS) to the cortex elicits bilateral muscle-twitch responses to both limbs with almost the same amplitude but with a shorter delay on the ipsilateral side. Studies on patients with cerebral palsy (nonprogressive damage to developing fetal or infant brain [41]) have also shown the same pathologies as those observed in animal models. In these patients, the bilateral pattern of innervation of the spinal motoneurons from the cortex persists and is not eliminated during maturation [42]. From a behavioral perspective, this lack of remodeling and selective elimination of the corticospinal tract connections could partly explain why children with cerebral palsy cannot tonically decrease the amplitude of the H-reflex (explained in Section 3, see below) during walking [43, 44]. In children with diplegic cerebral palsy, the corticospinal tracts of both sides have been affected. In these children, rhythmic modulation of the H-reflex during walking, which is suggested to be spinally regulated, is intact but the tonic depression of the H-reflex, which is assumed to be mediated through supraspinal centers is compromised. Therefore, it seems that the centrally driven modulation of the H-reflex is affected in these children [45]. This is one example in which understanding the underlying mechanisms is relevant for the development of behavioral specific interventions in individuals with motor dysfunction.

Comparison of the findings regarding the activity-dependent role of NMDA receptors at the level of the spinal cord and the importance of cortical input to the spinal cord strongly suggests that both peripheral and descending inputs are required for activity-dependent plasticity in the spinal cord. It is shown that these activity dependent eliminations of synapses are at least partly mediated by NMDA receptor activation. Recent investigations [46] have shown that the postsynaptic GluN2B subtypes of NMDA receptors play an important role for this elimination. The GluN2B-containing NMDA receptors are better conductors of Ca^{2+} into the cells. While it is understood that NMDA receptors mediate many activity-dependent changes during the early stages of spinal cord development, the exact mechanism by which NMDA receptors function to regulate development is unknown.

3. Activity-Dependent Plasticity in the Adult Spinal Cord

Unlike the literature on the developing spinal cord, much of our understanding of activity-dependent plasticity of the mature spinal cord comes from human studies. The H-reflex is a well-recognized and accepted method for investigating the function of the spinal circuits during various movements. For eliciting an H-reflex, an electrical stimulus (usually a single square-wave pulse with 1 ms duration) is applied to a peripheral nerve [47]. The largest sensory fibers (the Ia fibers), due to their axonal diameters are the first to be stimulated. These sensory afferents transmit the signal to the spinal cord and synapse both directly and indirectly onto alpha motoneurons. The resulting activation of the alpha motoneurons can be detected as a synchronized, coherent biphasic signal in the EMG activity of the corresponding muscle. For this reason, the H-reflex is regarded as an electrical analogue to the stretch reflex [48] (although there is considerable debate about this comparison). This reflex arc is nonetheless under the influence of descending drive and input from the periphery as well as other muscle spindles [15].

Applying this technique to any accessible mixed nerve will elicit the H-reflex in the corresponding muscles; however, this technique has been most widely used for examination of the soleus muscle due to the superficial location of its neural innervation. More importantly, the soleus is a crucial muscle for the control of posture and gait. Therefore, measuring the H-reflex in the soleus muscle is an appropriate model for studying the role that spinal circuits play in the control and modulation of a variety of bipedal movements. We would like to point out that the findings from this type of artificially induced reflex might be different than those of stretch reflexes. There are studies that show that modulations observed in the H-reflex are not present in the stretch reflex [49]. It is assumed that the H- and the stretch reflex are not equally sensitive to inhibitory mechanisms such as presynaptic inhibition. This difference can be partly explained by the fact that the H-reflex is temporally more synchronized than the stretch reflex and therefore, the temporal dispersion associated with the stretch

reflex might render the Ia fibers less sensitive to presynaptic inhibition [50]. This idea is supported by the fact that repetitive discharge of Ia fibers reduces their susceptibility to presynaptic inhibition [50].

3.1. Short-Term and Long-Term Changes in the Synaptic Strength of the Reflex Arc. In adult humans, monkeys, and rats learning new skills is accompanied by temporary or permanent changes in the spinal cord, and these changes have been extensively studied with the stretch reflex or the H-reflex.

It is well accepted that there exists short-term task-dependent modulation of spinal reflexes, and this modulation does not immediately impose any structural or long-lasting functional change in spinal circuits. The prevailing notion is that synapse strength is altered in a task-specific manner. However, practicing the same task or stimulating the same pathway for an extended period of time (e.g., days or years) can result in long-term structural changes in spinal circuits. One example from the athletic area is the reflex regulation in dancers in whom the amplitude of the H-reflex is substantially lower than the normal population [51–53]. Presumably, these long-term changes may in fact weight the contribution of the corticospinal tract in modulating segmental inputs during highly skilled movement, with less weight given to the peripheral input of the muscle spindles.

To examine the induction of such long-term change in the adult spinal cord, an operant conditioning model of spinal reflexes has routinely been used. In this model of learning, a spinal reflex (stretch or H-reflex) is elicited, and the resulting EMG response is recorded. The amplitude of the reflex is presented to the subject as a feedback. A reward is provided if the reflex response is modulated in one particular direction (increase or decrease) as determined by the examiner. This reward encourages the animal (or human) to purposefully direct its behavior toward the desired reflex response. Operant conditioning has been extensively used for documenting changes in the input-output relationship of both the spinal stretch and the H-reflex. This model has provided a powerful tool for the investigation of spinal circuits as well as any morphological alterations in the motoneurons associated with learning. It is now well established that both animals and humans can similarly increase or decrease the amplitude of the stretch or H-reflex [54]. Typically, the plasticity in these circuits has consistently been shown to be nearly 150% increases in amplitude for those rewarded for increases, and nearly 50% decreases in reflex amplitude for those rewarded for decreases [55, 56].

3.2. Presynaptic Inhibition as One Method for Altering Synaptic Transmission. How do these changes in the reflex pathway occur and how do they become permanent?

For the efficacy of the synaptic transmission to change (either transiently or permanently), there are some mechanisms which act on the presynaptic terminals and some mechanisms which affect the postsynaptic terminal. Collectively, such presynaptic or postsynaptic alterations can increase or decrease the amplitude of EPSPs or inhibitory postsynaptic potentials (IPSPs). There is a variety of these mechanisms throughout the central nervous system which are involved in almost all activities of the CNS from learning and memory [57], habituation [58], and gating of pain signals [59] to the control of movement [60–63]. At the level of spinal motoneurons, both types of mechanisms exist and have role in the modulation of the H-reflex and stretch reflex in different movements [64–67]. In general, postsynaptic mechanisms that exert inhibition on alpha motoneurons result in these motoneurons being less responsive to any type of excitatory input. Presynaptic inhibitory mechanisms, on the other hand, can affect the input to the motoneurons without affecting the motoneurons intrinsic properties. This type of inhibition selectively inhibits one input to the motoneurons without affecting other inputs. Likewise, inhibition of the Ia-motoneuron synapses presynaptically can render the reflex gain lower (can reduce the amplitude of the reflex) without affecting the excitability status of the motoneurons. In this case, the normal activity of the muscle will be secured, while its reflexive contraction (and thus its selective control of incoming sensory information) can be independently reduced.

Frank and Fuortes (1957) were among the first to report that sensory inflow can indeed be suppressed without affecting the resting potential of the postsynaptic alpha motoneuron [68]. However, they did not provide a reasonable explanation on how the monosynaptic transmission can be manipulated without any change in the input level or any change in the resting potential of the postsynaptic cell. Later, Frank [69] suggested that there could be what he termed a "remote inhibition" meaning that the site of this inhibition is remote from the soma [70, 71]. The existence of this phenomenon was confirmed in subsequent research [72], but it was not well understood until the pioneering work of Eccles, who suggested that Ia afferent synaptic strength can be affected through axoaxonic GABAergic inhibitory connections [72, 73]. The prevailing hypothesis for the mechanism of presynaptic inhibition of Ia afferents is that the GABAergic receptors in the active zone of the primary afferent terminal (presynaptic Ia terminals) are being activated by interneurons of other sources (refer to Figure 1). Because both sides of this synaptic terminal are axons (Ia afferent and the interneurons), this specific type of synaptic connection was termed axoaxonic to address this phenomenon. These interneurons, while being activated, act GABAergically on the Ia terminals [74, 75]. Upon the opening of the $GABA_A$ receptors in the Ia terminals, chloride ions leave the presynaptic terminal and thereby cause the active zone to depolarize. It is suggested that this GABAergic mechanism shunts the EPSP through $GABA_A$ receptor activation, or directly affects the Ca^{2+} channels through $GABA_B$ receptors [70, 76]. Without an influx of Ca^{2+}, vesicle mobilization is impaired, decreasing the probability of neurotransmitter release from the afferent terminals [70, 77]. It was shown in the cat that the interneurons which mediate this primary afferent depolarization (PAD), are under the influence from both peripheral sources such as Ib volleys and

Ia input from antagonistic muscles [73, 78, 79] and cutaneous afferents [80], as well as from the descending tracts such as rubrospinal tract [81] and corticospinal tract [82, 83]. How the nervous system affects these different pathways to reach the desired level of activity in literally thousands of motoneurons remains a mystery in neuroscience research.

3.3. Functional Significance of Presynaptic Inhibition. Presynaptic inhibition of Ia afferents is highly modifiable in response to postural changes [10] and motor tasks [84, 85]. Presynaptic modulation of Ia inflow could be a physiologic mechanism for adjusting the amount of feedback to the central nervous system.

Homonymous [86] as well as heteronymous [87] muscle afferents can presynaptically affect the sensory inflow of a given Ia afferent. These sources, due to their origin, are regarded as peripheral sources for presynaptic modulation. There are, on the other hand, centers in the brain (such as the red nucleus and vestibular nuclei) which can also affect the presynaptic terminals through their descending drive. Such a central influence on presynaptic interneurons can be collectively regarded as a central source for presynaptic modulation.

There is evidence to show that peripheral and central drives merge to the same common PAD interneurons [88] and therefore, these two sources can interact and integrate at the level of spinal cord [89]. Such an interaction can modify a reflexive activity that would elicit a large amplitude perturbation.

Taken together, it can be argued that adjusting the amount of presynaptic inhibition through the interaction of central and peripheral inputs has an important role in the execution of voluntary movements. For these reasons, it is now difficult to differentiate between reflexive and voluntary movements [90]. Whereas data indicate that presynaptic inhibition can significantly influence movement, it is not the only inhibitory mechanism in the spinal cord that has an effect on motor behavior. Other mechanisms such as postactivation depression [61], recurrent inhibition [91], and reciprocal inhibition [92, 93] all have functional roles in the control and execution of movement. However, prevailing evidence [16, 63, 80, 94–99] suggests that presynaptic inhibition has a critical role in the regulation of movement.

On the other hand, presynaptic inhibition has been repetitively shown to be modifiable in response to motor practice and learning new skills. In the following sections, we briefly review some key studies which have demonstrated short-term and long-term adaptations of the spinal circuits.

3.4. Goal Directed Changes in Presynaptic Inhibition of Ia Fiber Inputs to the Spinal Cord. During normal movement execution, such as changes in posture [100], movement initiation [101], and gait [102], presynaptic inhibition has been shown to be modulated. Besides the naturally occurring task specific modulation of presynaptic inhibition, the amount of presynaptic modulation expressed on spinal circuits is trainable. There is ample evidence in the literature to show that the amount of presynaptic inhibition can be purposefully changed. The experimental methods used to document this inhibition generally fall into operant conditioning of the reflexes and task-related feedback conditioning of the reflexes. It should be emphasized that none of these protocols exclusively target the PI circuits; rather, they exert various changes on spinal and/or even supraspinal circuits including alterations in presynaptic inhibition. However, both protocols can produce short-term as well as long-term changes in the neural circuits of the reflex pathway.

In operant-conditioning protocols, there seems to be a complex interaction of mechanisms involved in the induced plasticity including presynaptic modulation of the Ia terminals, specifically for the short-term adaptation phase [103]. While operant conditioning does not usually involve any specific task, there are protocols specially designed to modulate the H-reflex to fulfill some experimentally defined functional task. These task-related-feedback conditioning protocols usually provide feedback to the subject after each trial. Trimble and Koceja were the first to successfully implement such a functional protocol for short-term changes in spinal reflexes [97]. Their protocol involved a balance-control task in which subjects stood on a tilt board and were instructed to maintain their balance in a highly precarious posture. Applying an electrical stimulation for eliciting the H-reflex to the bilateral soleus muscles during this task produced enough ankle torque to destabilize the subjects during the trial. Over a single session of practice, subjects were able to learn to depress the H-reflex to minimize the destabilizing torque, as a strategy to maintain balance subsequent testing of the same subjects on a solid surface (normal upright standing) revealed that the H-reflex amplitude remained depressed for more than 30 minutes after the termination of the training session [97]. An ensuing study examined the effect of multisession training on the maintenance of the suppressed H-reflex. Two hours of H-reflex suppression training for three days significantly reduced the amplitude of the H-reflex which showed a trend to remain depressed for a longer period of time posttraining [98].

Such types of training-induced plasticity have also been observed in more complex movements. In a novel locomotion study, subjects were trained to walk backward on a treadmill for several weeks. In untrained subjects a large amplitude H-reflex was observed during the midswing phase of walking. Training progressively reduced the amplitude of the reflex. However, these changes in the reflex amplitude were not related to leg muscle motor evoked potentials (MEPs). It was suggested that the plasticity induced in the H-reflex circuits was heavily dependent on the presynaptic control of the inflow of sensory information [99]. It is interesting that a comparison of the results of studies using task-related-feedback conditioning with those using operant conditioning suggests that the two methods produce relatively the same percentage of change in the H-reflex. What remains to be determined, and may be an important distinction, is whether these two types of feedback result in the same types of functional and/or behavioral consequences. Studies using operant conditioning as a method for functional motor improvement have already been initiated, and thus far have provided promising results [104–106].

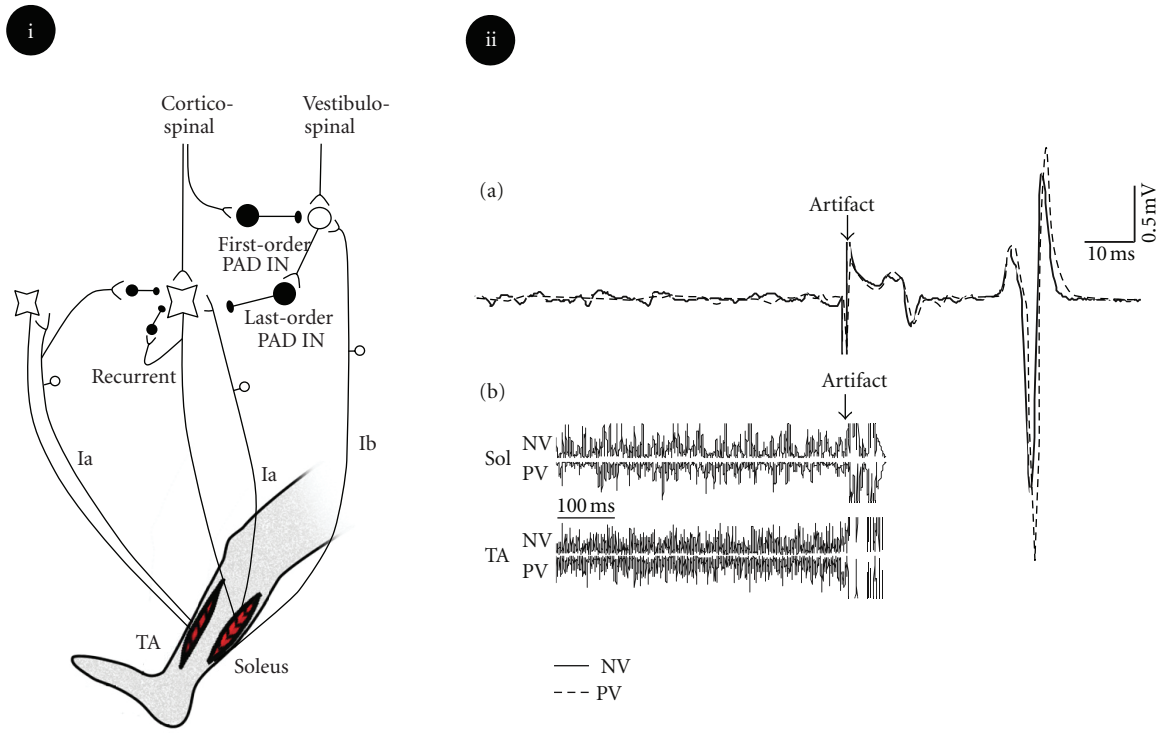


Figure 1: Presynaptic inhibition to Ia fibers. (i) Schematic diagram of different inputs to Ia afferents and alpha motoneurons. Proprioceptive input from Ia fiber can be selectively suppressed by presynaptic inhibition through PAD interneurons. The interneuron which makes axoaxonic connection with Ia fiber is GABAergic and regarded as last-order PAD IN. This interneuron is under the influence of an excitatory interneuron which is referred to as first-order PAD IN. This first-order PAD IN receives inputs from both descending tracts and from peripheral afferents [15]. In such a case, different inputs can interact to control the Ia input to motoneurons without affecting the intrinsic properties of motoneurons. (ii) During presynaptic inhibition, the normal activity of the muscle can remain unchanged, while the reflex gain reduces. In this example, standing with prism goggles (PV condition) suppressed the H-reflex in comparison to normal vision (NV) standing condition (a), while there was no change in the soleus and tibialis anterior muscle EMG activity (b). This is most likely due to the presynaptic inhibition of Ia fibers which spares the background activity of motoneurons. Part II adapted with permission from [16].

3.5. Practice Makes Permanence. In humans, it has been clearly established that long-term, repetitive activity produces changes in the reflex arc. For example, strength training has been shown to increase H-reflex amplitude; 14 weeks of muscle-specific heavy resistance training can increase the soleus H-reflex amplitude by 20% [107]. Research has also shown that ipsilateral resistance training increases the strength of both limbs, most likely due to neural adaptation, but that the H-reflex amplitude increases only in the trained side [108]. This finding supports the idea that direct increase in sensory inflow is necessary for the induction of plasticity in spinal circuits.

As another example, several studies have shown that the amplitude of the H-reflex is significantly reduced in trained dancers [51–53]. The reduction in the H-reflex amplitude is presumed to be caused by long-term performance of dance specific movements. Cocontraction of the lower limb muscles, which is frequently utilized in ballet dance, induces an increase in presynaptic inhibition, and causes a reduction in reciprocal inhibition. This activity-induced change in the H-reflex is most likely a part of the process of acquiring high-level skill and maintaining balance for dance-specific techniques. This reduction in response to peripheral sensory input could also be interpreted as an increase in a cortical role for the control of movement, and hence a more precise movement.

Taken together, these studies provide evidence that neural circuits can undergo long-lasting activity-induced plastic changes. However, these studies cannot unambiguously conclude that the plastic changes were induced solely in the spinal cord circuits. One possibility is that functional changes in these circuits are due to changes in descending drive rather than the spinal cord.

To determine whether the long-term changes occur at the spinal or supraspinal levels, Wolpaw and his colleagues examined the effect of operant conditioning on the stretch or the H-reflex in monkeys and human subjects [56, 109, 110]. Wolpaw and O'Keefe demonstrated both in monkeys and humans that the stretch reflex, as well as the H-reflex, can be down- or upregulated using operant conditioning. Wolpaw and colleagues also demonstrated that plasticity occurs in two distinct phases: an immediate (acute) phase which was observed in the same day of training (approximately 8–10% change) and a long lasting (approximately 1-2%/day

for many days) phase. The acute phase was readily observed in the stretch reflex but not the long-loop reflexes which are assumed to involve higher centers such as the cortices. This immediate phase was temporary and diminished within a few hours after the termination of the training session. However, by continuing the training sessions for 4–6 months in humans and monkeys, respectively, the plasticity became more permanent and the modulation persisted for months after termination of the training sessions. Severing the spinal cord after the reflexes were up- or downregulated (in two different groups of monkeys) did not diminish the up- or downregulated reflex [110], supporting the idea that the plasticity had resided within the spinal circuits.

3.6. Central versus Peripheral Contribution for the Induction of Plasticity and Memory Formation in the Spinal Cord. Acute changes in spinal pathways are believed to be triggered by descending inputs. However, changes in the descending input over a long period of time can produce permanent changes in the spinal cord which are regarded as spinal fixation. Animals with partial transection of the spinal cord with an intact corticospinal tract are still able to volitionally up- or downregulate the H-reflex in an operant conditioning protocol [111]. However, spinal circuits can undergo plastic changes in response to exercise and skill acquisition which is not dependent on corticospinal drive. Operant conditioning is a specific type of memory formation and due to its nature (volitional alteration of the reflexes based on the feedback and reward) the descending input is an indispensable part of it. While the results of the studies on operant conditioning have provided valuable information and insight about memory formation in spinal circuits, conclusions from these studies should be interpreted with caution. First, it should be considered that during an operant-conditioning task, changes in the amplitude of the reflexes are not necessarily the *consequences* of a motor demand. Second, no functional tasks are involved during classical operant conditioning, which means that this type of conditioning may not be behaviorally relevant and these results do not translate to real-life situations.

Does the spinal cord have the ability to acquire new motor skills without the need of the descending drive for this skill acquisition?

Spinalized cats are indeed able to develop functional tasks despite the permanent loss of descending input [112, 113]. Such task-dependent modulation in segmental reflexes have also been observed in spinalized human patients as well [114]. Unfortunately there are few studies performed on normal human subjects to parsimoniously demonstrate changes in the spinal circuits, independent from descending drive. One obvious reason for this scarcity of information is the difficulty in differentiating the role of descending and peripheral inputs to the spinal cord. It is possible that a given *pattern* of sensory input (such as that generated by a specific task) may induce plastic changes in spinal circuits without the involvement of descending drive. In an excellent investigation, Meunier and colleagues [115] examined this possibility by training the subjects to perform two different types of cycling movements. In one group subjects performed a cycling exercise in which the resistance of the pedaling changed every 15 seconds, and they were asked to keep the cycling speed constant (e.g., complex task). In a second group, subjects performed the same task under constant pedaling resistance (e.g., simple task). It was shown that homosynaptic depression (the depression in the Ia transmission of sensory information after an immediate preceding stimulation) substantially changed only in the complex task group. Since homosynaptic depression is confined exclusively to the previously activated Ia fibers and there is no anatomical connection from the upper centers, investigators concluded that it was the *pattern of sensory inflow* that produced the change in synaptic efficacy between the Ia afferents and the alpha motoneurons. Again, understanding this discrepancy is extremely important for the improvement of modern rehabilitation techniques for spinal cord injury patients.

4. From Behavior to Cellular Events and Back

The exact mechanism of long-term activity-dependent changes in spinal circuits is not yet well understood. In operant-conditioning experiments designed to modulate the reflexes, initially the induced changes (in terms of the modulation of the reflexes) are reversible and will be abolished if training is discontinued. However, by continuing the task, the changes in the amplitude of the reflexes become permanent. In contrast, in mature animals, the transection of the corticospinal tract before or during the learning phase prevents the induction of long-term plastic changes [111, 116, 117]. Histological analysis of alpha motoneurons that have undergone permanent changes have shown morphological changes in the C and F terminals of the neurons [109] as well as changes in the size of the motoneurons, their input resistance, and axonal conduction velocity [118]. Future research should focus on the mechanisms that trigger these changes in motoneurons.

Learning a new skill is accompanied by a novel combination of muscle activity patterns that are temporally and spatially timed. These novel biomechanical configurations produce new sensory information feedback to the nervous system. Timely coupling of the EPSPs with action potentials has been shown to alter synaptic efficacy [119]. The backfiring of action potentials from the axon to the dendrites, if coincident with the EPSP, can affect the EPSP magnitude and potentially alter synaptic strength. A similar mechanism could exist in the spinal cord which affects the synaptic efficacy through the timed arrival of the sensory input coincident with descending commands. Interestingly, blocking NMDA receptors prevents the modulatory effect of action potential on the EPSPs. The studies on long-term potentiation (LTP) and long-term depression (LTD) could be used as evidence to show that such timely coupled inputs could lead to the consolidation of new skills in the spinal circuits. LTP and LTD have been experimentally induced in superficial dorsal horn [120], intermediate gray area [121], and ventral horn [122] of the spinal cord, and blocking

Table 1: Different aspects of activity-dependent spinal plasticity in the developing and a mature spinal cord, discussed in this paper.

	Developing	Mature
Cat-301	Increase in response to movement and sensory input to SC during critical period. Large nerve crush inhibits the expression of the antibody.	Not substantial. After the critical period, nerve crush does not affect the expression of the antibody.
NMDA receptors	Have role in the induction of synaptic plasticity. Probably have role in the induction of morphological changes. Have role in dendritic growth and retraction.	Blocking the receptors does not affect motoneuron morphology. These receptors are being eliminated from almost all parts of the spinal cord except for substantia gelatinosa. Likely do not have substantial role in reflex transmission.
Elimination	Substantial elimination during maturation. Cortical connections to the ipsilateral side of the spinal cord will be eliminated during maturation. Dendrites grow and retract. This is a model of non-Hebbian activity dependent process. At the neuromuscular junction, many synaptic connections are lost which results in muscle fibers from polyneural innervation to mononeural innervation [23, 24].	Synaptic connections mostly follow Hebbian process. Activity-dependent plasticity does not seem to eliminate synapses.
Sensory input	Sensory input is essential for developing spinal cord. Sensory information generated my movement seems to have role in the development of spinal synapses and circuits.	Have role in both transitional as well as permanent changes in the spinal circuits. Pattern of sensory input has been shown to have role in the induction of plastic changes.
Presynaptic modulation	Likely presynaptic inhibition exists in infants and is being modulated in response to movement. However, the role of presynaptic inhibition in the acquisition of new skills in newborn infants and children has not been extensively studied. Recent studies on mouse models have shown that undernourishment substantially decreases the amount of presynaptic inhibition [25]	Has important role in the modulation of reflex gain during different movements, at the initiation of movement, and for postural control. Skill acquisition (such as dance) can permanently change the amount of presynaptic inhibition. Presynaptic inhibition can also be increased or decreased through operant conditioning (absence of any functional task) and task-related feedback conditioning (presence of a functional task)
Descending influence	Has important role in the expression of Cat-301 and in the elimination of synapses through development.	Has important role in the induction of plastic changes in spinal cord during skill acquisition, operant conditioning and movement control and modulation of presynaptic inhibition, and other spinal mechanisms.

NMDA receptors prevents LTP induction in these regions. Interestingly, EPSPs are not affected by NMDAR blockade, but blocking non-NMDA receptors substantially diminishes EPSPs. Therefore, under normal conditions, non-NMDA receptors appear to be predominantly responsible for the generation of EPSP's. Furthermore, it seems that NMDA receptors do not have a critical role in the maintenance of LTP, since blocking NMDA receptors after LTP induction has no effect on LTP. Conversely, blocking non-NMDA receptors after LTP induction substantially decreases LTP expression, demonstrating that non-NMDA receptors are necessary for the maintenance of LTP. Consistent with *in vitro* and *in vivo* animal studies, blocking NMDA receptors in human subjects using Dextromethorphan interferes with the acquisition of motor memory but does not impair motor memory recall [123].

The studies that have shown LTP in other areas of spinal cord have not investigated the mechanisms of LTP induction and maintenance, but it is unlikely that the role of NMDA receptors in LTP induction and maintenance is topographically distinct across spinal cord regions. A direct study between LTP and reflex regulation has not yet been reported however, it would be of value to examine the effect of NMDA receptor antagonists on the induction of H-reflex upregulation. If a behaving animal, treated with NMDA antagonist to the substantia gelatinosa, cannot upregulate the H-reflex, this might suggest the importance of the substantia gelatinosa on the memory capacity of the spinal cord for movement regulation. Such investigations on NMDA receptors might provide new advances for the restoration of spinal ability and motor control. Increasing the basic knowledge of activity-dependent plasticity throughout the life span of humans can substantially influence the treatment and rehabilitation methods used for various neurological conditions.

5. Concluding Remarks

Spinal circuits possess the ability for plastic changes to fulfill short- and long-term motor demands. These reversible changes in spinal circuits are typically accompanied by alterations in synaptic strength for acute adaptations, and by morphological and electrophysiological changes for long-term adaptations. Examining the modulation of spinal

reflexes during different tasks has provided much of our understanding about activity-dependent plasticity in the spinal cord. During normal walking, for example, stretch reflexes are modulated differently compared with upright standing. The amplitude of the stretch reflex is not constant throughout the cycle of gait, and the phases of gait also affect the strength of the stretch reflex. Practicing a particular skill for extended periods of time can also affect the amplitude of the reflexes. Such changes in reflex gain have been shown to be associated with the degree of performance. For example, the ability of subjects to maintain a constant pedaling speed against varying the resistance during the bout of exercise was shown to be strongly correlated to the degree of H-reflex modulation [124]. These findings open the doors for seeking rehabilitation methods to specifically train reflexes with the aim of improving the function. During motor pathologies, such as spinal cord injury or brain damage, spinal reflexes still pose the ability to be modified [125]. It is only through goal-directed, precise rehabilitation strategies that potential plastic abilities of the spinal circuits can be used to regain function. Therefore, understanding the mechanisms and sites of plasticity within spinal circuits is essential for the development of new methods that can be used to regain spinal cord function, including the control of movement, after injury. Table 1 summarizes the topics reviewed in this paper and provides a brief comparison about the factors which are involved in the plasticity of the developing and mature spinal cord.

Acknowledgment

The authors wish to thank Ms. Lauren M. Rudolph, Indiana University Program in Neuroscience for her critical evaluation and comments on the manuscript.

References

[1] D. H. Hubel and T. N. Wiesel, "The period of susceptibility to the physiological effects of unilateral eye closure in kittens.," *Journal of Physiology*, vol. 206, no. 2, pp. 419–436, 1970.

[2] D. H. Hubel and T. N. Wiesel, "Receptive fields of cells in striate cortex of very young, visually inexperienced kittens," *Journal of Neurophysiology*, vol. 26, pp. 994–1002, 1963.

[3] T. N. Wiesel and D. H. Hubel, "Single-cell responses in striate cortex of kittens deprived of vision in one eye," *Journal of Neurophysiology*, vol. 26, pp. 1003–1017, 1963.

[4] D. H. Hubel and T. N. Wiesel, "Effects of monocular deprivation in kittens," *Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie*, vol. 248, no. 6, pp. 492–497, 1964.

[5] T. N. Wiesel and D. H. Hubel, "Extent of recovery from the effects of visual deprivation in kittens.," *Journal of Neurophysiology*, vol. 28, no. 6, pp. 1060–1072, 1965.

[6] C. Assaiante and B. Amblard, "An ontogenetic model for the sensorimotor organization of balance control in humans," *Human Movement Science*, vol. 14, no. 1, pp. 13–43, 1995.

[7] P. R. Zelazo, N. A. Zelazo, and S. Kolb, "'Walking' in the newborn," *Science*, vol. 176, no. 4032, pp. 314–315, 1972.

[8] J. R. Wolpaw and A. M. Tennissen, "Activity-dependent spinal cord plasticity in health and disease," *Annual Review of Neuroscience*, vol. 24, pp. 807–843, 2001.

[9] M. Butz, F. Wörgötter, and A. van Ooyen, "Activity-dependent structural plasticity," *Brain Research Reviews*, vol. 60, no. 2, pp. 287–305, 2009.

[10] D. M. Koceja, C. A. Markus, and M. H. Trimble, "Postural modulation of the soleus H reflex in young and old subjects," *Electroencephalography and Clinical Neurophysiology*, vol. 97, no. 6, pp. 387–393, 1995.

[11] M. H. Woollacott, A. Shumway-Cook, and L. M. Nashner, "Aging and posture control: changes in sensory organization and muscular coordination," *International Journal of Aging and Human Development*, vol. 23, no. 2, pp. 97–114, 1986.

[12] A. Nardone, R. Siliotto, M. Grasso, and M. Schieppati, "Influence of aging on leg muscle reflex responses to stance perturbation," *Archives of Physical Medicine and Rehabilitation*, vol. 76, no. 2, pp. 158–165, 1995.

[13] D. L. Sturnieks, R. St George, and S. R. Lord, "Balance disorders in the elderly," *Neurophysiologie Clinique*, vol. 38, no. 6, pp. 467–478, 2008.

[14] D. H. Romero and G. E. Stelmach, "Changes in postural control with aging and Parkinson's disease," *IEEE Engineering in Medicine and Biology Magazine*, vol. 22, no. 2, pp. 27–31, 2003.

[15] E. Pierrot-Deseilligny and D. Burke, *The Circuitry of the Human Spinal Cord*, Cambridge University Press, Cambridge, UK, 2005.

[16] B. Tahayori, N. L. Port, and D. M. Koceja, "The inflow of sensory information for the control of standing is graded and bidirectional," *Experimental Brain Research*, vol. 218, no. 1, pp. 111–118, 2012.

[17] D. Purves and J. W. Lichtman, *Principles of Neural Development*, Sinauer Associates, Sunderland, Mass, USA, 1985.

[18] K. Sharma, A. E. Leonard, K. Lettieri, and S. L. Pfaff, "Genetic and epigenetic mechanisms contribute to motor neuron pathfinding," *Nature*, vol. 406, no. 6795, pp. 515–519, 2000.

[19] T. N. Wiesel, "Postnatal development of the visual cortex and the influence of environment," *Nature*, vol. 299, no. 5884, pp. 583–591, 1982.

[20] S. Conradi and L. O. Ronnevi, "Ultrastructure and synaptology of the initial axon segment of cat spinal motoneurons during early postnatal development," *Journal of Neurocytology*, vol. 6, no. 2, pp. 195–210, 1977.

[21] S. Hockfield and R. G. Kalb, "Activity-dependent structural changes during neuronal development," *Current Opinion in Neurobiology*, vol. 3, no. 1, pp. 87–92, 1993.

[22] R. G. Kalb and S. Hockfield, "Activity-dependent development of spinal cord motor neurons," *Brain Research Reviews*, vol. 17, no. 3, pp. 283–289, 1992.

[23] W. J. Thompson, "Activity and synapse elimination at the neuromuscular junction," *Cellular and Molecular Neurobiology*, vol. 5, no. 1-2, pp. 167–182, 1985.

[24] Y. Liu, R. D. Fields, S. Fitzgerald, B. W. Festoff, and P. G. Nelson, "Proteolytic activity, synapse elimination, and the Hebb synapse," *Journal of Neurobiology*, vol. 25, no. 3, pp. 325–335, 1994.

[25] S. Q. González, B. S. Alegría, J. C. G. Olmos, and I. Jiménez-Estrada, "Effect of chronic undernourishment on the cord dorsum potentials and the primary afferent depolarization evoked by cutaneous nerves in the rat spinal cord," *Brain Research Bulletin*, vol. 85, no. 1-2, pp. 68–74, 2011.

[26] R. G. Kalb and S. Hockfield, "Large diameter primary afferent input is required for expression of the Cat-301 proteoglycan on the surface of motor neurons," *Neuroscience*, vol. 34, no. 2, pp. 391–401, 1990.

[27] R. G. Kalb and S. Hockfield, "Molecular evidence for early activity-dependent development of hamster motor neurons," *Journal of Neuroscience*, vol. 8, no. 7, pp. 2350–2360, 1988.

[28] S. Farkas and H. Ono, "Participation of NMDA and non-NMDA excitatory amino acid receptors in the mediation of spinal reflex potentials in rats: an in vivo study," *British Journal of Pharmacology*, vol. 114, no. 6, pp. 1193–1205, 1995.

[29] P. G. Nelson, R. D. Fields, C. Yu, and E. A. Neale, "Mechanisms involved in activity-dependent synapse formation in mammalian central nervous system cell cultures," *Journal of Neurobiology*, vol. 21, no. 1, pp. 138–156, 1990.

[30] R. D. Fields, C. Yu, and P. G. Nelson, "Calcium, network activity, and the role of NMDA channels in synaptic plasticity in vitro," *Journal of Neuroscience*, vol. 11, no. 1, pp. 134–146, 1991.

[31] R. G. Kalb, "Regulation of motor neuron dendrite growth by NMDA receptor activation," *Development*, vol. 120, no. 11, pp. 3063–3071, 1994.

[32] R. G. Kalb and A. J. Fox, "Synchronized overproduction of AMPA, Kainate, and NMDA glutamate receptors during human spinal cord development," *Journal of Comparative Neurology*, vol. 384, no. 2, pp. 200–210, 1997.

[33] R. G. Kalb, M. S. Lidow, M. J. Halsted, and S. Hockfield, "N-methyl-D-aspartate receptors are transiently expressed in the developing spinal cord ventral horn," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 18, pp. 8502–8506, 1992.

[34] J. Sandkühler, J. G. Chen, G. Cheng, and M. Randić, "Low-frequency stimulation of afferent aδ-fibers induces long-term depression at primary afferent synapses with substantia gelatinosa neurons in the rat," *Journal of Neuroscience*, vol. 17, no. 16, pp. 6483–6491, 1997.

[35] R. L. Michaels and S. M. Rothman, "Glutamate neurotoxicity in vitro: antagonist pharmacology and intracellular calcium concentrations," *Journal of Neuroscience*, vol. 10, no. 1, pp. 283–292, 1990.

[36] T. M. Laughlin, T. W. Vanderah, J. Lashbrook et al., "Spinally administered dynorphin A produces long-lasting allodynia: involvement of NMDA but not opioid receptors," *Pain*, vol. 72, no. 1-2, pp. 253–260, 1997.

[37] J. A. Eyre, "Development and plasticity of the corticospinal system in man.," *Neural Plasticity*, vol. 10, no. 1-2, pp. 93–106, 2003.

[38] J. A. Eyre, J. P. Taylor, F. Villagra, M. Smith, and S. Miller, "Evidence of activity-dependent withdrawal of corticospinal projections during human development," *Neurology*, vol. 57, no. 9, pp. 1543–1554, 2001.

[39] M. P. Galea and I. Darian-Smith, "Multiple corticospinal neuron populations in the macaque monkey are specified by their unique cortical origins, spinal terminations, and connections," *Cerebral Cortex*, vol. 4, no. 2, pp. 166–194, 1994.

[40] J. Uematsu, K. Ono, T. Yamano, and M. Shimada, "Development of corticospinal tract fibers and their plasticity II. Neonatal unilateral cortical damage and subsequent development of the corticospinal tract in mice," *Brain and Development*, vol. 18, no. 3, pp. 173–178, 1996.

[41] M. Bax, M. Goldstein, P. Rosenbaun et al., "Proposed definition and classification of cerebral palsy, April 2005," *Developmental Medicine and Child Neurology*, vol. 47, no. 8, pp. 571–576, 2005.

[42] L. J. Carr, L. M. Harrison, A. L. Evans, and J. A. Stephens, "Patterns of central motor reorganization in hemiplegic cerebral palsy," *Brain*, vol. 116, no. 5, pp. 1223–1247, 1993.

[43] M. Hodapp, C. Klisch, W. Berger, V. Mall, and M. Faist, "Modulation of soleus H-reflexes during gait in healthy children," *Experimental Brain Research*, vol. 178, no. 2, pp. 252–260, 2007.

[44] M. Hodapp, J. Vry, V. Mall, and M. Faist, "Changes in soleus H-reflex modulation after treadmill training in children with cerebral palsy," *Brain*, vol. 132, no. 1, pp. 37–44, 2009.

[45] M. Hodapp, C. Klisch, V. Mall, J. Vry, W. Berger, and M. Faist, "Modulation of soleus H-reflexes during gait in children with cerebral palsy," *Journal of Neurophysiology*, vol. 98, no. 6, pp. 3263–3268, 2007.

[46] T. Ohno, H. Maeda, N. Murabe et al., "Specific involvement of postsynaptic GluN2B-containing NMDA receptors in the developmental elimination of corticospinal synapses," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 34, pp. 15252–15257, 2010.

[47] C. Kukulka, "Principles of neuromuscular excitation," in *Electrotherapy in Rehabilitation*, M. Gersh, Ed., pp. 3–25, Davis, Philadelphia, Pa, USA, 1992.

[48] M. Knikou, "The H-reflex as a probe: pathways and pitfalls," *Journal of Neuroscience Methods*, vol. 171, no. 1, pp. 1–12, 2008.

[49] H. Morita, N. Petersen, L. O. D. Christensen, T. Sinkjær, and J. Nielsen, "Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans," *Journal of Neurophysiology*, vol. 80, no. 2, pp. 610–620, 1998.

[50] M. Enríquez-Denton, H. Morita, L. O. D. Christensen, N. Petersen, T. Sinkjaer, and J. B. Nielsen, "Interaction between peripheral afferent activity and presynaptic inhibition of Ia afferents in the cat," *Journal of Neurophysiology*, vol. 88, no. 4, pp. 1664–1674, 2002.

[51] D. M. Koceja, J. R. Burke, and G. Kamen, "Organization of segmental reflexes in trained dancers," *International Journal of Sports Medicine*, vol. 12, no. 3, pp. 285–289, 1991.

[52] J. Nielsen, C. Crone, and H. Hultborn, "H-reflexes are smaller in dancers from the Royal Danish Ballet than in well-trained athletes," *European Journal of Applied Physiology and Occupational Physiology*, vol. 66, no. 2, pp. 116–121, 1993.

[53] R. Ryder, K. Kitano, and D. M. Koceja, "Spinal reflex adaptation in dancers changes with body orientation and role of pre-synaptic inhibition.," *Journal of Dance Medicine & Science*, vol. 14, no. 4, pp. 155–162, 2010.

[54] J. R. Wolpaw and C. L. Lee, "Memory traces in primate spinal cord produced by operant conditioning of H-reflex," *Journal of Neurophysiology*, vol. 61, no. 3, pp. 563–572, 1989.

[55] J. R. Wolpaw, "The education and re-education of the spinal cord," *Progress in Brain Research*, vol. 157, pp. 261–280, 2006.

[56] J. R. Wolpaw, D. J. Braitman, and R. F. Seegal, "Adaptive plasticity in primate spinal stretch reflex: initial development," *Journal of Neurophysiology*, vol. 50, no. 6, pp. 1296–1311, 1983.

[57] D. L. Glanzman, "Common mechanisms of synaptic plasticity in vertebrates and invertebrates," *Current Biology*, vol. 20, no. 1, pp. R31–R36, 2010.

[58] F. B. Krasne and J. S. Bryan, "Habituation: regulation through presynaptic inhibition," *Science*, vol. 182, no. 4112, pp. 590–592, 1973.

[59] R. Melzack and P. D. Wall, "Pain mechanisms: a new theory," *Science*, vol. 150, no. 3699, pp. 971–979, 1965.

[60] H. Hultborn, S. Lindstrom, and H. Wigstrom, "On the function of recurrent inhibition in the spinal cord," *Experimental Brain Research*, vol. 37, no. 2, pp. 399–403, 1979.

[61] H. Hultborn, M. Illert, J. Nielsen, A. Paul, M. Ballegaard, and H. Wiese, "On the mechanism of the post-activation

depression of the H-reflex in human subjects," *Experimental Brain Research*, vol. 108, no. 3, pp. 450–462, 1996.

[62] C. Crone and J. Nielsen, "Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot," *Journal of Physiology*, vol. 416, pp. 255–272, 1989.

[63] 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," *Journal of Physiology*, vol. 389, pp. 757–772, 1987.

[64] D. R. Earles, D. M. Koceja, and C. W. Shively, "Environmental changes in soleus H-reflex excitability in young and elderly subjects," *International Journal of Neuroscience*, vol. 105, no. 1-4, pp. 1–13, 2000.

[65] J. Duysens, A. A. M. Taxl, B. Van der Doelen, M. Trippel, and V. Dietz, "Selective activation of human soleus or gastrocnemius in reflex responses during walking and running," *Experimental Brain Research*, vol. 87, no. 1, pp. 193–204, 1991.

[66] B. Larsen, N. Mrachacz-Kersting, B. A. Lavoie, and M. Voigt, "The amplitude modulation of the quadriceps H-reflex in relation to the knee joint action during walking," *Experimental Brain Research*, vol. 170, no. 4, pp. 555–566, 2006.

[67] N. Mrachacz-Kersting, B. A. Lavoie, J. B. Andersen, and T. Sinkjaer, "Characterisation of the quadriceps stretch reflex during the transition from swing to stance phase of human walking," *Experimental Brain Research*, vol. 159, no. 1, pp. 108–122, 2004.

[68] K. Frank and M. G. F. Fuortes, "Presynaptic and postsynaptic inhibition of monosynaptic reflexes," *Federation Proceedings*, vol. 16, pp. 39–40, 1957.

[69] K. Frank, "Basic mechanisms of synaptic transmission in the central nervous system," *IRE Transitions on Medical Electronics*, vol. 6, no. 2, pp. 85–88, 1959.

[70] P. Rudomin and R. F. Schmidt, "Presynaptic inhibition in the vertebrate spinal cord revisited," *Experimental Brain Research*, vol. 129, no. 1, pp. 1–37, 1999.

[71] W. D. Willis, "John Eccles' studies of spinal cord presynaptic inhibition," *Progress in Neurobiology*, vol. 78, no. 3-5, pp. 189–214, 2006.

[72] J. C. Eccles, "Presynaptic inhibition in the spinal cord," in *Progress in Brain Research*, J. C. Eccles and J. P. Schadé, Eds., pp. 65–91, Elsevier, 1964.

[73] J. Eccles, F. Magni, and W. Willis, "Depolarization of central terminals of Group I afferent fibres from muscle," *The Journal of Physiology*, vol. 160, no. 1, pp. 62–93, 1962.

[74] B. Graham and S. Redman, "A simulation of action potentials in synaptic boutons during presynaptic inhibition," *Journal of Neurophysiology*, vol. 71, no. 2, pp. 538–549, 1994.

[75] R. J. Miller, "Presynaptic receptors," *Annual Review of Pharmacology and Toxicology*, vol. 38, pp. 201–227, 1998.

[76] J. D. Clements, I. D. Forsythe, and S. J. Redman, "Presynaptic inhibition of synaptic potentials evoked in cat spinal motoneurones by impulses in single group Ia axons," *Journal of Physiology*, vol. 383, pp. 153–169, 1987.

[77] P. Rudomin, "In search of lost presynaptic inhibition," *Experimental Brain Research*, vol. 196, no. 1, pp. 139–151, 2009.

[78] J. C. Eccles, *The Physiology of Synapses*, Springer, Berlin, Germany, 1964.

[79] P. Rudomin, I. Jimenez, M. Solodkin, and S. Duenas, "Sites of action of segmental and descending control of transmission on pathways mediating PAD of Ia- and Ib-afferent fibers in cat spinal cord," *Journal of Neurophysiology*, vol. 50, no. 4, pp. 743–769, 1983.

[80] K. Seki, S. I. Perlmutter, and E. E. Fetz, "Sensory input to primate spinal cord is presynaptically inhibited during voluntary movement," *Nature Neuroscience*, vol. 6, no. 12, pp. 1309–1316, 2003.

[81] T. Hongo, E. Jankowska, and A. Lundberg, "The rubrospinal tract. III. Effects on primary afferent terminals," *Experimental Brain Research*, vol. 15, no. 1, pp. 39–53, 1972.

[82] J. Nielsen and N. Petersen, "Is presynaptic inhibition distributed to corticospinal fibres in man?" *Journal of Physiology*, vol. 477, no. 1, pp. 47–58, 1994.

[83] 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.

[84] C. Capaday and R. B. Stein, "Amplitude modulation of the soleus H-reflex in the human during walking and standing," *Journal of Neuroscience*, vol. 6, no. 5, pp. 1308–1313, 1986.

[85] R. B. Stein and C. Capaday, "The modulation of human reflexes during functional motor tasks," *Trends in Neurosciences*, vol. 11, no. 7, pp. 328–332, 1988.

[86] H. Hultborn, S. Meunier, C. Morin, and E. Pierrot-Deseilligny, "Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat," *Journal of Physiology*, vol. 389, pp. 729–756, 1987.

[87] J. Nielsen and Y. Kagamihara, "The regulation of presynaptic inhibition during co-contraction of antagonistic muscles in man," *Journal of Physiology*, vol. 464, pp. 575–593, 1993.

[88] J. F. Iles, "Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb," *Journal of Physiology*, vol. 491, no. 1, pp. 197–207, 1996.

[89] J. B. Nielsen, "Sensorimotor integration at spinal level as a basis for muscle coordination during voluntary movement in humans," *Journal of Applied Physiology*, vol. 96, no. 5, pp. 1961–1967, 2004.

[90] A. Prochazka, F. Clarac, G. E. Loeb, J. C. Rothwell, and J. R. Wolpaw, "What do reflex and voluntary mean? Modern views on an ancient debate," *Experimental Brain Research*, vol. 130, no. 4, pp. 417–432, 2000.

[91] H. Hultborn and E. Pierrot-Deseilligny, "Changes in recurrent inhibition during voluntary soleus contractions in man studied by an H-reflex technique," *Journal of Physiology*, vol. 297, pp. 229–251, 1979.

[92] H. Morita, C. Crone, D. Christenhuis, N. T. Petersen, and J. B. Nielsen, "Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity," *Brain*, vol. 124, no. 4, pp. 826–837, 2001.

[93] T. Kasai, M. Kawanishi, and S. Yahagi, "Posture-dependent modulation of reciprocal inhibition upon initiation of ankle dorsiflexion in man," *Brain Research*, vol. 792, no. 1, pp. 159–163, 1998.

[94] D. R. Earles, J. T. Dierking, C. T. Robertson, and D. M. Koceja, "Pre- and post-synaptic control of motoneuron excitability in athletes," *Medicine and Science in Sports and Exercise*, vol. 34, no. 11, pp. 1766–1772, 2002.

[95] D. M. Koceja, M. H. Trimble, and D. R. Earles, "Inhibition of the soleus H-reflex in standing man," *Brain Research*, vol. 629, no. 1, pp. 155–158, 1993.

[96] R. G. Mynark and D. M. Koceja, "Down training of the elderly soleus H reflex with the use of a spinally induced balance perturbation," *Journal of Applied Physiology*, vol. 93, no. 1, pp. 127–133, 2002.

[97] M. H. Trimble and D. M. Koceja, "Modulation of the triceps surae H-reflex with training," *International Journal of Neuroscience*, vol. 76, no. 3-4, pp. 293–303, 1994.

[98] M. H. Trimble and D. M. Koceja, "Effect of a reduced base of support in standing and balance training on the soleus H-reflex," *International Journal of Neuroscience*, vol. 106, no. 1-2, pp. 1–20, 2001.

[99] R. V. Ung, M. A. Imbeault, C. Ethier, L. Brizzi, and C. Capaday, "On the potential role of the corticospinal tract in the control and progressive adaptation of the soleus H-reflex during backward walking," *Journal of Neurophysiology*, vol. 94, no. 2, pp. 1133–1142, 2005.

[100] R. M. Angulo-Kinzler, R. G. Mynark, and D. M. Koceja, "Soleus H-reflex gain in elderly and young adults: modulation due to body position," *Journals of Gerontology A*, vol. 53, no. 2, pp. M120–M125, 1998.

[101] A. Eichenberger and D. G. Ruegg, "Relation between the specific H reflex facilitation preceding a voluntary movement and movement parameters in man," *Journal of Physiology*, vol. 347, pp. 545–559, 1984.

[102] M. Faist, V. Dietz, and E. Pierrot-Deseilligny, "Modulation, probably presynaptic in origin, of monosynaptic Ia excitation during human gait," *Experimental Brain Research*, vol. 109, no. 3, pp. 441–449, 1996.

[103] J. R. Wolpaw, "The complex structure of a simple memory," *Trends in Neurosciences*, vol. 20, no. 12, pp. 588–594, 1997.

[104] A. K. Thompson, Y. C. Xiang, and J. R. Wolpaw, "Acquisition of a simple motor skill: task-dependent adaptation plus long-term change in the human soleus H-reflex," *Journal of Neuroscience*, vol. 29, no. 18, pp. 5784–5792, 2009.

[105] Y. Chen, Y. C. Xiang, 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.

[106] A. K. Thompson, R. B. Stein, X. Y. Chen, and J. R. Wolpaw, "Modulation in spinal circuits and corticospinal connections following nerve stimulation and operant conditioning," in *Proceedings of the 28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS '06)*, pp. 2138–2141, September 2006.

[107] P. Aagaard, E. B. Simonsen, J. L. Andersen, P. Magnusson, and P. Dyhre, "Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses," *Journal of Applied Physiology*, vol. 92, no. 6, pp. 2309–2318, 2002.

[108] O. Lagerquist, E. P. Zehr, and D. Docherty, "Increased spinal reflex excitability is not associated with neural plasticity underlying the cross-education effect," *Journal of Applied Physiology*, vol. 100, no. 1, pp. 83–90, 2006.

[109] K. C. Feng-Chen and J. R. Wolpaw, "Operant conditioning of H-reflex changes synaptic terminals on primate motoneurons," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 17, pp. 9206–9211, 1996.

[110] J. R. Wolpaw and J. A. O'Keefe, "Adaptive plasticity in the primate spinal stretch reflex: evidence for a two-phase process," *Journal of Neuroscience*, vol. 4, no. 11, pp. 2718–2724, 1984.

[111] Y. C. Xiang, J. S. Carp, L. Chen, and J. R. Wolpaw, "Corticospinal tract transection prevents operantly conditioned H-reflex increase in rats," *Experimental Brain Research*, vol. 144, no. 1, pp. 88–94, 2002.

[112] A. Frigon, M. D. Johnson, and C. J. Heckman, "Altered activation patterns by triceps surae stretch reflex pathways in acute and chronic spinal cord injury," *Journal of Neurophysiology*, vol. 106, no. 4, pp. 1669–1678, 2011.

[113] G. Barrière, A. Frigon, H. Leblond, J. Provencher, and S. Rossignol, "Dual spinal lesion paradigm in the cat: evolution of the kinematic locomotor pattern," *Journal of Neurophysiology*, vol. 104, no. 2, pp. 1119–1133, 2010.

[114] C. J. Dy, Y. P. Gerasimenko, V. R. Edgerton, P. Dyhre, G. Courtine, and S. J. Harkema, "Phase-dependent modulation of percutaneously elicited multisegmental muscle responses after spinal cord injury," *Journal of Neurophysiology*, vol. 103, no. 5, pp. 2808–2820, 2010.

[115] S. Meunier, J. Kwon, H. Russmann, S. Ravindran, R. Mazzocchio, and L. Cohen, "Spinal use-dependent plasticity of synaptic transmission in humans after a single cycling session," *Journal of Physiology*, vol. 579, no. 2, pp. 375–388, 2007.

[116] X. Y. Chen and J. R. Wolpaw, "Probable corticospinal tract control of spinal cord plasticity in the rat," *Journal of Neurophysiology*, vol. 87, no. 2, pp. 645–652, 2002.

[117] X. Y. Chen, L. Chen, and J. R. Wolpaw, "Conditioned H-reflex increase persists after transection of the main corticospinal tract in rats," *Journal of Neurophysiology*, vol. 90, no. 5, pp. 3572–3578, 2003.

[118] J. S. Carp and J. R. Wolpaw, "Motoneuron properties after operantly conditioned increase in primate H- reflex," *Journal of Neurophysiology*, vol. 73, no. 4, pp. 1365–1373, 1995.

[119] H. Markram, J. Lübke, 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.

[120] M. Ranclic, M. C. Jiang, and R. Cerne, "Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord," *Journal of Neuroscience*, vol. 13, no. 12, pp. 5228–5241, 1993.

[121] S. Pockett, "Long-term potentiation and depression in the intermediate gray matter of rat spinal cord in vitro," *Neuroscience*, vol. 67, no. 4, pp. 791–798, 1995.

[122] S. Pockett and A. Figurov, "Long-term potentiation and depression in the ventral horn of rat spinal cord in vitro," *NeuroReport*, vol. 4, no. 1, pp. 97–99, 1993.

[123] O. Donchin, L. Sawaki, G. Madupu, L. G. Cohen, and R. Shadmehr, "Mechanisms influencing acquisition and recall of motor memories," *Journal of Neurophysiology*, vol. 88, no. 4, pp. 2114–2123, 2002.

[124] R. Mazzocchio, T. Kitago, G. Liuzzi, J. R. Wolpaw, and L. G. Cohen, "Plastic changes in the human H-reflex pathway at rest following skillful cycling training," *Clinical Neurophysiology*, vol. 117, no. 8, pp. 1682–1691, 2006.

[125] M. Knikou, "Plasticity of corticospinal neural control after locomotor training in human spinal cord injury," *Neural Plasticity*, vol. 2012, Article ID 254948, 13 pages, 2012.

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 254948, 13 pages
doi:10.1155/2012/254948

Review Article

Plasticity of Corticospinal Neural Control after Locomotor Training in Human Spinal Cord Injury

Maria Knikou[1, 2, 3, 4]

[1] *Graduate Center and Physical Therapy Department, College of Staten Island, City University of New York, Staten Island, NY 10314, USA*
[2] *Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*
[3] *Sensory Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL 60611-2654, USA*
[4] *Electrophysiological Analysis of Gait and Posture Laboratory, Rehabilitation Institute of Chicago, Chicago, IL 60611, USA*

Correspondence should be addressed to Maria Knikou, maria.knikou@csi.cuny.edu

Received 14 February 2012; Revised 9 April 2012; Accepted 10 April 2012

Academic Editor: Marie-Hélène Canu

Spinal lesions substantially impair ambulation, occur generally in young and otherwise healthy individuals, and result in devastating effects on quality of life. Restoration of locomotion after damage to the spinal cord is challenging because axons of the damaged neurons do not regenerate spontaneously. Body-weight-supported treadmill training (BWSTT) is a therapeutic approach in which a person with a spinal cord injury (SCI) steps on a motorized treadmill while some body weight is removed through an upper body harness. BWSTT improves temporal gait parameters, muscle activation patterns, and clinical outcome measures in persons with SCI. These changes are likely the result of reorganization that occurs simultaneously in supraspinal and spinal cord neural circuits. This paper will focus on the cortical control of human locomotion and motor output, spinal reflex circuits, and spinal interneuronal circuits and how corticospinal control is reorganized after locomotor training in people with SCI. Based on neurophysiological studies, it is apparent that corticospinal plasticity is involved in restoration of locomotion after training. However, the neural mechanisms underlying restoration of lost voluntary motor function are not well understood and translational neuroscience research is needed so patient-orientated rehabilitation protocols to be developed.

1. Introduction

Spinal cord injuries (SCIs) cause substantial social, economic, and health burdens. In the majority of cases, the spinal cord is not completely severed and thus some fiber tracts and segmental spinal cord circuits remain intact [1], which determine the preserved functions and provide the basis for functional restoration. In incomplete SCI persons, recovery of sensorimotor function increases progressively during the first year [2], with reorganization of sensory and motor cortices [3] to lead to recovery of function and maladaptive behavior. In para- and tetraplegic patients, the cortical hand area was expanded towards the cortical leg area and was different based on the lesion level [4]. Further, in paraplegic patients the representation of the nonimpaired upper limb muscles was modified showing an increased activation in the corresponding primary motor cortex (M1), in the parietal cortex, supplementary motor area, and cerebellum [5]. An fMRI study in rats showed that after midthoracic spinal cord transection, deafferented hindlimb territories in S1 exhibited responses to electrical stimulation of the unaffected forepaw, presumably mediated by both spinothalamic and dorsal column nuclei pathways [6]. Evidence suggests that functional plasticity of motor cortical representations is mediated by an anatomical framework of preexisting projections that transverse representation borders [7].

In addition to spontaneous reorganization of the brain after SCI, spinal cord circuitries have the capacity to alter their structure and function with motor training [8], as supported by the physiological leg muscle activation patterns observed after locomotor training in spinalized animals [9–14]. Body weight-supported treadmill training (BWSTT) is a therapeutic approach in which a person with SCI steps on a motorized treadmill while some body weight is removed

through an upper body harness [15] and repetitive rhythmic leg movement patterns are promoted either through manual assistance provided by therapists or through a robotic exoskeleton system. Evidence that supports this intervention has been derived largely from studies conducted in spinalized animals [16–19]. Specifically, treadmill training increases axonal regrowth and collateral sprouting proximal to the lesion site in mice [20], phosphorylation of Erk1/2 in the motor cortex as well as the spinal cord injury area [21], expression of brain-derived neurotrophic factor (BDNF) in the spinal cord [22], ameliorates muscle atrophy in moderate contused SCI rats [23], and alters properties of spinal motor neurons [24]. These changes are only a small representation of activity-dependent plasticity located at the synaptic terminals of a variety of systems, that involves physiological, structural, and biochemical changes (see more in [25, 26]).

In humans, BWSTT improves lower extremity motor scores, increases the amplitude of muscle activity in the ankle extensors during the stance phase of walking, and improves walking ability and clinical outcome measures [27–31]. A recent single-blind, randomized clinical trial involving BWSTT with manual assistance, stimulation, over-ground training with stimulation and treadmill training with robotic assistance showed improvements in walking speed and distance [31]. Walking speed was not significantly different between groups, but distance gains were greatest with over-ground walking training. Further, lower extremity motor scores increased in all groups, regardless the type of intervention [31].

Based on the aforementioned findings, it is apparent that BWSTT contributes to restoration of locomotion. Because remodeling of neuronal circuits as a result of plasticity occurs at multiple sites of the central nervous system [8, 32] restoration of movement after training is anticipated to be the result of neural reorganization that occurs simultaneously in supraspinal and spinal cord circuits. The aim of this paper is to focus on the corticospinal neural plasticity after locomotor training in SCI.

2. Cortical Control of Locomotion

The corticospinal tract is the most direct pathway between the cerebral cortex and spinal cord with corticospinal axons monosynaptically synapsing onto spinal motor neurons. Even though neurons of the motor cortex are not required for simple locomotion, they exhibit a profound step-related frequency modulation in the cat [33–35]. This modulation is driven by a combination of signals from the spinal central pattern generators and sensory afferent feedback reflex mechanisms that support interlimb coordination [36]. The modulation of motor cortex neurons is necessary for accurate stepping on uneven terrain when adjustments of the limb trajectory are required to overstep an obstacle or to place the foot on a definite spot on the ground [37–39]. However, pyramidal tract stimulation evokes disynaptic excitatory postsynaptic potentials (EPSPs) in flexor motor neurons that are much bigger in the locomotor state than in the resting state, which are rhythmically modulated so that the facilitation occurs in the flexor-active phase [40]. While the spinal cord of vertebrates possesses the neural structures for genesis of the locomotor rhythm [41–43] and the spinal pattern generator plays a decisive role in the recovery of locomotion after incomplete SCI [12], lesions of the dorsolateral funiculi at Thoracic T13 level in the cat induced long-term deficits on the locomotor pattern [44], supporting that the corticospinal tract plays a prominent role in the neural control of locomotion.

The involvement of supraspinal neural control in human walking can be assessed by a variety of techniques utilized in isolation or in combination, including electroencephalography (EEG), electromyography (EMG), transcranial magnetic and electric stimulation (TMS and TES), and neuroimaging [45, 46]. Single-photon emission tomography and near-infrared spectroscopic topography have shown that the sensorimotor and supplementary motor cortices are activated during real and imagined locomotion [47, 48], while the prefrontal and premotor cortices were involved in adapting the locomotor speed on the treadmill [49]. A recent study postulated a significant coupling between EEG recordings over the leg motor area and EMG from the tibialis anterior (TA) muscle in the frequency band of 24–40 Hz prior to heel strike during the swing phase of walking [50], supporting a cortical involvement in human gait function [51]. (Time (cross-correlation) and frequency (coherence) domain techniques for the detection of coupling between signals provide an analytical framework from which functional coupling between localized cortical activity (measured by MEG or EEG) and motor output (EMG) can be identified in human subjects [52].)

A single stimulus of TMS produces a synchronized discharge of cortical interneurons and pyramidal neurons that travel down the corticospinal tract. Epidural electrodes in the spinal cord detect several waves following TMS, termed direct (D) and indirect (I) waves. I waves originate in the motor cortex most likely through activation of cortico-cortical projections onto corticospinal neurons [53], while D waves are thought to result from direct depolarization of the initial axon segment of the corticospinal neuron [46]. Recordings from the peripheral muscles demonstrate compound muscle action potentials known as motor evoked potentials (MEPs), which are a summation of multiple motor units depolarizing in response to D and I waves arriving onto the spinal motor neurons [54].

However, the MEP amplitude is not a reliable measure of corticospinal excitability. This is because TMS-induced action potentials in cortical axons spread transynaptically to many other neurons [55] that activate different descending pathways which are differently regulated during human movement [56]. Further, in order to support cortical excitability changes based on alterations of MEP amplitude due to motor plasticity, both need to be mediated by the same motor neurons and caused exclusively by direct monosynaptic projections from the motor cortex without any contamination through indirect interneuronal relays. The peaks in the peristimulus time histogram of the discharge probability of motor units induced by TMS have the same duration as those induced by Ia stimulation, and thus there is ample time for nonmonosynaptic effects to influence the MEP amplitude as

is the case for the H-reflex [57, 58]. Lastly, because MEPs are facilitated on average 12 ms before the reaction time to contraction during which antagonists are concomitantly facilitated by subcortical circuits [59, 60], it is apparent that they are sensitive to the excitability state of spinal α-motor neurons and interneurons [61].

The aforementioned limitations can be counteracted by reducing the TMS intensity below the MEP threshold. Direct recordings in awake human subjects have shown that TMS at subthreshold MEP intensities, which does not evoke any descending corticospinal volleys, depresses the MEP evoked by a subsequent suprathreshold TMS [62] and the EMG activity of ankle extensor muscles during the stance phase of walking, while the TA ongoing EMG activity is facilitated at a short-latency at early swing phase [63]. At subthreshold TMS intensities the excitability of spinal motor neurons at short latencies is influenced by intracortical inhibitory circuits and mechanisms [62, 64], including but not limited to intracortical and interhemispheric inhibition [65–70], that in turn influence soleus or TA coupled corticomotoneuronal cells. These findings support that cortical excitability changes can be assessed in awake humans and that cortical cells with direct motoneuronal connections change their excitability during human walking. Corticospinal drive of human locomotion is further addressed in Sections 3 and 4, whereas the cortical control of spinal reflex and interneuronal circuits is discussed.

2.1. Reorganization of Cortical Control of Motor Output after Training. Various training protocols in uninjured subjects induce reorganization of corticospinal actions on lumbosacral motor neurons. For example, balance training decreased the TA and soleus MEP amplitudes [71], while 32 min voluntary ankle dorsi- and plantar-flexion training increased the TA MEP amplitude regardless of the stimulation intensity level [72]. Repeated visuomotor skill training increased the maximal MEP and decreased the stimulation intensity needed to evoke an MEP, while opposite results were obtained after strength training [73], suggesting that reorganization of corticospinal actions on lumbosacral motor neurons depends on the type of training.

In motor incomplete SCI subjects at rest, MEPs are either absent or very small in amplitude with prolonged latencies, which are considered signs of impaired transmission of the fastest conducting corticospinal neurons [74–77]. Further, the absent or small TA MEPs prevail in SCI persons with increased foot drop [75]. Further, the peak coherence in the 10 to 20 Hz frequency band and synchronization within a narrow time band between paired TA EMG recordings taken during the swing phase were absent during the swing phase and were positively correlated to the degree of foot drop [75]. Because coherence in the frequency and time domain reflects the common synaptic drive, which may be corticospinal in origin, behavioral deficits in ambulatory SCI persons are driven by impaired corticospinal excitability.

Reorganization of corticospinal actions with training in neurological disorders has been shown in few studies. In 4 male SCI subjects with tetraparesis, *f*MRI showed a greater activation in sensorimotor cortical and cerebellar regions following 36 BWSTT sessions [78] consistent with the changes observed in the activation patterns of both hemispheres in poststroke subjects after 4 weeks of BWSTT [79]. Three-to-5 month BWSTT enhanced the MEP amplitude in 9 out of 13 muscles tested, increased the maximal MEP, and changed the slope of the MEP input-output curve in the majority of SCI subjects tested while seated [80]. Furthermore, in incomplete SCI participants whom their locomotor function improved following treadmill training, the coherence (24–40 Hz) of EMG activity, which is thought to indicate a common drive from corticospinal inputs, between antagonist muscles acting at the knee joint was increased and remained unaltered in participants that the locomotor ability was not improved [81]. The lower-frequency coherence (5–18 Hz), which is thought to contain common synaptic drive from spinal inputs, remained unchanged in both groups [81].

One person (49 yo female, 5 years after-injury) with an American Spinal Injury Association (ASIA) Impairment Scale (AIS) D at Thoracic 5–7 received 60 BWSTT sessions (1 h/day; 5 days/week) with a robotic exoskeleton device (Lokomat). Before training, the patient stepped at 0.5 m/s with 50% body weight support (BWS), and after training the patient stepped at 0.89 m/s with 20% BWS. Electrophysiological tests, illustrated as a schema in Figure 1, were conducted before and after training in the same patient while seated as well as during BWS assisted stepping. Data presented in this paper are original, have not been published elsewhere, and are from the same patient. Experiments and training were conducted following the written consent of the subject. All experimental procedures were approved by the Institutional Review Board of the Northwestern University IRB committee and were conducted in compliance with the 1964 Declaration of Helsinki.

The TA MEPs evoked at 1.3 TA MEP threshold during assisted stepping before and after training are shown in Figure 2. (The TA MEP threshold was established with the subject standing at equivalent BWS levels to that utilized during stepping. During stepping, TA MEPs were evoked randomly at different phases of the step cycle every 3 to 5 steps based on the signal from the ipsilateral foot switch. The step cycle of the right leg was divided into 16 equal time windows or bins.) Before training, the TA MEP amplitude was increased during early swing (bins 10–13) when compared to that observed at midstance (bins 3–5), but an MEP was not evocable from mid stance (bin 6) until swing phase initiation (bin 9). After training, the TA MEP amplitude increased significantly compared to that observed before training and was modulated in a phase-dependent pattern; that is, it was progressively depressed during the stance phase (bins 1–7) and was facilitated during the swing phase (bins 9–14) (Figure 2). This TA MEP modulation pattern during assisted stepping is consistent with that reported in uninjured subjects, which is generally increased when the muscle from which it is recorded is active and small when the antagonist muscle is active [82–84]. Although the findings reported in Figure 2 are from a single case, the altered MEP modulation pattern supports the notion that locomotor training alters the efficacy of corticospinal descending motor volleys

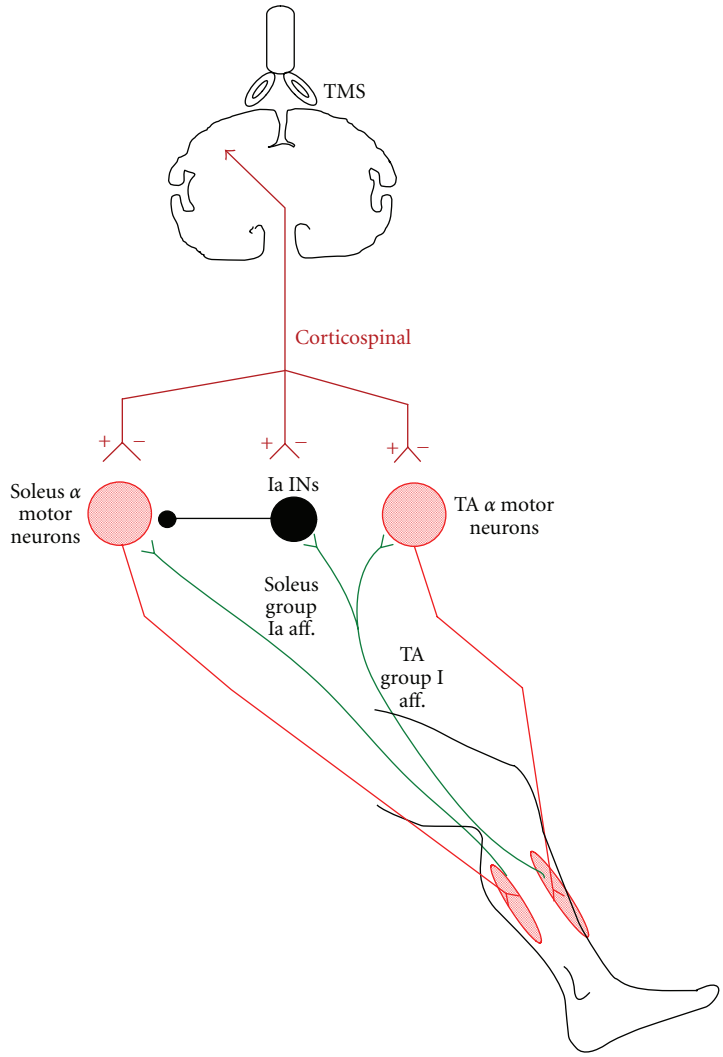


Figure 1: Schematic illustration of cortical control of spinal reflex circuits and spinal interneuronal circuits investigated after 60 sessions of locomotor training in the same SCI subject. The soleus H-reflex evoked by posterior tibial nerve stimulation, tibialis anterior (TA) muscle motor evoked potential (MEP), soleus H-reflex conditioned by subthreshold transcranial magnetic stimulation (TMS) delivered at an optimal site ("hot spot") for evoking an MEP in the right soleus muscle, soleus H-reflex depression by common peroneal nerve stimulation that is mediated by Ia inhibitory interneurons (Ia INs; reciprocal inhibition), and the reciprocal inhibition conditioned by subthreshold TMS delivered at an optimal site ("hot spot") for evoking an MEP in the right TA muscle were all investigated in the same patient at rest and/or during assisted stepping after locomotor training. Open triangles indicate excitatory synapses, while the filled circle indicates inhibitory synapses. The cortical control on these spinal circuits is indicated as a synapse that may increase (+) or decrease (−) actions of flexor-extensor α motor neurons and/or Ia inhibitory interneurons.

synapsing with TA spinal motor neurons in a manner that supports a physiologic gait pattern. It is apparent that more studies are needed on the neuronal mechanisms mediating improvement of locomotor function after training in spinal lesions of different segmental levels and types, in order that currently available rehabilitation strategies are optimized.

3. Cortical Control of Spinal Reflex Circuits

The spinal cord constitutes the final common pathway for segmental and supraspinal pathways underlying motor behavior. Electrical stimulation of a mixed peripheral nerve at low intensities activates primary (Ia) afferent axons which synapse in the spinal cord. Alpha motor neurons activated monosynaptically by Ia afferent volleys induce a synchronized reflex response known as the Hoffmann-(H-) reflex [85], which is the electrical analogue of the monosynaptic stretch reflex. When the H-reflex is used as a test reflex, the effects of conditioning volleys from other afferents or descending tracts on the motoneuron pool and synaptic actions from different sources in health and disease can be assessed [85, 86].

Cortical control of spinal reflex circuits has been extensively investigated in awake humans by means of TMS.

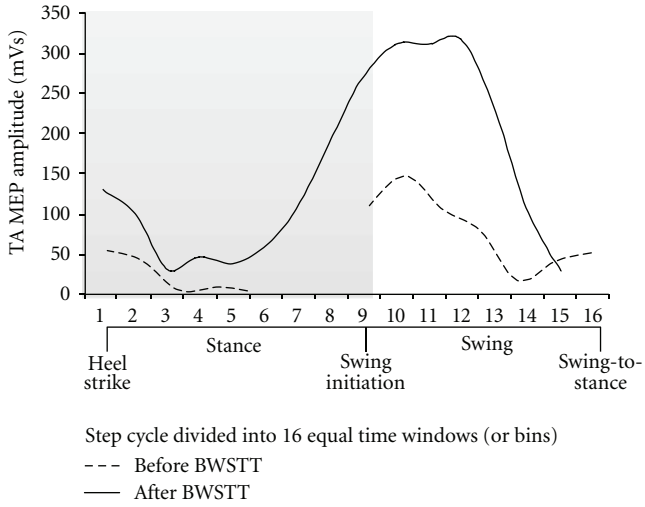


Figure 2: TA MEP modulation during stepping before and after locomotor training in SCI. The tibialis anterior (TA) motor evoked potential (MEP) amplitude before (dashed line) and after (solid line) 60 body weight-supported treadmill training (BWSTT) sessions is indicated as a function of the step cycle during body weight-supported (BWS) assisted stepping for one patient with American Spinal Injury Association (ASIA) Impairment Scale (AIS) D (49 yo female, 5 years after injury, T5–7). The TA MEP was evoked randomly every 3 to 4 steps at 1.3 times TA MEP threshold while stepping at 0.5 m/s with 50% BWS before training and at 0.89 m/s with 20% BWS after training. MEP threshold was established with subject standing at equivalent levels of BWS utilized during stepping. The step cycle was divided into 16 equal time windows or bins. Stance phase duration is identified by the grey region. Bin 1 corresponds to heel strike. Bins 8, 9, and 16 correspond approximately to stance-to-swing transition, swing phase initiation, and swing-to-stance transition, respectively.

Subthreshold TMS produces a short-latency inhibition on the soleus H-reflex followed by a period of facilitation [56, 87–89] with subjects at rest. In contrast, the TA H-reflex is facilitated at an early conditioning-test (C-T) interval [87]. Superficial peroneal or sural nerve stimulation potentiates the presumably monosynaptic facilitation of the TA H-reflex evoked by brain stimulation [90]. The cortical modulation of the soleus H-reflex depends largely on the position of the ankle joint, with subthreshold TMS to induce an early long-lasting facilitation or depression of the soleus H-reflex during tonic plantar flexion and dorsiflexion, respectively [87, 91]. Similar findings have been reported for pyramidal monkeys, cats, and baboons during which cortical inhibition predominated on the soleus and gastrocnemius monosynaptic reflex, while cortical facilitation influenced largely flexor motor neurons [92, 93]. It should be noted, however, that a single cortical D wave could produce changes in segmental motor neurons in the primates but not in the cat that required D and I waves or multiple D-waves [93].

In addition to the H-reflex, the TA long-latency (or M3) ankle stretch reflex was facilitated when the MEP arrived in the spinal cord at the same time [94]. However, subthreshold TMS intensities delivered 55–85 ms prior to the M3 depressed the long-latency TA stretch reflex [95]. Because the long-latency response was reduced in size following subthreshold TMS while the short-latency response remained unchanged [95, 96], it provides evidence that the long-latency stretch reflex is mediated in part by a transcortical path that can be affected by subthreshold TMS. During human walking, subthreshold TMS induces a short-latency, presumably monosynaptic, facilitation of the soleus H-reflex followed by a long-lasting inhibition [94]. Because potentiation of TA MEPs was synchronized with the peak TA ankle stretch reflex, corticospinal pathways are partly involved in the generation of spinal stretch reflexes during human walking [97, 98]. In human SCI, the conditioned H-reflex profile by subthreshold TMS varied significantly based on the AIS scores [99, 100]. In patients with severe paralysis (AIS A-B) an early or late soleus H-reflex facilitation by TMS was absent [99], suggesting for a nonphysiological interaction between descending inputs and spinal reflex excitability in patients with spastic paraparesis [100].

3.1. Reorganization of Cortical Control of Spinal Reflexes after Training. Persistent changes in H- or stretch reflex amplitudes may be regarded as signs of learning and plasticity as a result of training, which have been shown after various training protocols. For example, 30 min ankle cocontraction training decreased the ratio of maximal H-reflex versus maximal M wave (Hmax/Mmax) and improved motor performance defined as the difference between the maximum and minimum torque displacements within 1 min [101]. The soleus H-reflex amplitude was enhanced after 3 week isometric maximal plantar flexion training when measured at 20% and 60% of maximal voluntary contraction (MVC) [102], with similar results to be reported after 14 week of resistance training that involved heavy weight-lifting exercises for the leg muscles with reflexes measured during maximal isometric ramp contractions [103]. In contrast, 18 sessions eccentric strength training of the plantar flexor muscles for a 7 week period increased the Hmax/Mmax ratio during eccentric MVC but not during isometric or concentric contractions [104], suggesting that spinal reflex excitability is adjusted based on the type of exercise training protocol.

Nonetheless, the aforementioned changes in H-reflex amplitude can result from modifications of interneuronal circuits interposed in the spinal pathway or by changes on the strength of descending pathways, since the latter is potent regulator of spinal reflex circuits behavior [105–107]. This is supported by the failed operant conditioning of the H-reflex in rats when the corticospinal tract was transected at the spinal cord level [108, 109].

Limited evidence exists on plastic changes of the cortical control of spinal reflexes after locomotor training in neurological disorders. Forty BWSTT sessions in 29 patients with incomplete SCI reestablished the TMS-induced long-latency soleus H-reflex facilitation with subjects at rest [110]. It should be noted that BWS improves the efficacy of the sensorimotor cortex function [111], decreases the TA MEP threshold, and increases the map size for the TA in both hemispheres of stroke patients [112]. Nonetheless, when TMS effects on spinal reflexes are assessed with patients at

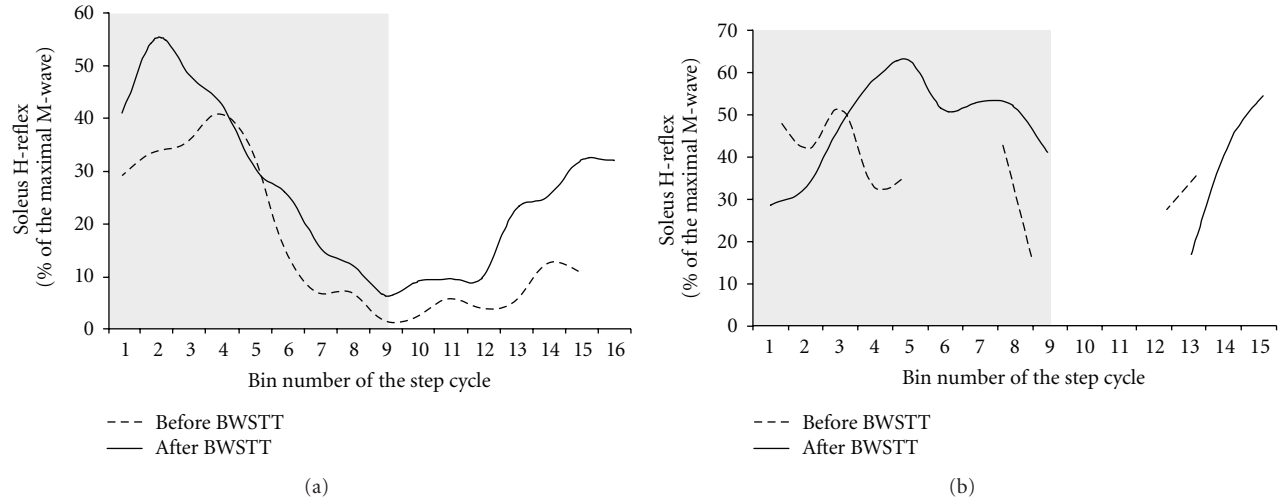


Figure 3: Soleus H-reflex modulation during assisted stepping before and after locomotor training in SCI. The unconditioned soleus H-reflex modulation before (dashed lines) and after (solid lines) 60 sessions of body weight-supported treadmill training (BWSTT) (a) and the conditioned soleus H-reflex by subthreshold TMS at the conditioning-test interval of 1 ms (b) are indicated as a function of the step cycle. The mean amplitude of the unconditioned and conditioned soleus H-reflexes evoked at each bin is expressed as a percentage of the maximal M-wave evoked 80 ms after the test H-reflex. TMS was delivered at 0.95 times MEP threshold for the soleus muscle at a conditioning-test interval of 1-ms. Unconditioned and conditioned soleus H-reflexes were accepted when the associated M-waves ranged from 4 to 8% of the maximal M-wave evoked at each bin. H-reflex values are not indicated for some of the bins after BWSTT because they were not accepted based on the M-wave amplitude as a percentage of the maximal M-wave, which is different from not being evocable as was the case for before BWSTT. The step cycle was divided into 16 equal time windows or bins. Stance phase duration is identified by the grey region. Bin 1 corresponds to heel strike. Bins 8, 9, and 16 correspond approximately to stance-to-swing transition, swing phase initiation, and swing-to-stance transition, respectively.

a resting state, it cannot be assumed that corticospinal changes due to training are transferrable at a locomotor state and thus be functional relevant. This is largely based on that (1) short-latency ankle or quadriceps extensor reflexes (H- or stretch reflexes) are modulated in a phase-dependent pattern in uninjured subjects [113–115], (2) the phase-dependent modulation of these reflexes is affected substantially in individuals with an SCI [115–117], and (3) cortical control constitutes one of the sources for the phasic patterned reflex excitability during human walking [86].

In Figure 3(a), the soleus H-reflex recorded during BWS assisted stepping according to methods described in detail [115, 118, 119], before and after 60 BWSTT sessions, is indicated for the same patient whose TA MEP modulation pattern was described in Figure 2. After 60 BWSTT sessions, the maximal reflex excitability shifted, with respect to the step cycle phase, from mid- to early stance (bins 1–3), while a maintained H-reflex excitability commonly observed throughout the stance phase in uninjured subjects [115] was absent before and after training (Figure 3(a)). However, after 60 BWSTT sessions the soleus H-reflex amplitude increased during the late swing phase (bins 12–16), consistent to a reflex behavior observed in some control subjects [120]. The effects of subthreshold TMS on the soleus H-reflex at a C-T interval of 1-ms during BWS assisted stepping are indicated as a function of the step cycle before and after 60 BWSTT sessions in Figure 3(b). It is clear that, after 60 BWSTT sessions, subthreshold TMS affected substantially the soleus H-reflex during the stance phase resulting in a progressive increase of the soleus H-reflex amplitude. The soleus H-reflex amplitude was maintained throughout the stance phase (compare bins 1–8 in Figures 3(a) and 3(b)). Modifications in synaptic actions of cortical inhibitory circuits exerted on soleus motor neurons might be the source of these changes since the phasic soleus H-reflex excitability during BWS assisted stepping with or without leg assistance by a robotic exoskeleton remains unaltered [115, 118].

4. Spinal Interneuronal Inhibitory Circuits: Reciprocal Ia Inhibition

One of the spinal interneuronal circuits with paramount contribution to the neural control of movement is that of disynaptic reciprocal Ia inhibition. Reciprocal inhibition refers to an automatic antagonist motor neuron inhibition when an agonist muscle contracts. Following an SCI, the reciprocal inhibition is either reduced or replaced by reciprocal facilitation [121–124] leading to coactivation of antagonist ankle muscles, spasticity, and poor movement performance.

Regulation of locomotion by reflexly mediated spinal circuits that integrate sensory inputs is well established. The contribution of muscle afferents mediating information about the amplitude and rate of muscle stretch is easily recognized by the phase-dependent modulation of short-latency spinal reflexes during walking. The short-latency soleus and quadriceps extensor reflexes (stretch, tendon, or H-reflex) in humans are modulated in a way that promotes

bipedal gait. The ankle stretch and soleus H-reflexes increase progressively from mid- to late stance in parallel with the soleus EMG activity and are significantly depressed or abolished during the swing phase of gait [113–115, 125]. A phase-dependent modulation has been demonstrated for the ankle stretch reflex in the high decerebrate mesencephalic cat [126].

The soleus H-reflex depression during the swing phase in humans has been partly ascribed to reciprocal Ia inhibition exerted from common peroneal nerve group I afferents on soleus motor neurons, which is regulated in a similar manner to that reported in animals and corresponds largely to absent reciprocal inhibition in the stance phase and maximal in the swing phase [127, 128]. During fictive locomotion in cats without brainstem connections, simultaneous extracellular recordings from Ia inhibitory interneurons and intracellular recordings from lumbar motor neurons revealed that hyperpolarization of soleus α motor neurons coincided with activity of Ia inhibitory interneurons [129, 130]. Ia inhibitory interneurons were rhythmically active due to periodic excitation and not due to periodic inhibition by other spinal inhibitory interneurons [130]. Recent evidence obtained from spinalized animals verified that reciprocal Ia inhibition contributes to hyperpolarization of motor neurons during the inactive (flexion) phase of locomotion [131].

4.1. Cortical Control of Reciprocal Ia Inhibition. Animal studies through intracellular recordings provided a detailed knowledge of the pathway and integration of segmental and supraspinal convergence at the interneuronal level [132–135] with volleys in the corticospinal tract to exert an excitatory effect over Ia inhibitory interneurons [136]. In monkeys, intracortical stimulation revealed that the same interneurons mediate the disynaptic inhibition of motor neurons evoked by corticospinal fibers and the disynaptic inhibition of motor neurons evoked by group Ia afferents of antagonist muscles [137]. Further, motor neurons and Ia inhibitory interneurons were activated in parallel by supraspinal centers in order to secure a coordinated contraction of agonists and relaxation of antagonists [138, 139].

Descending control of reciprocal inhibition has clearly been postulated in humans. In particular, the reciprocal inhibition exerted from common peroneal nerve group I afferents on soleus motor neurons was observed 50 ms before the onset of TA EMG activity [140]. Further, when subjects attempted to dorsiflex the ankle after the common peroneal nerve was blocked with a local anesthetic a strong soleus H-reflex depression was still evident [141]. The test H-reflex facilitation, induced by TES applied to the scalp below the intensity needed to produce a motor response, was quickly terminated by subsequent arrivals of IPSPs at the motor neurons [88]. These IPSPs might be produced by activity in Ia inhibitory interneurons, which in monkeys receive monosynaptic tract projections [142]. Single subthreshold TES reduced the inhibition of the flexor carpi radialis H-reflex evoked by radial nerve stimulation at a latency compatible with a monosynaptic or disynaptic corticospinal projection to Ia inhibitory interneurons [143]. Descending facilitation of Ia inhibitory interneurons has also been documented for the human leg [87, 89].

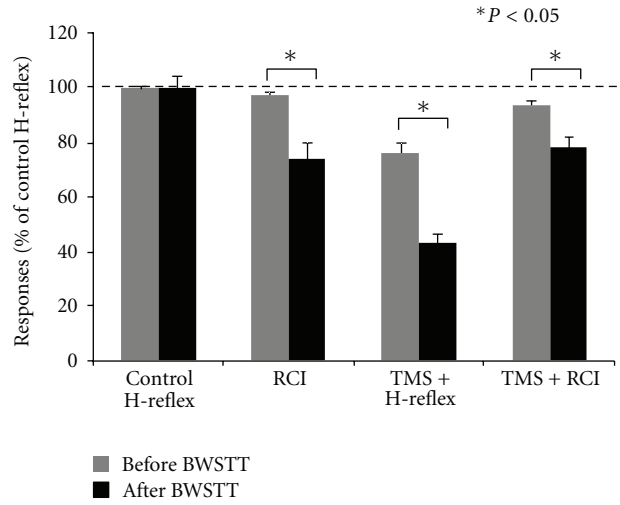


Figure 4: Cortical control of spinal reflex circuits after locomotor training in SCI. Mean size ($n = 20$) of soleus H-reflex conditioned by common peroneal nerve stimulation at the conditioning-test interval of 3 ms, which reflects the amount of reciprocal Ia inhibition (RCI), soleus H-reflex conditioned by subthreshold TMS (TMS + H-reflex) at a C-T interval of 1 ms, and reciprocal inhibition conditioned with subthreshold TMS (TMS + RCI) at C-T intervals of 1 and 3 ms, respectively. Data are from the same patient. The size of the conditioned H-reflexes is expressed as a percentage of the mean amplitude of the control soleus H-reflex. Error bars indicate the SEM, and asterisks denote a statistically significant difference (paired t-test, $P < 0.05$) for conditioned H-reflexes recorded before and after 60 BWSTT sessions.

4.2. Reorganization of Cortical Control of Reciprocal Ia Inhibition after Training. Findings on the reorganization of reciprocal inhibition as a result of motor training in health and disease are limited. Stimulation of the common peroneal nerve with a train of 10 pulses at 100 Hz with and without motor cortex stimulation potentiated reciprocal inhibition in control subjects [144]. Reciprocal inhibition was potentiated after 12 sessions of ankle dorsiflexion strength training when measured at the onset of ankle dorsiflexion but remained unchanged when measured with subjects at rest [145].

In Figure 4, the mean amplitude of the soleus H-reflex conditioned by stimulation of common peroneal nerve group I afferents at a C-T interval of 3 ms and established according to methods outlined in detail [146], which represents the amount of reciprocal inhibition (RCI), before and after 60 BWSTT sessions with subject seated (same patient for data previously described in Figures 2 and 3 is indicated as a percentage of the control H-reflex). Further, the soleus H-reflex conditioned by subthreshold TMS at a C-T interval of 1 ms and the reciprocal inhibition conditioned by subthreshold TMS (C-T intervals: 3 and 1 ms, resp.) as a percentage of the control H-reflex is indicated. It is apparent that locomotor training reestablished the reciprocal inhibition

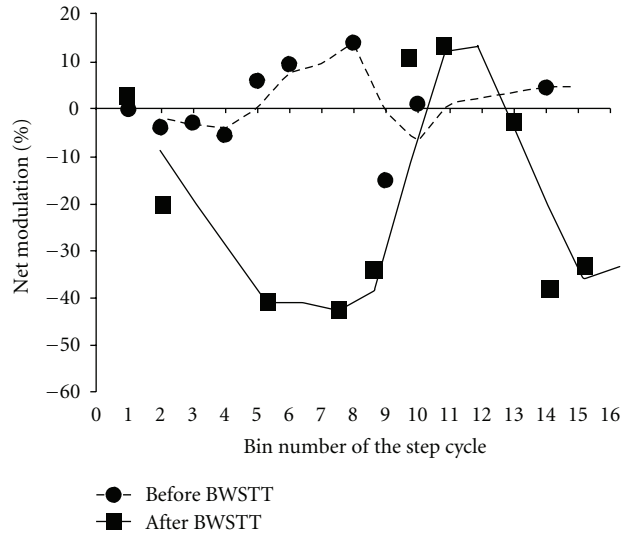


Figure 5: Changes in the cortical control of reciprocal Ia inhibition after locomotor training in SCI. Net effects of subthreshold transcranial magnetic stimulation (TMS) on reciprocal Ia inhibition during BWS assisted stepping before and after 60 body weight-supported treadmill training (BWSTT) sessions. The net effects of subthreshold TMS on reciprocal inhibition were estimated at each bin of the step cycle based on the equation (*D*-*C*)-(*B*-*A*) whereas *A* is the test H-reflex during stepping, *B* is the soleus H-reflex conditioned by subthreshold TMS during stepping at a conditioning-test (C-T) interval of 1 ms, *C* is the soleus H-reflex conditioned by common peroneal nerve stimulation (i.e., reciprocal inhibition) at a C-T interval of 3 ms during stepping, and *D* is the reciprocal inhibition conditioned by subthreshold TMS (3 and 1 ms C-T intervals). Positive values indicate potentiation of reciprocal inhibition and negative values indicate attenuation of reciprocal inhibition by cortical inputs.

exerted from flexor group I afferents on soleus motor neurons, potentiated the soleus H-reflex depression following subthreshold TMS, and potentiated the reciprocal inhibition conditioned by subthreshold TMS, consistent with findings reported in uninjured subjects (see Figure 4 in [147]).

The net effects of subthreshold TMS on the reciprocal inhibition during BWS-assisted stepping before and after 60 BWSTT sessions are indicated in Figure 5 for the same patient. The net effects (or net modulation) were estimated at each bin of the step cycle based on the equation (*D*-*C*)-(*B*-*A*) whereas *A* is the test soleus H-reflex (baseline soleus H-reflex modulation pattern during stepping), *B* is the soleus H-reflex conditioned by subthreshold TMS, *C* is the soleus H-reflex conditioned by common peroneal nerve stimulation (i.e., reciprocal inhibition), and *D* is the reciprocal inhibition conditioned by subthreshold TMS. Positive values indicate potentiation of reciprocal inhibition and negative values indicate attenuation of reciprocal inhibition. Locomotor training contributed significantly to attenuation of reciprocal inhibition exerted from ankle flexor afferents to extensor motor neurons during the stance phase. Most importantly, potentiation of reciprocal inhibition at swing phase initiation (i.e., bin 9 in Figure 5) was evident. Adaptation of cortical control of reciprocal inhibition after locomotor training supports that changes of corticospinal neuronal pathways interacting with Ia interneurons are possible in people with a chronic SCI, although altered corticospinal interactions with other spinal inhibitory interneurons, such as Renshaw cells and presynaptic inhibitory interneurons, cannot be excluded [85, 148, 149].

5. Conclusion

SCI changes the human body homeostasis leading to myriad changes of multiple systems. In most cases, the spinal cord is not completely severed and thus some fiber tracts and segmental spinal cord circuits remain intact. Based on the plastic capabilities of the central nervous system, it is apparent that the adult lesioned motor system reorganization occurs spontaneously after an injury and after training. Electrophysiological studies have shown that BWSTT increases the MEP amplitude, changes the common drive of antagonist muscles from corticospinal inputs with subjects seated, and alters the TA MEP modulation pattern during BWS assisted stepping. Further, BWSTT reestablished the TMS-induced long-latency soleus H-reflex facilitation and potentiated the short-latency soleus H-reflex depression following subthreshold TMS with subjects at rest, while cortical modulation of the soleus H-reflex during stepping changed significantly. Lastly, BWSTT changed the cortical control of reciprocal inhibition during BWS assisted stepping in a manner that promotes bipedal gait. These findings support the notion that improvements in locomotor function from treadmill training are mediated, in part, by changes in the corticospinal drive of spinal reflex circuits, spinal interneuronal circuits, and output of leg muscles during walking.

6. Perspective

Plasticity in the brain and spinal cord underlying restoration of lost function can be driven by appropriately designed interventions [150, 151]. Development of such interventions depends largely on gaining a detailed understanding of the underlying neural mechanisms that support restoration of motor function. Based on this brief paper it is clear that there is a need for translational neuroscience research in order that the neural mechanisms underlying restoration of lost voluntary motor function are outlined based on specific clinical cases. This body of knowledge will contribute significantly to the development of new rehabilitation strategies and/or optimization of the currently available strategies, and to patient-orientated rehabilitation protocols promoting evidence-based rehabilitation.

Abbreviations

BWS: Body weight support
BWSTT: Body weight-supported treadmill training
C-T: Conditioning-test
EMG: Electromyographic
EPSPs: Excitatory postsynaptic potentials
IPSPs: Inhibitory postsynaptic potentials

MEP: Motor evoked potentials
SCI: Spinal cord injury
TA: Tibialis anterior
TMS: Transcranial magnetic stimulation
TES: Transcranial electric stimulation.

Acknowledgments

Author's work presented here was supported by the New York State Department of Health (NYSDOH), Wadsworth Center, NY, USA, and the Craig H. Neilsen Foundation. The author thanks Chaithanya K. Mummidisetty, Andrew C. Smith, and Nupur Hajela for their help during data acquisition and the subject for her dedication and patience during the experiments and training.

References

[1] O. Raineteau and M. E. Schwab, "Plasticity of motor systems after incomplete spinal cord injury," *Nature Reviews Neuroscience*, vol. 2, no. 4, pp. 263–273, 2001.

[2] H. C. Smith, G. Savic, H. L. Frankel et al., "Corticospinal function studied over time following incomplete spinal cord injury," *Spinal Cord*, vol. 38, no. 5, pp. 292–300, 2000.

[3] J. H. Kaas, H. X. Qi, M. J. Burish, O. A. Gharbawie, S. M. Onifer, and J. M. Massey, "Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord," *Experimental Neurology*, vol. 209, no. 2, pp. 407–416, 2008.

[4] M. Bruehlmeier, V. Dietz, K. L. Leenders, U. Roelcke, J. Missimer, and A. Curt, "How does the human brain deal with a spinal cord injury?" *European Journal of Neuroscience*, vol. 10, no. 12, pp. 3918–3922, 1998.

[5] A. Curt, H. Alkadhi, G. R. Crelier, S. H. Boendermaker, M. C. Hepp-Reymond, and S. S. Kollias, "Changes of non-affected upper limb cortical representation in paraplegic patients as assessed by fMRI," *Brain*, vol. 125, no. 11, pp. 2567–2578, 2002.

[6] T. Endo, C. Spenger, T. Tominaga, S. Brené, and L. Olson, "Cortical sensory map rearrangement after spinal cord injury: fMRI responses linked to Nogo signalling," *Brain*, vol. 130, no. 11, pp. 2951–2961, 2007.

[7] G. W. Huntley, "Correlation between patterns of horizontal connectivity and the extent of short-term representational plasticity in rat motor cortex," *Cerebral Cortex*, vol. 7, no. 2, pp. 143–156, 1997.

[8] D. L. Adkins, J. Boychuk, M. S. Remple, and J. A. Kleim, "Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord," *Journal of Applied Physiology*, vol. 101, no. 6, pp. 1776–1782, 2006.

[9] R. D. de Leon, J. A. Hodgson, R. R. Roy, and V. R. Edgerton, "Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats," *Journal of Neurophysiology*, vol. 79, no. 3, pp. 1329–1340, 1998.

[10] M. Bélanger, T. Drew, J. Provencher, and S. Rossignol, "A comparison of treadmill locomotion in adult cats before and after spinal transection," *Journal of Neurophysiology*, vol. 76, no. 1, pp. 471–491, 1996.

[11] A. Frigon and S. Rossignol, "Adaptive changes of the locomotor pattern and cutaneous reflexes during locomotion studied in the same cats before and after spinalization," *Journal of Physiology*, vol. 586, no. 12, pp. 2927–2945, 2008.

[12] G. Barrière, H. Leblond, J. Provencher, and S. Rossignol, "Prominent role of the spinal central pattern generator in the recovery of locomotion after partial spinal cord injuries," *Journal of Neuroscience*, vol. 28, no. 15, pp. 3976–3987, 2008.

[13] S. Rossignol, C. Chau, E. Brustein, M. Bélanger, H. Barbeau, and T. Drew, "Locomotor capacities after complete and partial lesions of the spinal cord," *Acta Neurobiologiae Experimentalis*, vol. 56, no. 1, pp. 449–463, 1996.

[14] S. Rossignol and A. Frigon, "Recovery of locomotion after spinal cord injury: some facts and mechanisms," *Annual Review of Neuroscience*, vol. 34, pp. 413–440, 2011.

[15] H. Barbeau, M. Wainberg, and L. Finch, "Description and application of a system for locomotor rehabilitation," *Medical and Biological Engineering and Computing*, vol. 25, no. 3, pp. 341–344, 1987.

[16] H. Barbeau and S. Rossignol, "Recovery of locomotion after chronic spinalization in the adult cat," *Brain Research*, vol. 412, no. 1, pp. 84–95, 1987.

[17] G. Courtine, Y. Gerasimenko, R. Van Den Brand et al., "Transformation of nonfunctional spinal circuits into functional states after the loss of brain input," *Nature Neuroscience*, vol. 12, no. 10, pp. 1333–1342, 2009.

[18] R. D. de Leon, J. A. Hodgson, R. R. Roy, and V. R. Edgerton, "Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training," *Journal of Neurophysiology*, vol. 81, no. 1, pp. 85–94, 1999.

[19] R. G. Lovely, R. J. Gregor, R. R. Roy, and V. R. Edgerton, "Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat," *Experimental Neurology*, vol. 92, no. 2, pp. 421–435, 1986.

[20] Y. Goldshmit, N. Lythgo, M. P. Galea, and A. M. Turnley, "Treadmill training after spinal cord hemisection in mice promotes axonal sprouting and synapse formation and improves motor recovery," *Journal of Neurotrauma*, vol. 25, no. 5, pp. 449–465, 2008.

[21] M. J. Oh, T. B. Seo, K. B. Kwon et al., "Axonal outgrowth and Erk1/2 activation by training after spinal cord injury in rats," *Journal of Neurotrauma*, vol. 26, no. 11, pp. 2071–2082, 2009.

[22] K. J. Hutchinson, F. Gómez-Pinilla, M. J. Crowe, Z. Ying, and D. M. Basso, "Three exercise paradigms differentially improve sensory recovery after spinal cord contusion in rats," *Brain*, vol. 127, no. 6, pp. 1403–1414, 2004.

[23] M. Liu, J. E. Stevens-Lapsley, A. Jayaraman et al., "Impact of treadmill locomotor training on skeletal muscle IGF1 and myogenic regulatory factors in spinal cord injured rats," *European Journal of Applied Physiology*, vol. 109, no. 4, pp. 709–720, 2010.

[24] J. C. Petruska, R. M. Ichiyama, D. L. Jindrich et al., "Changes in motoneuron properties and synaptic inputs related to step training after spinal cord transection in rats," *Journal of Neuroscience*, vol. 27, no. 16, pp. 4460–4471, 2007.

[25] J. R. Wolpaw and J. S. Carp, "Plasticity from muscle to brain," *Progress in Neurobiology*, vol. 78, no. 3–5, pp. 233–263, 2006.

[26] L. L. Cai, G. Courtine, A. J. Fong, J. W. Burdick, R. R. Roy, and V. R. Edgerton, "Plasticity of functional connectivity in the adult spinal cord," *Philosophical Transactions of the Royal Society B*, vol. 361, no. 1473, pp. 1635–1646, 2006.

[27] A. L. Behrman, A. R. Lawless-Dixon, S. B. Davis et al., "Locomotor training progression and outcomes after incomplete spinal cord injury," *Physical Therapy*, vol. 85, no. 12, pp. 1356–1371, 2005.

[28] A. L. Behrman and S. J. Harkema, "Locomotor training after human spinal cord injury: a series of case studies," *Physical Therapy*, vol. 80, no. 7, pp. 688–700, 2000.

[29] V. Dietz, M. Wirz, A. Curt, and G. Colombo, "Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function," *Spinal Cord*, vol. 36, no. 6, pp. 380–390, 1998.

[30] E. C. Field-Fote, "Combined use of body weight support, functional electric stimulation, and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury," *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 6, pp. 818–824, 2001.

[31] E. C. Field-Fote and K. E. Roach, "Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial," *Physical Therapy*, vol. 91, no. 1, pp. 48–60, 2011.

[32] J. R. Wolpaw and A. M. Tennissen, "Activity-dependent spinal cord plasticity in health and disease," *Annual Review of Neuroscience*, vol. 24, pp. 807–843, 2001.

[33] D. M. Armstrong and T. Drew, "Discharges of pyramidal tract and other motor cortical neurones during locomotion in the cat," *Journal of Physiology*, vol. 346, pp. 471–495, 1984.

[34] D. M. Armstrong and T. Drew, "Locomotor-related neuronal discharges in cat motor cortex compared with peripheral receptive fields and evoked movements," *Journal of Physiology*, vol. 346, pp. 497–517, 1984.

[35] T. Drew, "Motor cortical activity during voluntary gait modifications in the cat. I. Cells related to the forelimbs," *Journal of Neurophysiology*, vol. 70, no. 1, pp. 179–199, 1993.

[36] P. V. Zelenin, T. G. Deliagina, G. N. Orlovsky et al., "Contribution of different limb controllers to modulation of motor cortex neurons during locomotion," *Journal of Neuroscience*, vol. 31, no. 12, pp. 4636–4649, 2011.

[37] I. N. Beloozerova and M. G. Sirota, "The role of the motor cortex in the control of accuracy of locomotor movements in the cat," *Journal of Physiology*, vol. 461, pp. 1–25, 1993.

[38] T. Drew, "Motor cortical cell discharge during voluntary gait modification," *Brain Research*, vol. 457, no. 1, pp. 181–187, 1988.

[39] T. Drew, "Visuomotor coordination in locomotion," *Current Opinion in Neurobiology*, vol. 1, no. 4, pp. 652–657, 1991.

[40] K. Seki, N. Kudo, F. Kolb, and T. Yamaguchi, "Effects of pyramidal tract stimulation on forelimb flexor motoneurons during fictive locomotion in cats," *Neuroscience Letters*, vol. 230, no. 3, pp. 195–198, 1997.

[41] S. Grillner, "Control of locomotion in bipeds, tetrapods, and fish," in *Handbook of Physiology: The Nervous System*, V. B. Brooks, Ed., vol. 2, pp. 1179–1236, American Physiological Society, Bethesda, Md, USA, 1981.

[42] S. Rossignol, A. Frigon, G. Barrière et al., "Spinal plasticity in the recovery of locomotion," *Progress in Brain Research*, vol. 188, pp. 229–241, 2011.

[43] S. Rossignol, "Plasticity of connections underlying locomotor recovery after central and/or peripheral lesions in the adult mammals," *Philosophical Transactions of the Royal Society B*, vol. 361, no. 1473, pp. 1647–1671, 2006.

[44] T. Drew, W. Jiang, and W. Widajewicz, "Contributions of the motor cortex to the control of the hindlimbs during locomotion in the cat," *Brain Research Reviews*, vol. 40, no. 1–3, pp. 178–191, 2002.

[45] U. Ziemann, "Transcranial magnetic stimulation at the interface with other techniques: a powerful tool for studying the human cortex," *Neuroscientist*, vol. 17, no. 4, pp. 368–381, 2011.

[46] J. Reis, O. B. Swayne, Y. Vandermeeren et al., "Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control," *Journal of Physiology*, vol. 586, no. 2, pp. 325–351, 2008.

[47] H. Fukuyama, Y. Ouchi, S. Matsuzaki et al., "Brain functional activity during gait in normal subjects: a SPECT study," *Neuroscience Letters*, vol. 228, no. 3, pp. 183–186, 1997.

[48] I. Miyai, H. C. Tanabe, I. Sase et al., "Cortical mapping of gait in humans: a near-infrared spectroscopic topography study," *NeuroImage*, vol. 14, no. 5, pp. 1186–1192, 2001.

[49] M. Suzuki, I. Miyai, T. Ono et al., "Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study," *NeuroImage*, vol. 23, no. 3, pp. 1020–1026, 2004.

[50] H. T. Petersen, M. Willerslev-Olsen, B. A. Conway, and J. B. Nielsen, "The motor cortex drives the muscles during walking in human subjects," *Journal of Physiology*, vol. 590, no. 10, pp. 2443–2452, 2012.

[51] D. Barthélemy, M. J. Grey, J. B. Nielsen, and L. Bouyer, "Involvement of the corticospinal tract in the control of human gait," *Progress in Brain Research*, vol. 192, pp. 181–197, 2011.

[52] D. M. Halliday, J. R. Rosenberg, A. M. Amjad, P. Breeze, B. A. Conway, and S. F. Farmer, "A framework for the analysis of mixed time series/point process data-theory and application to the study of physiological tremor, single motor unit discharges and electromyograms," *Progress in Biophysics and Molecular Biology*, vol. 64, no. 2-3, pp. 237–278, 1995.

[53] U. Ziemann and J. C. Rothwell, "I-waves in motor cortex," *Journal of Clinical Neurophysiology*, vol. 17, no. 4, pp. 397–405, 2000.

[54] V. Di Lazzaro, U. Ziemann, and R. N. Lemon, "State of the art: physiology of transcranial motor cortex stimulation," *Brain Stimulation*, vol. 1, no. 4, pp. 345–362, 2008.

[55] S. Groppa, B. H. Schlaak, A. Münchau et al., "The human dorsal premotor cortex facilitates the excitability of ipsilateral primary motor cortex via a short latency cortico-cortical route," *Human Brain Mapping*, vol. 33, no. 2, pp. 419–430, 2012.

[56] J. Nielsen and N. Petersen, "Evidence favouring different descending pathways to soleus motoneurones activated by magnetic brain stimulation in man," *Journal of Physiology*, vol. 486, no. 3, pp. 779–788, 1995.

[57] J. Nielsen, H. Morita, J. Baumgarten, N. Petersen, and L. O. Christensen, "On the comparability of H-reflexes and MEPs," *Electroencephalography and Clinical Neurophysiology*, vol. 51, pp. 93–101, 1999.

[58] D. Burke, S. C. Gandevia, and B. McKeon, "Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex," *Journal of Neurophysiology*, vol. 52, no. 3, pp. 435–448, 1984.

[59] S. S. Geertsen, A. T. Zuur, and J. B. Nielsen, "Voluntary activation of ankle muscles is accompanied by subcortical facilitation of their antagonists," *Journal of Physiology*, vol. 588, no. 13, pp. 2391–2402, 2010.

[60] C. Schneider, B. A. Lavoie, H. Barbeau, and C. Capaday, "Timing of cortical excitability changes during the reaction time of movements superimposed on tonic motor activity," *Journal of Applied Physiology*, vol. 97, no. 6, pp. 2220–2227, 2004.

[61] J. B. Nielsen, "Motoneuronal drive during human walking," *Brain Research Reviews*, vol. 40, no. 1–3, pp. 192–201, 2002.

[62] V. Di Lazzaro, D. Restuccia, A. Oliviero et al., "Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits," *Experimental Brain Research*, vol. 119, no. 2, pp. 265–268, 1998.

[63] N. T. Petersen, J. E. Butler, V. Marchand-Pauvert et al., "Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking," *Journal of Physiology*, vol. 537, no. 2, pp. 651–656, 2001.

[64] N. J. Davey, P. Romaiguere, D. W. Maskill, and P. H. Ellaway, "Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man," *Journal of Physiology*, vol. 477, no. 2, pp. 223–235, 1994.

[65] J. Valls-Solé, A. Pascual-Leone, E. M. Wassermann, and M. Hallett, "Human motor evoked responses to paired transcranial magnetic stimuli," *Electroencephalography and Clinical Neurophysiology*, vol. 85, no. 6, pp. 355–364, 1992.

[66] T. Kujirai, M. D. Caramia, J. C. Rothwell et al., "Corticocortical inhibition in human motor cortex," *Journal of Physiology*, vol. 471, pp. 501–519, 1993.

[67] E. M. Wassermann, A. Samii, B. Mercuri et al., "Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles," *Experimental Brain Research*, vol. 109, no. 1, pp. 158–163, 1996.

[68] H. Nakamura, H. Kitagawa, Y. Kawaguchi, and H. Tsuji, "Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans," *Journal of Physiology*, vol. 498, no. 3, pp. 817–823, 1997.

[69] T. D. Sanger, R. R. Garg, and R. Chen, "Interactions between two different inhibitory systems in the human motor cortex," *Journal of Physiology*, vol. 530, no. 2, pp. 307–317, 2001.

[70] A. Ferbert, A. Priori, J. C. Rothwell, B. L. Day, J. G. Colebatch, and C. D. Marsden, "Interhemispheric inhibition of the human motor cortex," *Journal of Physiology*, vol. 453, pp. 525–546, 1992.

[71] 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.

[72] M. A. Perez, B. K. S. Lungholt, K. Nyborg, and J. B. Nielsen, "Motor skill training induces changes in the excitability of the leg cortical area in healthy humans," *Experimental Brain Research*, vol. 159, no. 2, pp. 197–205, 2004.

[73] J. L. Jensen, P. C. D. Marstrand, and J. B. Nielsen, "Motor skill training and strength training are associated with different plastic changes in the central nervous system," *Journal of Applied Physiology*, vol. 99, no. 4, pp. 1558–1568, 2005.

[74] N. Alexeeva, J. G. Broton, and B. Calancie, "Latency of changes in spinal motoneuron excitability evoked by transcranial magnetic brain stimulation in spinal cord injured individuals," *Electroencephalography and Clinical Neurophysiology*, vol. 109, no. 4, pp. 297–303, 1998.

[75] D. Barthélemy, M. Willerslev-Olsen, H. Lundell et al., "Impaired transmission in the corticospinal tract and gait disability in spinal cord injured persons," *Journal of Neurophysiology*, vol. 104, no. 2, pp. 1167–1176, 2010.

[76] B. Calancie, N. Alexeeva, J. G. Broton, S. Suys, A. Hall, and K. J. Klose, "Distribution and latency of muscle responses to transcranial magnetic stimulation of motor cortex after spinal cord injury in humans," *Journal of Neurotrauma*, vol. 16, no. 1, pp. 49–67, 1999.

[77] B. Wirth, H. J. A. Van Hedel, and A. Curt, "Changes in corticospinal function and ankle motor control during recovery from incomplete spinal cord injury," *Journal of Neurotrauma*, vol. 25, no. 5, pp. 467–478, 2008.

[78] P. Winchester, R. McColl, R. Querry et al., "Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury," *Neurorehabilitation and Neural Repair*, vol. 19, no. 4, pp. 313–324, 2005.

[79] C. Enzinger, H. Dawes, H. Johansen-Berg et al., "Brain activity changes associated with treadmill training: after stroke," *Stroke*, vol. 40, no. 7, pp. 2460–2467, 2009.

[80] S. L. Thomas and M. A. Gorassini, "Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury," *Journal of Neurophysiology*, vol. 94, no. 4, pp. 2844–2855, 2005.

[81] J. A. Norton and M. A. Gorassini, "Changes in cortically related intermuscular coherence accompanying improvements in locomotor skills in incomplete spinal cord injury," *Journal of Neurophysiology*, vol. 95, no. 4, pp. 2580–2589, 2006.

[82] N. Petersen, L. O. D. Christensen, and J. Nielsen, "The effect of transcranial magnetic stimulation on the soleus H reflex during human walking," *Journal of Physiology*, vol. 513, no. 2, pp. 599–610, 1998.

[83] C. Capaday, B. A. Lavoie, H. Barbeau, C. Schneider, and M. Bonnard, "Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex," *Journal of Neurophysiology*, vol. 81, no. 1, pp. 129–139, 1999.

[84] M. Schubert, A. Curt, L. Jensen, and V. Dietz, "Corticospinal input in human gait: modulation of magnetically evoked motor responses," *Experimental Brain Research*, vol. 115, no. 2, pp. 234–246, 1997.

[85] M. Knikou, "The H-reflex as a probe: pathways and pitfalls," *Journal of Neuroscience Methods*, vol. 171, no. 1, pp. 1–12, 2008.

[86] M. Knikou, "Neural control of locomotion and training-induced plasticity after spinal and cerebral lesions," *Clinical Neurophysiology*, vol. 121, no. 10, pp. 1655–1668, 2010.

[87] J. Nielsen, N. Petersen, G. Deuschl, and M. Ballegaard, "Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man," *Journal of Physiology*, vol. 471, pp. 223–243, 1993.

[88] J. M. A. Cowan, B. L. Day, C. Marsden, and J. C. Rothwell, "The effect of percutaneous motor cortex stimulation on H reflexes in muscles of the arm and leg in intact man," *Journal of Physiology*, vol. 377, pp. 333–347, 1986.

[89] J. F. Iles and J. V. Pisini, "Cortical modulation of transmission in spinal reflex pathways of man," *Journal of Physiology*, vol. 455, pp. 425–446, 1992.

[90] J. Nielsen, N. Petersen, and B. Fedirchuk, "Evidence suggesting a transcortical pathway from cutaneous foot afferents to tibialis anterior motoneurones in man," *Journal of Physiology*, vol. 501, no. 2, pp. 473–484, 1997.

[91] J. Nielsen, C. Crone, T. Sinkjaer, E. Toft, and H. Hultborn, "Central control of reciprocal inhibition during fictive dorsiflexion in man," *Experimental Brain Research*, vol. 104, no. 1, pp. 99–106, 1995.

[92] J. B. Preston and D. G. Whitlock, "A comparison of motor cortex effects on slow and fast muscle innervations in the monkey," *Experimental Neurology*, vol. 7, no. 4, pp. 327–341, 1963.

[93] D. H. Stewart and J. B. Preston, "Functional coupling between the pyramidal tract and segmental motoneurons in cat and primate," *Journal of Neurophysiology*, vol. 30, no. 3, pp. 453–465, 1967.

[94] N. Petersen, L. O. D. Christensen, H. Morita, T. Sinkjær, and J. Nielsen, "Evidence that a transcortical pathway contributes to stretch reflexes in the tibialis anterior muscle in man," *Journal of Physiology*, vol. 512, no. 1, pp. 267–276, 1998.

[95] J. Van Doornik, Y. Masakado, T. Sinkjaer, and J. B. Nielsen, "The suppression of the long-latency stretch reflex in the human tibialis anterior muscle by transcranial magnetic stimulation," *Experimental Brain Research*, vol. 157, no. 3, pp. 403–406, 2004.

[96] J. L. Taylor, W. Fogel, B. L. Day, and J. C. Rothwell, "Ipsilateral cortical stimulation inhibited the long-latency response to stretch in the long finger flexors in humans," *Journal of Physiology*, vol. 488, no. 3, pp. 821–831, 1995.

[97] L. O. D. Christensen, J. B. Andersen, T. Sinkjær, and J. Nielsen, "Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking," *Journal of Physiology*, vol. 531, no. 2, pp. 545–557, 2001.

[98] B. L. Day, H. Riescher, A. Struppler, J. C. Rothwell, and C. D. Marsden, "Changes in the response to magnetic and electrical stimulation of the motor cortex following muscle stretch in man," *Journal of Physiology*, vol. 433, pp. 41–57, 1991.

[99] D. L. Wolfe, K. C. Hayes, P. J. Potter, and G. A. Delaney, "Conditioning lower limb H-reflexes by transcranial magnetic stimulation of motor cortex reveals preserved innervation in SCI patients," *Journal of Neurotrauma*, vol. 13, no. 6, pp. 281–291, 1996.

[100] T. Serranova, J. Valls-Sole, E. Munoz, D. Genis, R. Jech, and P. Seeman, "Abnormal corticospinal tract modulation of the soleus H reflex in patients with pure spastic paraparesis," *Neuroscience Letters*, vol. 437, no. 1, pp. 15–19, 2008.

[101] M. A. Perez, J. Lundbye-Jensen, and J. B. Nielsen, "Task-specific depression of the soleus H-reflex after cocontraction training of antagonistic ankle muscles," *Journal of Neurophysiology*, vol. 98, no. 6, pp. 3677–3687, 2007.

[102] A. Holtermann, K. Roeleveld, M. Engstrøm, and T. Sand, "Enhanced H-reflex with resistance training is related to increased rate of force development," *European Journal of Applied Physiology*, vol. 101, no. 3, pp. 301–312, 2007.

[103] P. Aagaard, E. B. Simonsen, J. L. Andersen, P. Magnusson, and P. Dyhre, "Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses," *Journal of Applied Physiology*, vol. 92, no. 6, pp. 2309–2318, 2002.

[104] J. Duclay, A. Martin, A. Robbe, and M. Pousson, "Spinal reflex plasticity during maximal dynamic contractions after eccentric training," *Medicine and Science in Sports and Exercise*, vol. 40, no. 4, pp. 722–734, 2008.

[105] R. M. Eccles and A. Lundberg, "Significance of supraspinal control of reflex actions by impulses in muscle afferents," *Experientia*, vol. 14, no. 6, pp. 197–199, 1958.

[106] A. Lundberg and P. Voorhoeve, "Effects from the pyramidal tract on spinal reflex arcs," *Acta Physiologica Scandinavica*, vol. 56, pp. 201–219, 1962.

[107] A. Lundberg, "Multisensory control of spinal reflex pathways," *Progress in Brain Research C*, vol. 50, pp. 11–28, 1979.

[108] X. Y. Chen, J. S. Carp, L. Chen, and J. R. Wolpaw, "Corticospinal tract transection prevents operantly conditioned H-reflex increase in rats," *Experimental Brain Research*, vol. 144, no. 1, pp. 88–94, 2002.

[109] X. Y. Chen and J. R. Wolpaw, "Probable corticospinal tract control of spinal cord plasticity in the rat," *Journal of Neurophysiology*, vol. 87, no. 2, pp. 645–652, 2002.

[110] J. Benito Penalva, E. Opisso, J. Medina et al., "H reflex modulation by transcranial magnetic stimulation in spinal cord injury subjects after gait training with electromechanical systems," *Spinal Cord*, vol. 48, no. 5, pp. 400–406, 2010.

[111] I. Miyai, M. Suzuki, M. Hatakenaka, and K. Kubota, "Effect of body weight support on cortical activation during gait in patients with stroke," *Experimental Brain Research*, vol. 169, no. 1, pp. 85–91, 2006.

[112] C.-L. Yen, R. Y. Wang, K. K. Liao, C. C. Huang, and Y. R. Yang, "Gait training-induced change in corticomotor excitability in patients with chronic stroke," *Neurorehabilitation and Neural Repair*, vol. 22, no. 1, pp. 22–30, 2008.

[113] C. Capaday and R. B. Stein, "Amplitude modulation of the soleus H-reflex in the human during walking and standing," *Journal of Neuroscience*, vol. 6, no. 5, pp. 1308–1313, 1986.

[114] T. Sinkjær, J. B. Andersen, and B. Larsen, "Soleus stretch reflex modulation during gait in humans," *Journal of Neurophysiology*, vol. 76, no. 2, pp. 1112–1120, 1996.

[115] M. Knikou, C. A. Angeli, C. K. Ferreira, and S. J. Harkema, "Soleus H-reflex modulation during body weight support treadmill walking in spinal cord intact and injured subjects," *Experimental Brain Research*, vol. 193, no. 3, pp. 397–407, 2009.

[116] M. Faist, M. Ertel, W. Berger, and V. Dietz, "Impaired modulation of quadriceps tendon jerk reflex during spastic gait: differences between spinal and cerebral lesions," *Brain*, vol. 122, no. 3, pp. 567–579, 1999.

[117] J. F. Yang, J. Fung, M. Edamura, R. Blunt, R. B. Stein, and H. Barbeau, "H-reflex modulation during walking in spastic paretic subjects," *Canadian Journal of Neurological Sciences*, vol. 18, no. 4, pp. 443–452, 1991.

[118] M. Knikou, N. Hajela, C. K. Mummidisetty, M. Xiao, and A. C. Smith, "Soleus H-reflex phase-dependent modulation is preserved during stepping within a robotic exoskeleton," *Clinical Neurophysiology*, vol. 122, no. 7, pp. 1396–1404, 2011.

[119] M. Knikou, "Plantar cutaneous afferents normalize the reflex modulation patterns during stepping in chronic human spinal cord injury," *Journal of Neurophysiology*, vol. 103, no. 3, pp. 1304–1314, 2010.

[120] E. B. Simonsen and P. Dyhre, "Test-retest reliability of the soleus H-reflex excitability measured during human walking," *Human Movement Science*, vol. 30, no. 2, pp. 333–340, 2011.

[121] C. Crone, J. Nielsen, N. Petersen, M. Ballegaard, and H. Hultborn, "Disynaptic reciprocal inhibition of ankle extensors in spastic patients," *Brain*, vol. 117, no. 5, pp. 1161–1168, 1994.

[122] M. Knikou and C. K. Mummidisetty, "Reduced reciprocal inhibition during assisted stepping in human spinal cord injury," *Experimental Neurology*, vol. 231, no. 1, pp. 104–112, 2011.

[123] G. I. Boorman, R. G. Lee, W. J. Becker, and U. R. Windhorst, "Impaired "natural reciprocal inhibition" in patients with spasticity due to incomplete spinal cord injury," *Electroencephalography and Clinical Neurophysiology*, vol. 101, no. 2, pp. 84–92, 1996.

[124] C. Crone, L. L. Johnsen, F. Biering-Sørensen, and J. B. Nielsen, "Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury," *Brain*, vol. 126, no. 2, pp. 495–507, 2003.

[125] P. Crenna and C. Frigo, "Excitability of the soleus H-reflex arc during walking and stepping in man," *Experimental Brain Research*, vol. 66, no. 1, pp. 49–60, 1987.

[126] K. Akazawa, J. W. Aldridge, J. D. Steeves, and R. B. Stein, "Modulation of stretch reflexes during locomotion in the mesencephalic cat," *Journal of Physiology*, vol. 329, pp. 553–567, 1982.

[127] B. A. Lavoie, H. Devanne, and C. Capaday, "Differential control of reciprocal inhibition during walking versus postural

and voluntary motor tasks in humans," *Journal of Neurophysiology*, vol. 78, no. 1, pp. 429–438, 1997.

[128] N. Petersen, H. Morita, and J. Nielsen, "Modulation of reciprocal inhibition between ankle extensors and flexors during walking in man," *Journal of Physiology*, vol. 520, no. 2, pp. 605–619, 1999.

[129] A. M. Degtyarenko, E. S. Simon, and R. E. Burke, "Differential modulation of disynaptic cutaneous inhibition and excitation in ankle flexor motoneurons during fictive locomotion," *Journal of Neurophysiology*, vol. 76, no. 5, pp. 2972–2985, 1996.

[130] C. A. Pratt and L. M. Jordan, "Ia inhibitory interneurons and Renshaw cells as contributors to the spinal mechanisms of fictive locomotion," *Journal of Neurophysiology*, vol. 57, no. 1, pp. 56–71, 1987.

[131] S. S. Geertsen, K. Stecina, C. F. Meehan, J. B. Nielsen, and H. Hultborn, "Reciprocal Ia inhibition contributes to motoneuronal hyperpolarisation during the inactive phase of locomotion and scratching in the cat," *Journal of Physiology*, vol. 589, no. 1, pp. 119–134, 2011.

[132] J. C. Eccles, P. Fatt, and S. Landgren, "The inhibitory pathway to motoneurones," *Progress in Neurobiology*, no. 2, pp. 72–82, 1956.

[133] H. Hultborn, M. Illert, and M. Santini, "Convergence on interneurones mediating the reciprocal Ia inhibition of motoneurones. III. Effects from supraspinal pathways," *Acta Physiologica Scandinavica*, vol. 96, no. 3, pp. 368–391, 1976.

[134] H. Hultborn, E. Jankowska, and S. Lindström, "Recurrent inhibition from motor axon collaterals of transmission in the Ia inhibitory pathway to motoneurones," *Journal of Physiology*, vol. 215, no. 3, pp. 591–612, 1971.

[135] T. Hongo, E. Jankowska, and A. Lundberg, "The rubrospinal tract. II. Facilitation of interneuronal transmission in reflex paths to motoneurones," *Experimental Brain Research*, vol. 7, no. 4, pp. 365–391, 1969.

[136] A. Lundgren and P. Voorhoeve, "Effects from the pyramidal tract on spinal reflex arcs," *Acta Physiologica Scandinavica*, vol. 56, pp. 201–219, 1962.

[137] E. Jankowska, Y. Padel, and R. Tanaka, "Disynaptic inhibition of spinal motoneurones from the motor cortex in the monkey," *Journal of Physiology*, vol. 258, no. 2, pp. 467–487, 1976.

[138] A. Lundberg, "Supraspinal control of transmission in reflex paths to motoneurones and primary afferents," *Progress in Brain Research*, vol. 12, no. C, pp. 197–221, 1964.

[139] A. Lundberg, "Multisensory control of spinal reflex pathways," *Progress in Brain Research C*, vol. 50, pp. 11–28, 1979.

[140] C. Crone, H. Hultborn, B. Jespersen, and J. Nielsen, "Reciprocal Ia inhibition between ankle flexors and extensors in man," *Journal of Physiology*, vol. 389, pp. 163–185, 1987.

[141] C. Crone and J. Nielsen, "Central control of disynaptic reciprocal inhibition in humans," *Acta Physiologica Scandinavica*, vol. 152, no. 4, pp. 351–363, 1994.

[142] E. Jankowska and R. Tanaka, "Neuronal mechanism of the disynaptic inhibition evoked in primate spinal motoneurones from the corticospinal tract," *Brain Research*, vol. 75, no. 1, pp. 163–166, 1974.

[143] J. C. Rothwell, B. L. Day, A. Berardelli, and C. D. Marsden, "Effects of motor cortex stimulation on spinal interneurones in intact man," *Experimental Brain Research*, vol. 54, no. 2, pp. 382–384, 1984.

[144] M. A. Perez, E. C. Field-Fote, and M. K. Floeter, "Patterned sensory stimulation induces plasticity in reciprocal Ia inhibition in humans," *Journal of Neuroscience*, vol. 23, no. 6, pp. 2014–2018, 2003.

[145] S. S. Geertsen, J. Lundbye-Jensen, and J. B. Nielsen, "Increased central facilitation of antagonist reciprocal inhibition at the onset of dorsiflexion following explosive strength training," *Journal of Applied Physiology*, vol. 105, no. 3, pp. 915–922, 2008.

[146] M. Knikou and C. Taglianetti, "On the methods employed to record and measure the human soleus H-reflex," *Somatosensory and Motor Research*, vol. 23, no. 1-2, pp. 55–62, 2006.

[147] L. Kudina, P. Ashby, and L. Downes, "Effects of cortical stimulation on reciprocal inhibition in humans," *Experimental Brain Research*, vol. 94, no. 3, pp. 533–538, 1993.

[148] M. Baret, R. Katz, J. C. Lamy, A. Pénicaud, and I. Wargon, "Evidence for recurrent inhibition of reciprocal inhibition from soleus to tibialis anterior in Man," *Experimental Brain Research*, vol. 152, no. 1, pp. 133–136, 2003.

[149] S. Meunier, "Modulation by corticospinal volleys of presynaptic inhibition to Ia afferents in man," *Journal of Physiology Paris*, vol. 93, no. 4, pp. 387–394, 1999.

[150] F. C. Hummel and L. G. Cohen, "Drivers of brain plasticity," *Current Opinion in Neurology*, vol. 18, no. 6, pp. 667–674, 2005.

[151] R. J. Nudo, "Plasticity," *NeuroRx*, vol. 3, no. 4, pp. 420–427, 2006.

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 350574, 12 pages
doi:10.1155/2012/350574

Review Article

Plasticity-Inducing TMS Protocols to Investigate Somatosensory Control of Hand Function

M. Jacobs,[1] A. Premji,[2] and A. J. Nelson[1]

[1] *Department of Kinesiology, University of Waterloo, 200 University Avenue West, Waterloo, ON, Canada N2L 3G1*
[2] *Department of Medicine, University of Toronto, Toronto, ON, Canada M5S 1A1*

Correspondence should be addressed to A. J. Nelson, ajnelson@uwaterloo.ca

Received 17 January 2012; Revised 27 February 2012; Accepted 14 March 2012

Academic Editor: Marie-Hélène Canu

Hand function depends on sensory feedback to direct an appropriate motor response. There is clear evidence that somatosensory cortices modulate motor behaviour and physiology within primary motor cortex. However, this information is mainly from research in animals and the bridge to human hand control is needed. Emerging evidence in humans supports the notion that somatosensory cortices modulate motor behaviour, physiology and sensory perception. Transcranial magnetic stimulation (TMS) allows for the investigation of primary and higher-order somatosensory cortices and their role in control of hand movement in humans. This review provides a summary of several TMS protocols in the investigation of hand control via the somatosensory cortices. TMS plasticity inducing protocols reviewed include paired associative stimulation, repetitive TMS, theta-burst stimulation as well as other techniques that aim to modulate cortical excitability in sensorimotor cortices. Although the discussed techniques may modulate cortical excitability, careful consideration of experimental design is needed to isolate factors that may interfere with desired results of the plasticity-inducing protocol, specifically events that may lead to metaplasticity within the targeted cortex.

1. Introduction

There is emerging evidence that alterations in somatosensory processing may underlie challenges in hand control after neurological injury. Abnormalities in somatosensory physiology and perception are observed in clinical populations such as stroke and focal hand dystonia [1, 2]. Evidence suggests that somatosensory-based therapies provide temporary benefits [3–5]. To translate fundamental science into effective therapies aimed at long-term improvements in hand function, a comprehensive understanding of the role of somatosensory cortex must be incorporated into models of hand control. In recent years, the use of plasticity-inducing transcranial magnetic stimulation (TMS) protocols has become a powerful tool to investigate the neural activity within the hand representations in primary somatosensory (SI) and primary motor (M1) cortices, touch perception and motor behavior. Such protocols have furthered our understanding of the somatosensory contributions to hand function.

Somatosensory input is represented in multiple cortical areas, similar to other sensory areas. The significance of multiple cortical representations of the hand remains unclear, although one hypothesis is that each area contributes a particular attribute to the process of sensory-guided movement [6]. Emphasis has largely been directed to understanding processing in SI. This information has served clinical neuroscience well as decades of monkey research have exposed fundamental principles of neural plasticity that have instructed formulas for rehabilitation training in patient groups [4]. SI which encompasses the postcentral gyrus is composed of at least four subareas in monkeys [7, 8] and humans [9, 10] that include 3a, 3b, 1, and 2. With the exception of 3b, evidence in monkey species demonstrates that all sub-areas project directly to M1 [11–18]. Higher-order somatic loci such as the secondary somatosensory cortex or Brodmann's area 5 share particular features such as large neural receptive fields and gross somatotopy [19, 20]. Area 5, located in the superior parietal lobule, is particularly interesting since it appears to be dominated by

the representation of the hand and upper limb [21, 22] and is largely absent in species lacking opposable thumbs [21, 22] suggesting its emergence with skilled thumb manipulation [21]. The projection from area 5 to M1 is considered to be as dense as that which originates from SI [23].

There is substantial evidence that alterations in SI activity can affect somatosensation, M1 physiology, and motor control. In monkeys, manipulation of peripheral input through nerve crush or digit amputation [24] or experience [25] leads to neuroplastic changes within the postcentral gyrus. Lesions directly to SI such as the removal of the hand and arm representations within areas 1, 2, and 3 elevate detection thresholds by 3–6 times [26], while damage to area 1 leads to deficits in texture perception, and damage to area 2 impairs the percepts of curvature and form [27]. In monkeys, direct manipulation of SI activity alters motor behaviour. Injection of muscimol in the SI region leads to loss of finger coordination [28], cooling the postcentral gyrus leads to clumsy, slow movements, and poor coordination [29], and lesioning impairs the acquisition of new motor skills [30]. Direct manipulation of SI activity also alters neural responsiveness within M1. Tetanic stimulation applied to SI in cats increases the responsiveness in M1 neurons [31, 32]. Cooling the postcentral gyrus increases the background activity in M1 neurons, suggesting that SI may have a net inhibitory influence on M1 [29]. In another study, the SI versus M1 effects on EMG activity were compared using intracortical microstimulation during wrist movements. Compared to M1, stimulation to SI yielded a smaller percentage of neurons that altered EMG activity, and this change was more often suppression rather than facilitation of EMG activity [33]. Collectively, these data indicate that alterations to SI influence neural mechanisms that underpin somatosensory and motor processing.

In humans, understanding somatosensory physiology and its influence on M1 activity and motor control of the hand is important to basic and clinical neuroscience. This review is focussed on the use of plasticity-inducing TMS protocols to further the understanding of somatosensory contributions to hand function. Identifying methods to increase or decrease neural activity within hand representations may advance the development of therapies intended to improve hand function in clinical populations. We focus primarily on evidence that three TMS protocols applied to SI modulate perception and neural activity within SI and M1 and include paired associative stimulation, repetitive TMS and theta-burst TMS. For each, we briefly describe the neural mechanisms that appear to underpin effects, the influence on somatosensory and motor physiology, tactile perception and motor behaviour when delivered over SI, and the potential limitations of the technique. We subsequently describe additional paradigms that have also provided evidence of modulating SI activity.

2. TMS Plasticity-Inducing Protocols

Investigations into the somatosensory influence on M1 activity in humans often employ TMS paradigms to examine corticospinal excitability and specific neural circuitry. We briefly review specific TMS paradigms to measure such circuitry and refer the reader to other reviews intended to cover these topics more thoroughly [34, 35].

2.1. TMS Paradigms to Measure Corticospinal Excitability and Intracortical Circuitry. Single-pulse TMS delivered over a particular muscle representation within M1 at intensities above threshold can evoke a motor response in that contralateral muscle. The amplitude of the resultant motor-evoked potential (MEP) recorded from the target muscle reflects the excitability of corticospinal circuitry and spinal motoneurons [36–38]. Using dual-pulse TMS paradigms, intracortical inhibitory circuits within M1 may be tested by controlling the interstimulus interval (ISI) between the two TMS pulses delivered to M1. Short-interval intracortical inhibition (SICI) occurs when the ISI is in the range of 1–6 ms [39–41], and long-interval intracortical inhibition (LICI) occurs when the ISI is in the range of 50–200 ms [42]. In SICI and LICI, the first TMS pulse acts to inhibit the corticospinal output produced by the second TMS pulse such that the MEP amplitude is reduced. In contrast, an ISI in the range of 8–30 ms results in an increase in MEP amplitude, circuitry referred to as intracortical facilitation (ICF) [39]. ICF occurs when the first TMS pulse facilitates the corticospinal output produced by the second pulse [39, 41]. In addition to circuitry within M1, interhemispheric interactions between M1 in opposite hemispheres can be studied. Using two TMS coils, one TMS pulse called the conditioning stimulus (CS) is applied to M1 in one hemisphere and is followed by a TMS pulse called the test stimulus (TS) delivered to the opposite M1 [43]. This circuitry is known as interhemispheric inhibition (IHI) and is subdivided into short and long intervals with maximal inhibition at ~10 and 40 ms, respectively [44, 45]. Short- (SIHI-) and long- (LIHI-) interval IHI appear to mediated by different mechanisms since baclofen, a $GABA_B$ receptor agonist, alters LIHI without changing SIHI [46]. In addition to circuitry probed within and between motor cortices, other neural interactions can be assessed by pairing peripheral nerve stimulation or cutaneous stimulation of the hand with a TMS pulse over M1. ISIs of approximately 20–50 ms or 200–1000 ms decrease motor excitability, effects known as short-latency afferent inhibition (SAI) or long-latency afferent inhibition (LAI), respectively [47–49].

2.1.1. Paired Associative Stimulation. Paired associative stimulation (PAS) involves peripheral nerve stimulation followed by a TMS pulse delivered over the cortex, typically M1. Pairs of nerve-cortex stimuli are applied repetitively and result in long-lasting changes in cortical excitability [50]. Depending on the interstimulus interval (ISI) between the peripheral nerve stimulation and the TMS pulse, PAS can elicit changes in corticospinal excitability, indexed by increases or decreases in MEP amplitude, respectively. PAS applied with an ISI of 25 ms (PAS_{25}) increases MEP amplitude [50, 51], while a 10 ms ISI (PAS_{10}) decreases MEP amplitude [52]. Changes in cortical excitability persist for approximately 30 to 60 minutes following PAS [50, 53].

The PAS protocol was developed based on animal models of spike timing-dependent plasticity, particularly long-term potentiation (LTP)/depression (LTD) (for review, see [54, 55]). It has been proposed that PAS induces long-lasting changes in M1 circuitry via LTP/LTD-like mechanisms of cortical synapses, with the direction of excitability dependent on the interval between stimuli [50–52]. The bidirectional effects of PAS are dependent upon the temporal order of the paired stimuli. This timing is known to modulate the levels of postsynaptic calcium concentrations via N-methyl-D-aspartate (NMDA) receptor activation which ultimately determines the LTP- or LTD-like effects [54]. The arrival of peripheral afferent stimuli to the motor cortex via horizontal corticocortical fibres with the near simultaneous TMS pulse delivered over M1 leads to MEP facilitation suggesting LTP-like effects. In contrast, if the temporal order is reversed with the TMS pulse reaching the motor area first, the MEPs show LTD-like suppression. Temporal order is a feature associated with LTP/LTD [54]. Further, PAS effects localized to the target APB muscle do not carry over to muscle representations distant from the paired electrical inputs [56]. This is in line with LTP/LTD mechanisms thought to be associated with input specificity demonstrated in the rat motor cortex [54, 57]. Last, blocking NMDA receptor activity abolishes the PAS effects in humans [58, 59] and rats [60].

Long-lasting changes in M1 excitability are induced for up to an hour following the use of the PAS technique which combines somatosensory afferent input and direct modulation of cortical activity using TMS. Though several studies have demonstrated the influence of PAS on corticospinal excitability as measured via MEPs [50, 52], it appears that intracortical circuits are unaffected [51, 61]. However, using a lower-intensity PAS protocol whereby median nerve stimulation is paired with single-pulse TMS over M1 (i.e., intensity to elicit a 0.5 mV MEP versus 1 mV used in other studies), long-lasting changes in inhibitory intracortical circuits of M1 were observed [62]. Specifically, following PAS_{25}, long-interval intracortical inhibition (LICI) was reduced and long-latency afferent inhibition (LAI) was reduced when the ISI between the CS and TS was 150 ms. In contrast, PAS_{10} increased LICI, while LAI showed a nonsignificant increase. Interestingly, at an ISI of 240, the direction of LAI reversed with PAS_{25} and PAS_{10}, emphasizing the importance of intervals between stimulation. PAS_{10} decreased SICI, while the effects of PAS_{25} were inconsistent [62]. Overall, this work demonstrates that PAS, a technique that manipulates the arrival of the somatosensory afferent volley and M1 cortical activity, can indeed modulate intracortical circuitry within M1.

PAS has also been used to demonstrate changes in SI excitability. PAS may be performed by pairing median nerve stimulation with TMS pulses delivered directly over SI. The interval between the nerve and SI stimulation may be determined by using the individual latencies of the N20 SEP potential. Using this technique, intervals that aim to closely time the arrival of the afferent volley with the TMS pulse applied to SI lead to a facilitation of the P25 SEP. In contrast, when the SI TMS pulse is delivered in advance of the arrival of the afferent volley by ~20 ms, the P25 is decreased [63] in line with an inhibitory versus excitatory effect of short versus long intervals, respectively. However, a recent study was unable to replicate these findings [64] possibly related to the lower intensities used for the SI TMS pulse (120% versus 150% RMT) and median nerve stimulation (110% of motor threshold versus 300% perceptual threshold). Thus, it may be that PAS over SI may require higher TMS intensities than that required by PAS over M1. In one study using a similar paradigm, the effects of PAS on single- and paired-median nerve SEPs were evaluated in controls and patients with focal hand dystonia [65]. In contrast to the previous report, PAS did not significantly alter SEPs in the healthy control group. PAS did however increase SEPs and intracortical inhibition in FHD [66].

2.2. PAS Considerations. The facilitatory and inhibitory effects of PAS 25 and 10 ms are altered by prior neural activity. This effect known as metaplasticity describes a change in the neuroplasticity effects as a result of the recent history [67]. Preconditioning with 250 suprathreshold TMS pulses delivered at 0.1 Hz eliminates the PAS 25 facilitation and PAS 10 suppression. Subthreshold TMS and also median nerve stimulation preconditioning did not abolish the PAS-25-induced facilitation though they did prevent the increase from achieving statistical significance [68]. Similarly, motor training involving the thumb blocks the PAS- 25-induced facilitation [69, 70] and either leaves PAS-induced inhibition unchanged [69] or enhances the inhibition [70]. These data suggest that limiting neural activity is an important determinant for observing PAS facilitation and inhibition, and that a prior history of activity within the neural targets of PAS will affect the outcome of this plasticity-inducing protocol.

The after effects of PAS seem to be more effective depending on the time of day, suggesting that circadian rhythms and hormonal fluctuations may influence the magnitude of PAS effects [71]. PAS was significantly more effective in the afternoon compared to morning sessions [71]. Having the subject directed their attention to the stimulated hand also increases the magnitude of PAS effects [72].

There is conflicting evidence of the effects of PAS on spinal circuit excitability. While authors report no changes in spinal excitability with the use of F-waves [56, 59], others have recently found changes at the spinal level with the use of H-reflex recruitment curves [73, 74]. The authors conclude that the PAS-induced increase of the H-reflex is due to a decrease in the presynaptic inhibition of Ia terminals [74]. It is important to note, however, that the latter group used a modified version of PAS in which the stimulation protocol was delivered at a faster rate of 0.2 Hz and applied 240 paired pulses [73, 74]. Facilitatory PAS protocols which deliver more stimuli at a higher rate [71] comparably induce greater increases in MEP amplitude than standard PAS [56]. It is possible that paired stimulus parameters of greater intensity, frequency, and number of pulses may induce a greater degree of descending modulation of spinal circuitry than standard PAS protocols.

2.2.1. Repetitive TMS. TMS, applied repetitively, can be used to induce short-term changes in cortical excitability. The effects of repetitive TMS (rTMS) are dependent on the stimulus parameters of the protocol, with the main determinants being the frequency of pulse delivery and the intensity [75]. RTMS delivered at frequencies ≤1 Hz lead to the suppression of MEP amplitude [76] and increased MEP amplitude when applied at frequencies ≥1 Hz [77, 78]. RTMS has also been shown to alter intracortical circuitry such that SICI decreases [79].

The physiological basis of increases and decreases in cortical excitability with high- versus low-frequency rTMS has been attributed to LTP and LTD of cortical synapses [34, 80]. In rat models, 1 Hz rTMS reduced the number of calbindin D-28k- (CB-) positive cells suggesting that inhibitory activity of interneurons controlling synaptic input to pyramidal cells was altered [81]. Within two hours following 1 Hz rTMS, GAD 67 expression related to GABA synthesis in the cytosol was reduced, while GAD 65 related to GABA synthesis for neurotransmission was unaltered [82]. However, one to seven days following stimulation, GAD 65, GAD 67, and GAT1 GABA transport expression increased suggesting longer-term changes in inhibitory neural circuits [82].

In humans, Satow et al. (2003) investigated the influence of low-frequency rTMS (0.9 Hz) over the left-hemisphere motor hotspot for APB and at two alternate positions 3 cm anterior and 3 cm posterior to the hotspot. Effects were only induced at the APB site which the authors refer to as the "sensorimotor" site [83]. Somatosensory-evoked potentials (SEPs) were unchanged though thresholds for the detection of tactile stimuli using Von Frey filaments increased for 0–8 minutes on the right index finger [83]. Tactile frequency discrimination on the left hand was impaired following 1 Hz rTMS over right SI with the duration of impairment related to the duration of rTMS [84]. The longest perceptual impairment persisted for 8 minutes and occurred following twenty minutes of rTMS low-frequency rTMS [84]. Spatial acuity measured using 2-point discrimination is also impaired following 1 Hz rTMS over SI, although the effects on wrist proprioception were variable [85].

High-frequency rTMS applied to SI alters tactile acuity and physiology. Gains in tactile spatial acuity achieved using tactile coactivation paradigms were further improved by combining it with high-frequency rTMS (5 Hz) over SI [86]. A subsequent report by this group used paired-median nerve stimulation whereby 5 Hz rTMS over SI reduced the inhibition of the second SEP within the pair [87]. 5 Hz rTMS applied over SI was subsequently shown to improve tactile spatial acuity on the index finger and increase the representation of that finger within SI [88]. Similar findings for tactile frequency discrimination and enlarged cortical activation within SI were subsequently reported [89]. There is also evidence to suggest that high-frequency rTMS facilitates somatosensory learning. The learning of a spatial discrimination task was improved when paired with high-frequency (15 Hz) rTMS over SI. In contrast, rTMS did not improve the learning of a frequency discrimination task [90].

In humans, rTMS has been applied to SI to investigate the after effects on motor behaviour and M1 physiology. Vidoni et al. (2010) studied the influence of low-frequency rTMS over SI on the ability to learn a motor tracking task. Real and sham 1 Hz rTMS was applied over SI, while participants learned to perform a visually cued wrist flexion/extension tracking task. Participants receiving real rTMS demonstrated greater errors in tracking during task acquisition and at a second testing session the following day when no rTMS was delivered [85]. Pleger et al (2006) used high-frequency rTMS over SI to investigate effects on SI and M1 physiology. Following 5 Hz rTMS, functional magnetic resonance imaging (fMRI) revealed that a cluster of voxels within ipsilateral M1 was shown to be negatively correlated with improvements in tactile frequency discrimination. Further, participants who showed the best perceptual performance had the greatest activation increases in SI and the lowest activation increases within M1. This study also demonstrated that 5 Hz rTMS over SI increases the effective connectivity between SI and M1 [89].

2.3. Repetitive TMS Considerations. One consideration in attempting to induce rTMS effects relates to monitoring muscle activity during stimulation. In one study, the effects of 5 Hz rTMS over M1 were modified by flexion or extension of the wrist during rTMS application [91]. SICI in flexor carpi radialis was decreased following rTMS paired with wrist flexion and increased with wrist extension. Similarly, SICI in extensor carpi radialis was decreased following rTMS paired with wrist extension and increased with wrist flexion [91]. No effects on ICF were observed. A recent review highlights evidence that neural activity prior to rTMS either by priming with an independent TMS protocol or voluntary muscle activation influences the after effects of the interventional rTMS protocol [92] suggesting metaplasticity. These data suggest that the state of muscle activity during rTMS can strongly modify select circuitry within M1.

Low-frequency rTMS over SI has been shown to have only slight, nonsignificant effects on SEPs recorded from ipsilateral SI [93]. Interestingly, median nerve stimulation followed by single-pulse TMS to M1 at ISIs of 150 ms has shown reductions in contralateral SI SEP components (N20p-P25 & P25-N33), possibly through secondary effects of corticocortical projections from the contralateral, non-stimulated M1 [94]. This suggests that SI changes may be more responsive to TMS manipulations of activity within M1 compared with those directly applied to SI.

Technical aspects of rTMS are an important consideration. In general, the coil orientation, stimulus intensity and frequency are factors that can be controlled by the experimenter. Tings et al. (2005) performed 5 Hz rTMS over M1 using both PA and AP orientations in separate sessions. Monophasic rTMS in the PA orientation induced facilitation of MEP amplitudes, whereas monophasic rTMS with AP orientation suppressed MEP amplitudes [95]. Berger et al. (2011) delivered 1 Hz rTMS at intensities of 40%, 80%, and 100% RMT. MEP amplitudes decreased for the lowest intensity, while no significant change was observed at 80% RMT, and facilitation was recorded at 100% RMT

[96]. Quartarone et al. (2005) also showed an intensity-dependent relationship. No increase in MEP amplitude was found following rTMS at 90% AMT, but when intensity was increased to 90% RMT, MEP amplitude significantly increased over time [97]. Overall, the technical parameters of rTMS should be carefully considered in order to produce the desired after effect (for further review, see [98, 99]).

2.3.1. Theta-Burst Stimulation. A novel form of repetitive TMS called theta-burst stimulation (TBS) is composed of bursts of three pulses delivered at 50 Hz and repeated at 5 Hz [100] and is designed to mimic LTP and LTD inducing paradigms in animal models [57, 101–104]. TBS can be applied in a continuous (cTBS) or an intermittent (iTBS) pattern to induce short-term plasticity changes within the cortex. CTBS involves uninterrupted bursts of TBS pulses over a short period of time, while iTBS consists of a 2-second train of TBS repeated every 10 seconds [100].

The neural mechanisms that mediate TBS effects in humans remain unclear, though information obtained from rat models is advancing our understanding. At the cellular level, TBS delivered over rat cortex alters the expression of glutamic acid isoforms GAD 65 and GAD 67 and GAT-1 [82]. GAT-1 is a presynaptic GABA transporter, GAD 65 is important for GABA synthesis for the purpose of neurotransmission [105], and GAD 67 supports GABA synthesis within the cytosol [106]. Two hours following TBS, GAD 65, and GAT-1 expression were increased, while GAD 67 was decreased [82]. One to seven days following stimulation opposite effects were found; GAD 65 and GAT-1 expression decreased while GAD 67 increased. The acute and longer-term effects were observed for both iTBS and cTBS [82]. These findings demonstrate that both TBS protocols promote GABA-related activity within targeted cortex. However, iTBS versus cTBS protocols appear to have different effects on the expression of cortical proteins involved in inhibitory cortical systems. Inhibitory neurons that influence the synchronization of pyramidal cells express parvalbumin (PV), while those that control dendritic input to pyramidal cells and other interneurons express calbindin D-28k (CB) [107]. ITBS reduced the number of PV-positive cells, while CTBS decreased the number of CB expressing cells [81]. The suggestion from these authors is that iTBS may target the inhibition of pyramidal cell output neurons, and cTBS alters the inhibitory activity of interneurons that control the synaptic inputs to pyramidal cells [81]. Collectively, the rat model has demonstrated that neural mechanisms of TBS involve changes to the inhibitory neuronal circuitry within the targeted cortex. It remains unclear whether the findings in the rat model are translatable to human TBS studies that typically employ a single-600-pulse TBS protocol.

In humans, evidence suggests that TBS paradigms may be related to LTP/LTD-like effects and GABAergic activity [108]. Using magnetic resonance spectroscopy (MRS), cTBS increased GABA concentration within targeted cortex [109], and it was suggested that cTBS at 80% AMT stimulates $GABA_A$ interneurons whose elevated activity is maintained via GAD 65 expression, and later, by elevated GABA within the cytoplasm via GAD 67. In addition to altering cortical inhibition, evidence in humans also suggests that TBS modulates activity in glutamatergic systems. Although MRS revealed no change in glutamate concentration following cTBS [109], the effects of cTBS are abolished after NMDA receptor blockage [110, 111]. Therefore, cTBS protocols may alter activity in both inhibitory and excitatory circuitry. Dopamine also contributes to the mechanisms of iTBS and cTBS, and effects are abolished following D2 receptor blockage [112].

Several studies have examined TBS paradigms applied over M1. CTBS over M1 decreases MEPs for 20–60 minutes [100, 113, 114] and reduces SICI [100, 113, 115]. In contrast, iTBS applied over M1 increases MEP amplitude for 15–20 minutes [100, 114] and increases SICI [100, 115]. TBS provides an opportunity to modulate cortical excitability at both the site of stimulation and remote areas. For example, cTBS over M1 reduces MEP amplitude bilaterally [116]. In another study, cTBS over M1 decreases MEPs in the stimulated hemisphere and increases MEPs evoked from the nonstimulated M1 [115]. ITBS applied over M1 increases MEPs in the stimulated hemisphere [100, 115] and decreases MEP amplitude in the non-stimulated hemisphere [115].

Investigating the effects of TBS over SI, Ishikawa et al. (2007) delivered cTBS to left SI (2 cm posterior to M1) and recorded SEPs elicited from right and left median nerve stimulation. Following cTBS over left SI, a reduction in the amplitude of SEP components P22-N30 and P25-N33, elicited from the right but not left median nerve, was observed for 13 minutes following stimulation as measured by two time blocks at 0–3 and 10–13 minutes [116]. No significant suppression of SEP amplitude was observed at 20 minutes following stimulation [116]. To probe the perceptual effects of the reduced SEP amplitude following cTBS, Rai et al. 2011 (in press) examined tactile temporal and spatial amplitude discrimination thresholds before and following cTBS over left SI defined as a point 2 cm posterior to motor hotspot. In line with the reduction in SEP amplitude following cTBS over left SI [116], temporal discrimination threshold (TDT) and spatial amplitude discrimination threshold (SDT) were impaired, and thresholds were elevated following stimulation at certain time intervals for up to 18 minutes. It is notable that the psychophysical changes (up to 18 minutes) appear to slightly exceed the physiological changes (13 minutes) following cTBS. In particular, changes in TDT between 1–3 and 11–14 minutes are in line with SEP changes following cTBS [117]. A recent study explored SEPs and high-frequency oscillations (HFOs) before and following cTBS and found that HFOs only were suppressed at 15 minutes following stimulation [118].

Intermittent TBS applied over SI also provides the opportunity to modulate SI physiology and perception. Katayama and Rothwell (2007) applied iTBS over left SI (2 cm posterior to left M1) and measured SEPs elicited from the right median nerve. Following stimulation, SEP amplitudes (N200-N20p, N20p-P25, and P25-N33) were increased at 15 and 30 minutes following stimulation [119]. In another study, Premji et al., (2010) applied iTBS over left SI and measured SEPs elicited from the right and left median nerves before and at 5, 15, and 25 minutes

following stimulation. The amplitude of the N20-P25 SEP was increased at 15 to 25 minutes in the stimulated SI and for 5 minutes in the non-stimulated hemisphere [120]. Similarly, iTBS applied to left SI facilitated SEPs at 15 and 30 minutes (N20o-N20p at 15 min; N20p-P25 at 15 and 30 minutes) [118]. In the same study, following iTBS, no changes were observed in early or late HFOs. Perceptual benefits have also been observed following iTBS over SI. An improvement in tactile spatial acuity on the right index finger was observed for up to 30 minutes following iTBS over left SI [121].

Continuous TBS has been used to investigate the influence of SI on the excitability within M1. Ishikawa et al., (2007) delivered cTBS over SI and observed that MEPs were unchanged. Our lab has recently furthered this investigation by probing the influence SI on corticospinal excitability, intracortical and interhemispheric motor circuitry for the representation of the first dorsal interosseous muscle (FDI) of the hand (paper in preparation). We observed that cTBS over left-hemisphere SI increases the corticospinal output of the contralateral hand (increased MEPs), leads to modest but insignificant increases in contralateral ICF and ipsilateral SIHI, and does not alter SICI. Importantly, the influence on corticospinal excitability is specific to the direction of induced current, a topic that will be discussed later within this paper, and relates to the discrepancy between previous findings [116] and ours.

In addition to the influence of SI, higher-order somatosensory loci may also influence M1 activity. One such area that has been a focus of interest in our lab is Brodmann's area 5. Using dual coil TMS, we observed that area 5 facilitates M1 output to the FDI muscle of the hand when the thumb and index finger receive tactile stimulation [122]. We recently investigated the influence of area 5 on M1 corticospinal excitability and circuitry [123]. CTBS, iTBS, and sham TBS were delivered over area 5, and MEPs, SICI, and ICF were measured from the FDI muscle on each hand for up to one hour following stimulation. MEPs were increased bilaterally following cTBS, increased in the contralateral hand following iTBS and unchanged in the sham group. ICF and SICI were unchanged [123]. Further, cTBS over left-hemisphere area 5 increases SIHI in the ipsilateral hand [124]. Our studies in area 5 have led to the conclusion that higher-order somatic loci provide powerful modulation over the corticospinal and transcallosal output of M1 neurons. Comparing the results of our studies from area 5 versus SI, it appears that higher-order loci have may have a more potent influence on M1 activity, at least by the measures we obtained.

2.4. TBS Considerations. Although cTBS and iTBS protocols have been in use since the original publication appeared in 2005 [100], evidence continues to accumulate that the after effects are not always as predicted. We observed that both iTBS, thought to induce LTP-like effects, and cTBS, thought to induce LTD effects, lead to the same outcome following delivery over area 5 [125]. Similarly, another study has shown that cTBS and iTBS delivered over SI act similarly, such that both cTBS and iTBS each act to reduce the amplitude of laser-evoked potentials [126].

The effects of TBS are also dependent on stimulus intensity and the direction of induced current within the cortex. Some studies have demonstrated a lack of excitability change, or an effect in the opposite direction to the original observations by Huang et al. (2005), and this may relate to the intensity of TBS delivered. In contrast to the MEP suppression following cTBS delivered at 80% active motor threshold [100], cTBS at 70% rest motor threshold increases MEP amplitude [127, 128]. Less intense cTBS and iTBS delivered at 70% active motor threshold did not alter MEP amplitudes [129]. Another important consideration is the direction of induced current in the cortex. TBS is a biphasic waveform paradigm that may be applied with a coil orientation to induce a posterior-to-anterior initial phase followed by anterior-to-posterior (PA-AP) current in the cortex or vice versa (AP-PA). When applied with an AP-PA-induced current flow, cTBS led to increased MEP amplitude in the ipsilateral hand, in contrast to PA-AP cTBS which had no bilateral effect [115]. CTBS delivered in the AP-PA orientation induced a stronger effect on MEP amplitudes when the two orientations were matched in absolute stimulus intensity [113]. Together, these studies indicate that the effects of TBS are determined by parameters of stimulus intensity and direction of induced current in the brain.

Metaplasticity is also a consideration for TBS protocols. Muscle activity preceding, during, or immediately following TBS may alter after effects. CTBS-induced suppression and iTBS-induced facilitation of MEPs were abolished when stimulation was applied during simultaneous 10% MVC of the target muscle [130]. In contrast, muscle contraction performed for 1 minute following iTBS enhanced MEP facilitation and reduced the MEP inhibition [130]. Similarly, facilitation of MEP amplitude was observed following 300-pulse cTBS [127]. However, facilitation was replaced with inhibition when cTBS was preceded by 5 minutes of isometric thumb contraction at ~25% MVC [127]. When a brief cTBS protocol of 150 pulses is delivered one minute after facilitatory iTBS, the enhancement effect is abolished [131]. Likewise, a brief iTBS protocol shortly following cTBS abolishes any depressive effects on MEP amplitude [131].

3. Additional TMS Protocols to Induce SI Plasticity

In monkeys, the excitability of M1 pyramidal tract neurons is altered in response to stimulation of peripheral nerves [132]. In humans, peripheral nerve stimulation also modulates corticospinal excitability and circuitry within M1. Corticospinal excitability is decreased for 20–1000 ms following median nerve stimulation [49], and with the addition of cutaneous stimulation to the digit, ICF is enhanced [133]. SICI is reduced following cutaneous stimulation of the index finger [134]. Magnetoencephalography studies have demonstrated that the 20 Hz rhythm generated in the motor cortex is increased 20–1000 ms (tested at intervals of 200 ms) following median nerve stimulation and suppressed during voluntary movement and motor imagery of the hand [135, 136]. At shorter intervals and in contrast to SAI and LAI,

median nerve stimulation followed by single-pulse TMS to M1 at ISIs of 45–70 ms facilitates corticospinal excitability circuitry involved in ICF, while decreasing SICI, an effect named afferent-induced facilitation [137]. The aforementioned studies demonstrate that somatosensory afferent input is capable of transiently modifying M1 circuitry directed at muscles of the hand.

Longer-lasting changes in M1 excitability can be observed following manipulation of somatosensory afferent input. Blocking the peripheral afferent volley from synapsing within SI may also induce changes within M1. In humans, ischemic nerve block (INB) has been used to reproduce deafferentation, and TMS protocols may be used to examine changes in motor excitability. Compared to pre-INB measures, muscles proximal to the INB in the upper [138–140] and lower limb [140] demonstrate increased MEP amplitude, indicating that alterations in afferent input modulate the corticospinal excitability of M1. After INB, low-frequency rTMS (0.1 Hz) at a rate which does not induce excitability changes in the cortex in normal conditions significantly increased MEP amplitude, SICI, and ICF to a greater extent than INB alone [138]. However, in the same study, rTMS applied to the ipsilateral side of the INB canceled the MEP enhancement and decreased ICF, indicating M1 interhemispheric effects. The authors suggest that deafferentation permits the circuitry within M1 to be more susceptible to plastic changes [138]. Furthermore, MRS has clearly indicated that GABA, an inhibitory neurotransmitter, is decreased following INB in humans [141] leading the authors to suggest that INB-induced changes may involve a release of the SI to M1 inhibitory influence allowing the motor circuitry to be subsequently enhanced.

Another promising TMS-plasticity approach is called quadripulse stimulation (QPS) and involves four monophasic pulses delivered at 0.2 Hz for 30 minutes with effects that persist for 75 minutes following stimulation [142]. QPS is thought to modulate activity within M1 excitatory neural circuits [143, 144]. At short interpulse intervals ranging from 1.5 to 10 ms, MEPs are facilitated, while longer intervals (50, 100 ms) lead to a decrease in MEP amplitude. The greatest facilitation and suppression are observed at intervals of 5 and 50 ms, respectively [145]. One study has examined the use of QPS over M1 to alter excitability within contralateral SI as measured using SEPs [146]. The amplitude of the P25-N33 component was enhanced during both 5 and 50 ms QPS. However, at 30 minutes following QPS, only the 5 ms QPS paradigm led to a sustained increase in the P25-N33 that persisted for up to 90 minutes following stimulation [146]. These data suggest that QPS at 5 ms is a powerful modulator of SI excitability with effects that may outlast other TMS plasticity-inducing approaches. The threshold from LTD to LTP-like effects is modified by prior history of cortical activity [145], similar to the reversal of effects seen when voluntary contraction precedes TBS protocols [127].

4. Conclusion

This paper has illustrated the importance of understanding hand function through contributions of the somatosensory cortex using TMS plasticity-inducing protocols. Evidence clearly demonstrates that plasticity-inducing TMS protocols are a powerful tool to modulate SI physiology, tactile perception, and neural activity within M1. PAS, rTMS, and TBS are repetitive forms of TMS brain stimulation that may be used to alter the neurophysiology of cortical circuitry related to hand control. TMS paired with measures of physiology and/or perception further the understanding of the neural mechanisms that underpin somatosensory-guided hand control. This information is fundamental to creating new therapeutic applications of TMS plasticity protocols for clinical populations such as stroke and dystonia that present with impaired hand movement. An important consideration in all TMS techniques described in this paper is the state of neural activity within cortex prior to application of the plasticity-inducing stimulation since all protocols appear to be sensitive to metaplastic effects. Further, stimulus parameters such as intensity, orientation, and frequency influence the outcome of TMS protocols and are therefore important considerations in experimental design. Through further use of TMS plasticity-inducing protocols, we will continue to advance the understanding of sensorimotor hand control and further optimize protocols to evoke desired effects. This latter step will be a key element for future studies that aim to use plasticity-inducing TMS protocols as a potential therapeutic avenue to improve hand function.

References

[1] R. J. Nudo and K. M. Friel, "Cortical plasticity after stroke: implications for rehabilitation," *Revue Neurologique*, vol. 155, no. 9, pp. 713–717, 1999.

[2] T. Elbert, V. Candia, E. Altenmüller et al., "Alteration of digital representations in somatosensory cortex in focal hand dystonia," *NeuroReport*, vol. 9, no. 16, pp. 3571–3575, 1998.

[3] N. N. Byl, E. A. Pitsch, and G. M. Abrams, "Functional outcomes can vary by dose: learning-based sensorimotor training for patients stable poststroke," *Neurorehabilitation and Neural Repair*, vol. 22, no. 5, pp. 494–504, 2008.

[4] K. E. Zeuner, W. Bara-Jimenez, P. S. Noguchi, S. R. Goldstein, J. M. Dambrosia, and M. Hallett, "Sensory training for patients with focal hand dystonia," *Annals of Neurology*, vol. 51, no. 5, pp. 593–598, 2002.

[5] K. E. Zeuner and F. M. Molloy, "Abnormal reorganization in focal hand dystonia—sensory and motor training programs to retrain cortical function," *NeuroRehabilitation*, vol. 23, no. 1, pp. 43–53, 2008.

[6] V. B. Mountcastle, *The Sensory Hand, Neural Mechanisms of Somatic Sensation*, Harvard University Press, Cambridge, Mass, USA, 2005.

[7] J. H. Kaas, R. J. Nelson, and M. Sur, "Multiple representations of the body within the primary somatosensory cortex of primates," *Science*, vol. 204, no. 4392, pp. 521–523, 1979.

[8] M. M. Merzenich, J. H. Kaas, M. Sur, and C. S. Lin, "Double representation of the body surface within cytoarchitectonic areas 3b and 1 in 'SI' in the owl monkey (Aotus trivirgatus)," *Journal of Comparative Neurology*, vol. 181, no. 1, pp. 41–73, 1978.

[9] P. A. Gelnar, B. R. Krauss, N. M. Szeverenyi, and A. V. Apkarian, "Fingertip representation in the human somatosensory

cortex: an fMRI study," *NeuroImage*, vol. 7, no. 4, pp. 261–283, 1998.

[10] A. J. Nelson and R. Chen, "Digit somatotopy within cortical areas of the postcentral gyrus in humans," *Cerebral Cortex*, vol. 18, no. 10, pp. 2341–2351, 2008.

[11] S. Ghosh, C. Brinkman, and R. Porter, "A quantitative study of the distribution of neurons projecting to the precentral motor cortex in the monkey (M. fascicularis)," *Journal of Comparative Neurology*, vol. 259, no. 3, pp. 424–444, 1987.

[12] H. Aizawa and J. Tanji, "Corticocortical and thalamocortical responses of neurons in the monkey primary motor cortex and their relation to a trained motor task," *Journal of Neurophysiology*, vol. 71, no. 2, pp. 550–560, 1994.

[13] E. G. Jones, J. D. Coulter, and S. H. C. Hendry, "Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys," *Journal of Comparative Neurology*, vol. 181, no. 2, pp. 291–347, 1978.

[14] E. G. Jones and T. P. S. Powell, "Connexions of the somatic sensory cortex of the rhesus monkey: II.-Contralateral cortical connexions," *Brain*, vol. 92, no. 4, pp. 717–730, 1969.

[15] E. G. Jones and T. P. S. Powell, "Connexions of the somatic sensory cortex of the rhesus monkey: I.-ipsilateral CORTICAL connexions," *Brain*, vol. 92, no. 3, pp. 477–502, 1969.

[16] T. P. Pons and J. H. Kaas, "Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study," *Journal of Comparative Neurology*, vol. 248, no. 3, pp. 313–335, 1986.

[17] B. A. Vogt and D. N. Pandya, "Cortico-cortical connections of somatic sensory cortex (areas 3, 1 and 2) in the rhesus monkey," *Journal of Comparative Neurology*, vol. 177, no. 2, pp. 179–191, 1978.

[18] P. Zarzecki, Y. Shinoda, and H. Asanuma, "Projection from area 3a to the motor cortex by neurons activated from group I muscle afferents," *Experimental Brain Research*, vol. 33, no. 2, pp. 269–282, 1978.

[19] H. Sakata, Y. Takaoka, A. Kawarasaki, and H. Shibutani, "Somatosensory properties of neurons in the superior parietal cortex (area 5) of the rhesus monkey," *Brain Research*, vol. 64, pp. 85–102, 1973.

[20] Y. Iwamura, A. Iriki, and M. Tanaka, "Bilateral hand representation in the postcentral somatosensory cortex," *Nature*, vol. 369, no. 6481, pp. 554–556, 1994.

[21] J. Padberg, J. G. Franca, D. F. Cooke et al., "Parallel evolution of cortical areas involved in skilled hand use," *Journal of Neuroscience*, vol. 27, no. 38, pp. 10106–10115, 2007.

[22] J. Padberg, E. Disbrow, and L. Krubitzer, "The organization and connections of anterior and posterior parietal cortex in titi monkeys: do new world monkeys have an area 2?" *Cerebral Cortex*, vol. 15, no. 12, pp. 1938–1963, 2005.

[23] G. R. Leichnetz, "Afferent and efferent connections of the dorsolateral precentral gyrus (area 4, hand/arm region) in the macaque monkey, with comparisons to area 8," *Journal of Comparative Neurology*, vol. 254, no. 4, pp. 460–492, 1986.

[24] M. M. Merzenich, R. J. Nelson, M. P. Stryker, M. S. Cynader, A. Schoppmann, and J. M. Zook, "Somatosensory cortical map changes following digit amputation in adult monkeys," *The Journal of Comparative Neurology*, vol. 224, pp. 591–605, 1984.

[25] C. Xerri, M. M. Merzenich, W. Jenkins, and S. Santucci, "Representational plasticity in cortical area 3b paralleling tactual- motor skill acquisition in adult monkeys," *Cerebral Cortex*, vol. 9, no. 3, pp. 264–276, 1999.

[26] R. H. LaMotte and V. B. Mountcastle, "Disorders in somesthesis following lesions of parietal lobe," *Journal of Neurophysiology*, vol. 42, no. 2, pp. 400–419, 1979.

[27] M. Carlson, "Characteristics of sensory deficits following lesions of Brodmann's areas 1 and 2 in the postcentral gyrus of Macaca mulatta," *Brain Research*, vol. 204, no. 2, pp. 424–430, 1981.

[28] O. Hikosaka, M. Tanaka, M. Sakamoto, and Y. Iwamura, "Deficits in manipulative behaviors induced by local injections of muscimol in the first somatosensory cortex of the conscious monkey," *Brain Research*, vol. 325, no. 1-2, pp. 375–380, 1985.

[29] J. Brinkman, J. G. Colebatch, R. Porter, and D. H. York, "Responses of precentral cells during cooling of post-central cortex in conscious monkeys," *Journal of Physiology*, vol. 368, pp. 611–625, 1985.

[30] C. Pavlides, E. Miyashita, and H. Asanuma, "Projection from the sensory to the motor cortex is important in learning motor skills in the monkey," *Journal of Neurophysiology*, vol. 70, no. 2, pp. 733–741, 1993.

[31] A. Iriki, C. Pavlides, A. Keller, and H. Asanuma, "Long-term potentiation in the motor cortex," *Science*, vol. 245, no. 4924, pp. 1385–1387, 1989.

[32] T. Sakamoto, L. L. Porter, and H. Asanuma, "Long-lasting potentiation of synaptic potentials in the motor cortex produced by stimulation of the sensory cortex in the cat: a basis of motor learning," *Brain Research*, vol. 413, no. 2, pp. 360–364, 1987.

[33] G. L. Widener and P. D. Cheney, "Effects on muscle activity from microstimuli applied to somatosensory and motor cortex during voluntary movement in the monkey," *Journal of Neurophysiology*, vol. 77, no. 5, pp. 2446–2465, 1997.

[34] M. Hallett, "Transcranial magnetic stimulation: a primer," *Neuron*, vol. 55, no. 2, pp. 187–199, 2007.

[35] J. Reis, O. B. Swayne, Y. Vandermeeren et al., "Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control," *Journal of Physiology*, vol. 586, no. 2, pp. 325–351, 2008.

[36] B. L. Day, J. C. Rothwell, P. D. Thompson et al., "Motor cortex stimulation in intact man. 2. Multiple descending volleys," *Brain*, vol. 110, no. 5, pp. 1191–1209, 1987.

[37] J. C. Rothwell, P. D. Thompson, B. L. Day et al., "Motor cortex stimulation in intact man. I. General characteristics of EMG responses in different muscles," *Brain*, vol. 110, no. 5, pp. 1173–1190, 1987.

[38] N. T. Petersen, H. S. Pyndt, and J. B. Nielsen, "Investigating human motor control by transcranial magnetic stimulation," *Experimental Brain Research*, vol. 152, no. 1, pp. 1–16, 2003.

[39] T. Kujirai, M. D. Caramia, J. C. Rothwell et al., "Corticocortical inhibition in human motor cortex," *Journal of Physiology*, vol. 471, pp. 501–519, 1993.

[40] L. Roshan, G. O. Paradiso, and R. Chen, "Two phases of short-interval intracortical inhibition," *Experimental Brain Research*, vol. 151, no. 3, pp. 330–337, 2003.

[41] Z. Ni, C. Gunraj, and R. Chen, "Short interval intracortical inhibition and facilitation during the silent period in human," *Journal of Physiology*, vol. 583, no. 3, pp. 971–982, 2007.

[42] J. Valls-Solé, A. Pascual-Leone, E. M. Wassermann, and M. Hallett, "Human motor evoked responses to paired transcranial magnetic stimuli," *Electroencephalography and Clinical Neurophysiology*, vol. 85, no. 6, pp. 355–364, 1992.

[43] A. Ferbert, A. Priori, J. C. Rothwell, B. L. Day, J. G. Colebatch, and C. D. Marsden, "Interhemispheric inhibition of the

human motor cortex," *Journal of Physiology*, vol. 453, pp. 525–546, 1992.

[44] S. Kukaswadia, A. Wagle-Shukla, F. Morgante, C. Gunraj, and R. Chen, "Interactions between long latency afferent inhibition and interhemispheric inhibitions in the human motor cortex," *Journal of Physiology*, vol. 563, no. 3, pp. 915–924, 2005.

[45] Z. J. Daskalakis, B. K. Christensen, P. B. Fitzgerald, L. Roshan, and R. Chen, "The mechanisms of interhemispheric inhibition in the human motor cortex," *Journal of Physiology*, vol. 543, no. 1, pp. 317–326, 2002.

[46] K. Irlbacher, J. Brocke, J. V. Mechow, and S. A. Brandt, "Effects of GABAA and GABAB agonists on interhemispheric inhibition in man," *Clinical Neurophysiology*, vol. 118, no. 2, pp. 308–316, 2007.

[47] R. C. G. Helmich, T. Bäumer, H. R. Siebner, B. R. Bloem, and A. Münchau, "Hemispheric asymmetry and somatotopy of afferent inhibition in healthy humans," *Experimental Brain Research*, vol. 167, no. 2, pp. 211–219, 2005.

[48] P. J. Delwaide and E. Olivier, "Conditioning transcranial cortical stimulation (TCCS) by exteroceptive stimulation in parkinsonian patients.," *Advances in neurology*, vol. 53, pp. 175–181, 1990.

[49] R. Chen, B. Corwell, and M. Hallett, "Modulation of motor cortex excitability by median nerve and digit stimulation," *Experimental Brain Research*, vol. 129, no. 1, pp. 77–86, 1999.

[50] K. Stefan, E. Kunesch, L. G. Cohen, R. Benecke, and J. Classen, "Induction of plasticity in the human motor cortex by paired associative stimulation," *Brain*, vol. 123, no. 3, pp. 572–584, 2000.

[51] K. Stefan, E. Kunesch, R. Benecke, L. G. Cohen, and J. Classen, "Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation," *Journal of Physiology*, vol. 543, no. 2, pp. 699–708, 2002.

[52] A. Wolters, F. Sandbrink, A. Schlottmann et al., "A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex," *Journal of Neurophysiology*, vol. 89, no. 5, pp. 2339–2345, 2003.

[53] M. C. Ridding and U. Ziemann, "Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects," *Journal of Physiology*, vol. 588, no. 13, pp. 2291–2304, 2010.

[54] Y. Dan and M. M. Poo, "Spike timing-dependent plasticity of neural circuits," *Neuron*, vol. 44, no. 1, pp. 23–30, 2004.

[55] S. F. Cooke and T. V. P. Bliss, "Plasticity in the human central nervous system," *Brain*, vol. 129, no. 7, pp. 1659–1673, 2006.

[56] K. Stefan, E. Kunesch, L. G. Cohen, R. Benecke, and J. Classen, "Induction of plasticity in the human motor cortex by paired associative stimulation," *Brain*, vol. 123, no. 3, pp. 572–584, 2000.

[57] G. Hess and J. P. Donoghue, "Long-term potentiation and long-term depression of horizontal connections in rat motor cortex," *Acta Neurobiologiae Experimentalis*, vol. 56, no. 1, pp. 397–405, 1996.

[58] K. Stefan, E. Kunesch, R. Benecke, L. G. Cohen, and J. Classen, "Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation," *Journal of Physiology*, vol. 543, no. 2, pp. 699–708, 2002.

[59] A. Wolters, F. Sandbrink, A. Schlottmann et al., "A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex," *Journal of Neurophysiology*, vol. 89, no. 5, pp. 2339–2345, 2003.

[60] M. A. Castro-Alamancos, J. P. Donoghue, and B. W. Connors, "Different forms of synaptic plasticity in somatosensory and motor areas of the neocortex," *Journal of Neuroscience*, vol. 15, no. 7, pp. 5324–5333, 1995.

[61] M. C. Ridding and J. L. Taylor, "Mechanisms of motor-evoked potential facilitation following prolonged dual peripheral and central stimulation in humans," *Journal of Physiology*, vol. 537, no. 2, pp. 623–631, 2001.

[62] H. Russmann, J. C. Lamy, E. A. Shamim, S. Meunier, and M. Hallett, "Associative plasticity in intracortical inhibitory circuits in human motor cortex," *Clinical Neurophysiology*, vol. 120, no. 6, pp. 1204–1212, 2009.

[63] A. Wolters, A. Schmidt, A. Schramm et al., "Timing-dependent plasticity in human primary somatosensory cortex," *Journal of Physiology*, vol. 565, no. 3, pp. 1039–1052, 2005.

[64] L. Krivanekova, M. K. Lu, B. Bliem, and U. Ziemann, "Modulation of excitability in human primary somatosensory and motor cortex by paired associative stimulation targeting the primary somatosensory cortex," *European Journal of Neuroscience*, vol. 34, pp. 1292–1300, 2011.

[65] Y. Tamura, Y. Ueki, P. Lin et al., "Disordered plasticity in the primary somatosensory cortex in focal hand dystonia," *Brain*, vol. 132, no. 3, pp. 749–755, 2009.

[66] Y. Tamura, Y. Ueki, P. Lin et al., "Disordered plasticity in the primary somatosensory cortex in focal hand dystonia," *Brain*, vol. 132, no. 3, pp. 749–755, 2009.

[67] W. C. Abraham, "Metaplasticity: tuning synapses and networks for plasticity," *Nature Reviews Neuroscience*, vol. 9, no. 5, pp. 387–399, 2008.

[68] I. Delvendahl, N. H. Jung, F. Mainberger, N. G. Kuhnke, M. Cronjaeger, and V. Mall, "Occlusion of bidirectional plasticity by preceding low-frequency stimulation in the human motor cortex," *Clinical Neurophysiology*, vol. 121, no. 4, pp. 594–602, 2010.

[69] K. Stefan, M. Wycislo, R. Gentner et al., "Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training," *Cerebral Cortex*, vol. 16, no. 3, pp. 376–385, 2006.

[70] U. Ziemann, T. V. Iliać, C. Pauli, F. Meintzschel, and D. Ruge, "Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex," *Journal of Neuroscience*, vol. 24, no. 7, pp. 1666–1672, 2004.

[71] M. V. Sale, M. C. Ridding, and M. A. Nordstrom, "Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation," *Experimental Brain Research*, vol. 181, no. 4, pp. 615–626, 2007.

[72] K. Stefan, M. Wycislo, and J. Classen, "Modulation of associative human motor cortical plasticity by attention," *Journal of Neurophysiology*, vol. 92, no. 1, pp. 66–72, 2004.

[73] S. Meunier, H. Russmann, M. Simonetta-Moreau, and M. Hallett, "Changes in spinal excitability after PAS," *Journal of Neurophysiology*, vol. 97, no. 4, pp. 3131–3135, 2007.

[74] J. C. Lamy, H. Russmann, E. A. Shamim, S. Meunier, and M. Hallett, "Paired associative stimulation induces change in presynaptic inhibition of Ia terminals in wrist flexors in humans," *Journal of Neurophysiology*, vol. 104, no. 2, pp. 755–764, 2010.

[75] Y. Terao and Y. Ugawa, "Basic mechanisms of TMS," *Journal of Clinical Neurophysiology*, vol. 19, no. 4, pp. 322–343, 2002.

[76] R. Chen, J. Classen, C. Gerloff et al., "Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation," *Neurology*, vol. 48, no. 5, pp. 1398–1403, 1997.

[77] A. Pascual-Leone, J. Valls-Sole, E. M. Wassermann, and M. Hallett, "Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex," *Brain*, vol. 117, no. 4, pp. 847–858, 1994.

[78] A. Berardelli, M. Inghilleri, J. C. Rothwell et al., "Facilitation of muscle evoked responses after repetitive cortical stimulation in man," *Experimental Brain Research*, vol. 122, no. 1, pp. 79–84, 1998.

[79] A. Peinemann, C. Lehner, C. Mentschel, A. Münchau, B. Conrad, and H. R. Siebner, "Subthreshold 5-Hz repetitive transcranial magnetic stimulation of the human primary motor cortex reduces intracortical paired-pulse inhibition," *Neuroscience Letters*, vol. 296, no. 1, pp. 21–24, 2000.

[80] G. W. Thickbroom, "Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models," *Experimental Brain Research*, vol. 180, no. 4, pp. 583–593, 2007.

[81] A. Benali, J. Trippe, E. Weiler et al., "Theta-burst transcranial magnetic stimulation alters cortical inhibition," *Journal of Neuroscience*, vol. 31, no. 4, pp. 1193–1203, 2011.

[82] J. Trippe, A. Mix, S. Aydin-Abidin, K. Funke, and A. Benali, "Theta burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex," *Experimental Brain Research*, vol. 199, no. 3-4, pp. 411–421, 2009.

[83] T. Satow, T. Mima, J. Yamamoto et al., "Short-lasting impairment of tactile perception by 0.9Hz-rTMS of the sensorimotor cortex," *Neurology*, vol. 60, no. 6, pp. 1045–1047, 2003.

[84] S. Knecht, T. Ellger, C. Breitenstein, E. B. Ringelstein, and H. Henningsen, "Changing cortical excitability with low-frequency transcranial magnetic stimulation can induce sustained disruption of tactile perception," *Biological Psychiatry*, vol. 53, no. 2, pp. 175–179, 2003.

[85] E. D. Vidoni, N. E. Acerra, E. Dao, S. K. Meehan, and L. A. Boyd, "Role of the primary somatosensory cortex in motor learning: an rTMS study," *Neurobiology of Learning and Memory*, vol. 93, no. 4, pp. 532–539, 2010.

[86] P. Ragert, H. R. Dinse, B. Pleger et al., "Combination of 5 Hz repetitive transcranial magnetic stimulation (rTMS) and tactile coactivation boosts tactile discrimination in humans," *Neuroscience Letters*, vol. 348, no. 2, pp. 105–108, 2003.

[87] P. Ragert, M. Becker, M. Tegenthoff, B. Pleger, and H. R. Dinse, "Sustained increase of somatosensory cortex excitability by 5 Hz repetitive transcranial magnetic stimulation studied by paired median nerve stimulation in humans," *Neuroscience Letters*, vol. 356, no. 2, pp. 91–94, 2004.

[88] M. Tegenthoff, P. Ragert, B. Pleger et al., "Improvement of tactile discrimination performance and enlargement of cortical somatosensory maps after 5 Hz rTMS," *PLoS Biology*, vol. 3, no. 11, article e362, 2005.

[89] B. Pleger, F. Blankenburg, S. Bestmann et al., "Repetitive transcranial magnetic stimulation-induced changes in sensorimotor coupling parallel improvements of somatosensation in humans," *Journal of Neuroscience*, vol. 26, no. 7, pp. 1945–1952, 2006.

[90] A. A. Karim, A. Schüler, Y. L. Hegner, E. Friedel, and B. Godde, "Facilitating effect of 15-Hz repetitive transcranial magnetic stimulation on tactile perceptual learning," *Journal of Cognitive Neuroscience*, vol. 18, no. 9, pp. 1577–1585, 2006.

[91] T. Fujiwara and J. C. Rothwell, "The after effects of motor cortex rTMS depend on the state of contraction when rTMS is applied," *Clinical Neurophysiology*, vol. 115, no. 7, pp. 1514–1518, 2004.

[92] G. Todd and M. C. Ridding, "The response to repetitive stimulation of human motor cortex is influenced by the history of synaptic activity," *Restorative Neurology and Neuroscience*, vol. 28, no. 4, pp. 459–467, 2010.

[93] H. Enomoto, Y. Ugawa, R. Hanajima et al., "Decreased sensory cortical excitability after 1 Hz rTMS over the ipsilateral primary motor cortex," *Clinical Neurophysiology*, vol. 112, no. 11, pp. 2154–2158, 2001.

[94] H. Mochizuki, Y. Terao, S. Okabe et al., "Effects of motor cortical stimulation on the excitability of contralateral motor and sensory cortices," *Experimental Brain Research*, vol. 158, no. 4, pp. 519–526, 2004.

[95] T. Tings, N. Lang, F. Tergau, W. Paulus, and M. Sommer, "Orientation-specific fast rTMS maximizes corticospinal inhibition and facilitation," *Experimental Brain Research*, vol. 164, no. 3, pp. 323–333, 2005.

[96] U. Berger, A. Korngreen, I. Bar-Gad, A. Friedman, S. Wolfus, Y. Yeshurun et al., "Magnetic stimulation intensity modulates motor inhibition," *Neuroscience Letters*, vol. 504, pp. 93–97, 2011.

[97] A. Quartarone, S. Bagnato, V. Rizzo et al., "Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex," *Experimental Brain Research*, vol. 161, no. 1, pp. 114–124, 2005.

[98] P. B. Fitzgerald, S. Fountain, and Z. J. Daskalakis, "A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition," *Clinical Neurophysiology*, vol. 117, no. 12, pp. 2584–2596, 2006.

[99] G. S. Pell, Y. Roth, and A. Zangen, "Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms," *Progress in Neurobiology*, vol. 93, no. 1, pp. 59–98, 2011.

[100] Y. Z. Huang, M. J. Edwards, E. Rounis, K. P. Bhatia, and J. C. Rothwell, "Theta burst stimulation of the human motor cortex," *Neuron*, vol. 45, no. 2, pp. 201–206, 2005.

[101] R. M. Vickery, S. H. Morris, and L. J. Bindman, "Metabotropic glutamate receptors are involved in long-term potentiation in isolated slices of rat medial frontal cortex," *Journal of Neurophysiology*, vol. 78, no. 6, pp. 3039–3046, 1997.

[102] J. Larson, D. Wong, and G. Lynch, "Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation," *Brain Research*, vol. 368, no. 2, pp. 347–350, 1986.

[103] D. S. Barr, N. A. Lambert, K. L. Hoyt, S. D. Moore, and W. A. Wilson, "Induction and reversal of long-term potentiation by low- and high- intensity theta pattern stimulation," *Journal of Neuroscience*, vol. 15, no. 7, pp. 5402–5410, 1995.

[104] T. Otto, H. Eichenbaum, S. I. Wiener, and C. G. Wible, "Learning-related patterns of CA1 spike trains parallel stimulation parameters optimal for inducing hippocampal long-term potentiation.," *Hippocampus*, vol. 1, no. 2, pp. 181–192, 1991.

[105] D. L. Martin and K. Rimvall, "Regulation of gamma-aminobutyric acid synthesis in the brain," *Journal of Neurochemistry*, vol. 60, pp. 395–407, 1993.

[106] J. Wei, K. M. Davis, H. Wu, and J. Y. Wu, "Protein phosphorylation of human brain glutamic acid decarboxylase (GAD)65

and GAD67 and its physiological implications," *Biochemistry*, vol. 43, no. 20, pp. 6182–6189, 2004.

[107] H. Markram, M. Toledo-Rodriguez, Y. Wang, A. Gupta, G. Silberberg, and C. Wu, "Interneurons of the neocortical inhibitory system," *Nature Reviews Neuroscience*, vol. 5, no. 10, pp. 793–807, 2004.

[108] L. Cardenas-Morales, D. A. Nowak, T. Kammer, R. C. Wolf, and C. Schonfeldt-Lecuona, "Mechanisms and applications of theta-burst rTMS on the human motor cortex," *Brain Topography*, vol. 22, pp. 294–306, 2010.

[109] C. J. Stagg, M. Wylezinska, P. M. Matthews et al., "Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy," *Journal of Neurophysiology*, vol. 101, no. 6, pp. 2872–2877, 2009.

[110] Y. Z. Huang, R. S. Chen, J. C. Rothwell, and H. Y. Wen, "The after-effect of human theta burst stimulation is NMDA receptor dependent," *Clinical Neurophysiology*, vol. 118, no. 5, pp. 1028–1032, 2007.

[111] J. T. H. Teo, O. B. Swayne, and J. C. Rothwell, "Further evidence for NMDA-dependence of the after-effects of human theta burst stimulation," *Clinical Neurophysiology*, vol. 118, no. 7, pp. 1649–1651, 2007.

[112] K. Monte-Silva, D. Ruge, J. T. Teo, W. Paulus, J. C. Rothwell, and M. A. Nitsche, "D2 receptor block abolishes theta burst stimulation-induced neuroplasticity in the human motor cortex," *Neuropsychopharmacology*, vol. 36, pp. 2097–2102, 2011.

[113] P. Talelli, B. J. Cheeran, J. T. H. Teo, and J. C. Rothwell, "Pattern-specific role of the current orientation used to deliver Theta Burst Stimulation," *Clinical Neurophysiology*, vol. 118, no. 8, pp. 1815–1823, 2007.

[114] N. Zafar, W. Paulus, and M. Sommer, "Comparative assessment of best conventional with best theta burst repetitive transcranial magnetic stimulation protocols on human motor cortex excitability," *Clinical Neurophysiology*, vol. 119, no. 6, pp. 1393–1399, 2008.

[115] A. Suppa, E. Ortu, N. Zafar et al., "Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans," *Journal of Physiology*, vol. 586, no. 18, pp. 4489–4500, 2008.

[116] S. Ishikawa, K. Matsunaga, R. Nakanishi et al., "Effect of Theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials," *Clinical Neurophysiology*, vol. 118, no. 5, pp. 1033–1043, 2007.

[117] N. Rai, A. Premji, M. Tommerdahl, and A. J. Nelson, "Continuous Theta-burst rTMS over primary somatosensory cortex modulates tactile perception on the hand," *Clinical Neurophysiology*. In press.

[118] T. Katayama, A. Suppa, and J. C. Rothwell, "Somatosensory evoked potentials and high frequency oscillations are differently modulated by theta burst stimulation over primary somatosensory cortex in humans," *Clinical Neurophysiology*, vol. 121, no. 12, pp. 2097–2103, 2010.

[119] T. Katayama and J. C. Rothwell, "Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation," *Clinical Neurophysiology*, vol. 118, no. 11, pp. 2506–2511, 2007.

[120] A. Premji, A. Ziluk, and A. J. Nelson, "Bilateral somatosensory evoked potentials following intermittent theta-burst repetitive transcranial magnetic stimulation," *BMC Neuroscience*, vol. 11, article 91, 2010.

[121] P. Ragert, S. Franzkowiak, P. Schwenkreis, M. Tegenthoff, and H. R. Dinse, "Improvement of tactile perception and enhancement of cortical excitability through intermittent theta burst rTMS over human primary somatosensory cortex," *Experimental Brain Research*, vol. 184, no. 1, pp. 1–11, 2008.

[122] A. Ziluk, A. Premji, and A. J. Nelson, "Functional connectivity from area 5 to primary motor cortex via paired-pulse transcranial magnetic stimulation," *Neuroscience Letters*, vol. 484, no. 1, pp. 81–85, 2010.

[123] A. Premji, N. Rai, and A. Nelson, "Area 5 influences excitability within the primary motor cortex in humans," *PLoS ONE*, vol. 6, no. 5, Article ID e20023, 2011.

[124] A. Premji, C. Zapallow, P. Tsang, R. Tang, M. Jacobs, and A. J. Nelson, "Influence of area 5 on interhemispheric inhibition," *NeuroReport*, vol. 22, pp. 974–978, 2011.

[125] A. Premji, N. Rai, and A. Nelson, "Area 5 influences excitability within the primary motor cortex in humans," *PLoS ONE*, vol. 6, no. 5, Article ID e20023, 2011.

[126] C. Poreisz, G. Csifcsák, A. Antal, M. Levold, F. Hillers, and W. Paulus, "Theta burst stimulation of the motor cortex reduces laser-evoked pain perception," *NeuroReport*, vol. 19, no. 2, pp. 193–196, 2008.

[127] R. Gentner, K. Wankerl, C. Reinsberger, D. Zeller, and J. Classen, "Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity," *Cerebral Cortex*, vol. 18, no. 9, pp. 2046–2053, 2008.

[128] S. H. Doeltgen and M. C. Ridding, "Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks," *Clinical Neurophysiology*, vol. 122, no. 7, pp. 1411–1416, 2011.

[129] S. M. McAllister, J. C. Rothwell, and M. C. Ridding, "Selective modulation of intracortical inhibition by low-intensity Theta Burst Stimulation," *Clinical Neurophysiology*, vol. 120, no. 4, pp. 820–826, 2009.

[130] Y. Z. Huang, J. C. Rothwell, M. J. Edwards, and R. S. Chen, "Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human," *Cerebral Cortex*, vol. 18, no. 3, pp. 563–570, 2008.

[131] Y. Z. Huang, J. C. Rothwell, C. S. Lu, W. L. Chuang, W. Y. Lin, and R. S. Chen, "Reversal of plasticity-like effects in the human motor cortex," *Journal of Physiology*, vol. 588, no. 19, pp. 3683–3693, 2010.

[132] R. Porter and P. M. H. Rack, "Timing of the responses in the motor cortex of monkeys to an unexpected disturbance of finger position," *Brain Research*, vol. 103, no. 2, pp. 201–213, 1976.

[133] M. Kobayashi, J. Ng, H. Théoret, and A. Pascual-Leone, "Modulation of intracortical neuronal circuits in human hand motor area by digit stimulation," *Experimental Brain Research*, vol. 149, no. 1, pp. 1–8, 2003.

[134] M. C. Ridding and J. C. Rothwell, "Afferent input and cortical organisation: a study with magnetic stimulation," *Experimental Brain Research*, vol. 126, no. 4, pp. 536–544, 1999.

[135] R. Salmelin and R. Hari, "Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement," *Neuroscience*, vol. 60, no. 2, pp. 537–550, 1994.

[136] R. Salmelin and R. Hari, "Characterization of spontaneous MEG rhythms in healthy adults," *Electroencephalography and Clinical Neurophysiology*, vol. 91, pp. 237–248, 1994.

[137] H. Devanne, A. Degardin, L. Tyvaert et al., "Afferent-induced facilitation of primary motor cortex excitability in the region controlling hand muscles in humans," *European Journal of Neuroscience*, vol. 30, no. 3, pp. 439–448, 2009.

[138] U. Ziemann, B. Corwell, and L. G. Cohen, "Modulation of plasticity in human motor cortex after forearm ischemic nerve block," *Journal of Neuroscience*, vol. 18, no. 3, pp. 1115–1123, 1998.

[139] U. Ziemann, M. Hallett, and L. G. Cohen, "Mechanisms of deafferentation-induced plasticity in human motor cortex," *Journal of Neuroscience*, vol. 18, no. 17, pp. 7000–7007, 1998.

[140] J. P. Brasil-Neto, J. Valls-Sole, A. Pascual-Leone et al., "Rapid modulation of human cortical motor outputs following ischaemic nerve block," *Brain*, vol. 116, no. 3, pp. 511–525, 1993.

[141] L. M. Levy, U. Ziemann, R. Chen, and L. G. Cohen, "Rapid modulation of GABA in sensorimotor cortex induced by acute deafferentation," *Annals of Neurology*, vol. 52, no. 6, pp. 755–761, 2002.

[142] M. Hamada, R. Hanajima, Y. Terao et al., "Quadro-pulse stimulation is more effective than paired-pulse stimulation for plasticity induction of the human motor cortex," *Clinical Neurophysiology*, vol. 118, no. 12, pp. 2672–2682, 2007.

[143] M. Hamada and Y. Ugawa, "Quadripulse stimulation—a new patterned rTMS," *Restorative Neurology and Neuroscience*, vol. 28, no. 4, pp. 419–424, 2010.

[144] Y. Z. Huang, M. Sommer, G. Thickbroom et al., "Consensus: new methodologies for brain stimulation," *Brain Stimulation*, vol. 2, no. 1, pp. 2–13, 2009.

[145] M. Hamada, Y. Terao, R. Hanajima et al., "Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation," *Journal of Physiology*, vol. 586, no. 16, pp. 3927–3947, 2008.

[146] M. Hirose, H. Mochizuki, S. J. Groiss, Y. Tanji, K. Nakamura, and S. Nakatani-Enomoto, "On-line effects of quadripulse transcranial magnetic stimulation (QPS) on the contralateral hemisphere studied with somatosensory evoked potentials and near infrared spectroscopy," *Experimental Brain Research*, vol. 214, pp. 577–586, 2011.

Hindawi Publishing Corporation
Neural Plasticity
Volume 2012, Article ID 970136, 10 pages
doi:10.1155/2012/970136

Review Article

Plasticity of Adult Sensorimotor System in Severe Brain Infarcts: Challenges and Opportunities

Annette Sterr[1] and Adriana Bastos Conforto[2,3]

[1] *School of Psychology, University of Surrey, Guildford GU2 7XH, UK*
[2] *Neurology Clincal Division, Hospital das Clinicas, São Paulo University, 05403-000 São Paulo, SP, Brazil*
[3] *Instituto Israelita de Ensino e Pesquisa, Hospital Israelita Albert Einstein, 05652-900 São Paulo, SP, Brazil*

Correspondence should be addressed to Annette Sterr, a.sterr@surrey.ac.uk

Received 4 December 2011; Accepted 9 January 2012

Academic Editor: Jacques-Olivier Coq

Functional reorganization forms the critical mechanism for the recovery of function after brain damage. These processes are driven by inherent changes within the central nervous system (CNS) triggered by the insult and further depend on the neural input the recovering system is processing. Therefore these processes interact with not only the interventions a patient receives, but also the activities and behaviors a patient engages in. In recent years, a wide range of research programs has addressed the association between functional reorganization and the spontaneous and treatment-induced recovery. The bulk of this work has focused on upper-limb and hand function, and today there are new treatments available that capitalize on the neuroplasticity of the brain. However, this is only true for patients with mild to moderated impairments; for those with very limited hand function, the basic understanding is much poorer and directly translates into limited treatment opportunities for these patients. The present paper aims to highlight the knowledge gap on severe stroke with a brief summary of the literature followed by a discussion of the challenges involved in the study and treatment of severe stroke and poor long-term outcome.

1. Background

The seminal discovery of adult brain plasticity in animals and humans has hugely influenced the theories and concepts applied in neurorehabilitation research and their translation into practice, in particular with regards to movement deficits in acquired brain injury [1, 2]. This work directly translated into new and, in some cases, more efficient interventions for patients with mild to moderate hemiparesis (e.g., [3–5]). However, much less research has specifically investigated the reorganization of the motor system in patients with poor or minimal functional abilities and, most critically, the rehabilitation of these patients [6, 7]. This gap in the literature may be present for a number of reasons. Firstly, standard rehabilitation approaches are difficult to apply when patients have little voluntary movement. Secondly, the lack of funding for regular one-to-one physical therapy sessions beyond the postacute phase, together with the common assumption that substantial improvements in functional motor ability are unlikely once the first 6 months of recovery have passed, primes the health care system and patients to accept the status quo. While the latter is true for the whole range of functional recovery, the impact is particularly grave for patients with poor functional recovery and also affects the research effort. Thirdly, the motor system of patients with poor residual recovery cannot easily be studied with the paradigms adopted from basic science research, such as finger opposition or grip movements. These methodological challenges can be overcome by excluding patients with high levels of spasm or by limiting the study group to those with relatively good levels of motor control. As a result, the motor system of patients with very poor recovery, in particular in chronic state, has been studied much less than that of patients with mild or moderate impairment. This translates directly into studies on treatment efficacy, and indeed, the availability of suitable treatments per se.

Based on the aforementioned considerations we argue that research on the mechanisms of long-term recovery, and

their interaction with treatment efficacy, needs to widen its focus to the population of stroke survivors with severe long-term motor deficits. Hereinafter we briefly summarise the present literature and further discuss the challenges involved in the study and treatment of patients with minimal motor recovery.

2. Animal Models of Focal Ischemia versus Human Strokes

On average, 80% of all strokes are ischemic, and 20% are hemorrhagic [8]. Upper limb paresis occurs in 85% of the patients and substantially impacts disability in the long term [9]. Animal models have tried to reproduce stroke lesions that occur in humans, with variable degrees of success. The majority of focal ischemia models involve the middle cerebral artery (MCA) territory, the most commonly affected arterial territory in ischemic strokes in humans [10].

2.1. Animal Models of Focal Ischemia. Rat focal ischemia models are frequently used because of low cost, similarities between vasculatures of rats and humans, fewer concerns from the general public compared to nonrodents, and availability of clear behavioral outcomes [11–13].

Severe MCA infarcts in rodents leading to long-lasting sensorimotor and cognitive deficits can be produced by proximal MCA occlusion induced by electrocoagulation. Complete or partial MCA occlusion can be also achieved by insertion of an intraluminal filament. In the filament model, mortality can be high if a large stroke is produced [14].

Other models lead to less severe morbidity and mortality. For example, if endothelin-1 [15], a vasoconstrictor drug, is injected topically or intracerebrally, the forelimb motor cortex is typically spared, but infarcts vary in location and extension depending on the sites and route of drug administration. In models of occlusion of the distal MCA or its branches, cortical frontoparietal infarcts are associated with less severe deficits than in the cortico-subcortical infarcts produced by proximal MCA occlusion [16]. Furthermore, multiple embolic infarcts can be produced in brain areas supplied by the MCA, after injection of microspheres [17], macrospheres [18], a thrombotic clot, or purified thrombin into the internal carotid artery [19, 20]. Finally, light activation of photosensitive dyes such as Rose Bengal makes small cortical infarcts possible, by occlusion of cortical vessels [21].

Many of these techniques have not been applied exclusively to small animals such as rats, mice, gerbils, or rabbits, but also to cats, dogs, pigs, and monkeys. Larger animals have proportions of gray/white matter that are more similar to those found in human brains, in contrast with lissencephalic brains of rats and mice [22]. However, technical limitations and costs limit widespread use of focal ischemia models in larger animals. It is recommended, for instance, that new drugs be tested first in rodents, before efficacy is investigated in gyrencephalic species [23].

Animal models are a double-edged sword when used to understand stroke pathogenesis. They offer powerful opportunities: the possibility to objectively monitor behavioral outcomes, manipulate experimental conditions, and obtain images (MRI, microPET) or intracortical recordings of neuronal activity in living animals; to scrutinize molecular mechanisms of cell death and recovery; to work with strains and transgenic animals that present hypertension, atherosclerosis and obesity, among other factors that are common in patients with stroke; and to perform post-mortem histological evaluations.

Still, conclusions based on animal models of focal ischemia must be examined with caution. For instance, small, selective cortical infarcts leading to mild sensorimotor deficits that tend to improve quickly are present in some of the models but are not common in humans, even though similar clinical features can occur in subcortical, lacunar infarcts. In addition, background pathophysiology is not shared between focal cerebral ischemia in rodents and humans. Fast arterial recanalization is achieved in several animal models, while in humans recanalization can occur either after r-tPA administration or spontaneously but, unfortunately, does not happen at an early phase after ischemic injury in most patients [8, 24–27]. Lack of arterial recanalization is strongly associated with more severe strokes and lower probabilities of recovery. Furthermore, rodent models have often included young healthy animals while, in humans, the bulk of strokes is concentrated in the elderly [28–32].

Age is a potent predictor of poor outcome in humans [33, 34]. Interestingly, despite high mortality rates in old mice, levels of recovery at four weeks have been reported to be similar in aged and young animals [35]. Other factors may contribute to poor outcome in humans, ranging from different mechanisms underlying strokes in different age groups to self-fulfilling prophecies in stroke care in the aged, and importantly, to comorbidities that impact recovery. Diabetes mellitus and atrial fibrillation, for instance, are significantly associated with more severe outcomes and lower chances of recovery [36, 37].

Hypertensive rats have poorer collateral blow flow and also worse outcomes after focal ischemia than nonhypertensive animals [38]. The demand for stroke models in hypertensive, obese, and aged rodents has been underlined [22]. Contrasts between the compelling efficacy of a myriad of drugs in animal models of neuroprotection and the systematic failure of the same drugs when administered to patients in clinical trials underscore the requirement for animal models that more realistically approach human strokes [13, 22, 39]. However, bigger rates of complications and mortality in aged or unhealthy animals, technical difficulties (anesthesia, complex surgeries in less flexible arteries, etc.), and hence the greater costs involved present challenges for advancements of research in the field. In particular, high mortality rates limit the opportunity to study recovery of animals with severe strokes in the chronic phase.

In summary, there is a gap between pathogenesis and clinical features of severe strokes in humans and pathogenesis and clinical features of the most widely used models of focal ischemia in animals. High costs and lower expectations for substantial improvements in activity or quality of life

are also major obstacles for rehabilitation of patients with severe strokes. Still, as stroke mortality decreases in parallel with advances in health care, it is expected that more patients with severe strokes will survive the acute phase over the next decades. At the moment, successful rehabilitation strategies for these patients are largely insufficient. Thus, animal models of focal ischemia that match severe human strokes more closely are deeply needed.

Despite these limitations, animal models have provided unique insight on plastic mechanisms underlying sensorimotor recovery after focal ischemia, and on how to enhance beneficial patterns of reorganization to obtain behavioral gains (e.g., [40]). Constraint-induced movement therapy, for instance, shown to improve motor outcomes in humans with different types and sizes of strokes, was developed based on seminal studies that underscored the importance of the amount of use of the paretic limb to promote enhancement of motor function [41, 42]. The phenomenon was observed in monkeys with small cortical infarcts submitted to intracortical microstimulation and behavioral testing [42]. As mentioned before, such small infarcts are rarely observed in humans, but still, the information gained by the model was a major step forward in stroke rehabilitation. Constraint-induced therapy has now been successfully applied to patients with various types of strokes, with more severe deficits and worse motor prognoses than the monkeys included in the model of forced use of the affected limb [1, 3, 43, 44].

2.2. Studying Recovery after Stroke in Humans: Neurophysiology and Neuroimaging. Over the past decades, neuroimaging and neurophysiology techniques have emerged as paramount tools to study brain reorganization in humans [45–50]. Overall, functional neuroimaging studies in patients with stroke have shown that good performance is associated with augmented activity in preexisting networks during a motor task, rather than assignment of networks that are not overtly active during these tasks in healthy subjects. Furthermore, incremental activity in undamaged areas may negatively impact motor performance.

For instance, according to the model of interhemispheric inhibition, an imbalance in activity between the ipsilesional and the contralesional primary motor cortex (M1) can occur after stroke [51, 52]. The ipsilesional M1 may be less able to inhibit the contralateral M1. The disinhibited contralesional M1, in turn, may excessively inhibit the ipsilesional M1. A number of studies have shown that this imbalance in activity between the two hemispheres can impair motor performance of the affected hand, at least in some patients in the chronic phase after stroke [51, 52]. Whether interhemispheric callosal fibers mediate this phenomenon or whether it depends on changes in activity of cerebellar or thalamic pathways, remains an open question [52]. However, the vast majority of published studies that investigated effects of modulation of interhemispheric inhibition only included patients with mild to moderate motor impairments, likely due to difficulties in developing tasks and applying available neurophysiology and neuroimaging tools to more severely affected patients [51–59].

In regard to recruitment of ipsilesional or contralesional secondary motor areas, striking differences in patterns of function were unveiled when paradigms of investigation were applied to patients with poor recovery, compared to those of less affected patients or healthy subjects. Recruitment of secondary motor areas occurs when the outflow from M1 is disconnected from the spinal cord in large cortical, corticosubcortical or subcortical strokes, as well as in strokes that strategically damage the corticospinal tract [60, 61]. At least in part, more pronounced patterns of activity in secondary motor areas in the ipsilesional and/or contralesional areas are associated with more severe disruption of the corticospinal pathway, and excessive activation of secondary motor areas correlates with poorer motor behavior [48, 50, 62]. Whether excessive activations of secondary motor areas or contralesional M1 are maladaptive, whether they represent the best possible remodeling option after severe injury, or whether they may play "hero" or "villain" roles depending on motor tasks/circumstances remains to be determined.

There are indications that motor performance may actually rely on activity of contralesional areas in more severely affected patients. For instance, it has been shown that transient disruption of the contralesional dorsal premotor cortex by transcranial magnetic stimulation slows motor performance of the paretic hand to a greater extent in patients with worse motor performance compared to less impaired patients [63]. In addition, activation of the *contralesional* dorsal premotor cortex has been demonstrated to be greater in patients with more severe hand motor impairment, compared to healthy subjects and to less affected patients [63]. On the other hand, disruption of the *ipsilesional* dorsal premotor cortex increases reaction times in patients with chronic stroke and mild motor impairments [64].

Together, these studies provide evidence that (1) contralesional areas are positively, functionally relevant in at least some well-recovered patients in the chronic phase; (2) in patients with severe motor deficits, behavioral gains, albeit small, may occur by augmented activity of networks that are normally either minimally active or not active at all in healthy brains. Severity of motor impairment seems to be a key factor influencing patterns of rewiring after stroke, but age, brain status before stroke, intensity, and timing of rehabilitative interventions, among other factors, are also likely to play pivotal roles in the process [33, 34, 65–67].

A key concept to develop effective rehabilitation interventions is heterogeneity of mechanisms underlying stroke as well as plastic processes that lead to recovery of function after neuronal injury. As they say, "different strokes for different folks". Stroke lesions and clinical presentations vary across patients. Mechanisms underlying neurological impairment, recovery of activity, and participation are also distinct.

Until now, most proof-of-principle studies or clinical trials have excluded patients with severe sensorimotor impairments and the lack of evidence-based effective interventions has nurtured a nihilistic approach for rehabilitation of these patients. Therefore, expansion of research about mechanisms underlying reorganization after severe strokes is imperative.

Moreover, patients with severe sensorimotor impairments often present with cognitive impairments, depression and are faced with massive changes in psychosocial interactions [68–70]. Further research efforts must not only address restoration of sensorimotor function but also incorporate an integrative approach to target neuropsychiatric domains, personal experience/expectations, environmental conditions, and psychosocial factors.

3. Capitalizing on Adult Brain Plasticity to Enhance Motor Recovery: Neural and Behavioral Considerations

Changes to the functional organization of neural representations and their behavioral concomitants have been described for a number of human study models such as amputates (e.g., [71, 72], musicians [73, 74], blind (e.g., [75–78]) and deaf persons (e.g., [79, 80]), as well as learning paradigms (e.g., [81–84]). Together these studies suggest that sensory representations are sensitive to enhanced or altered sensory stimulation. This knowledge has the prospect to devise interventions that capitalize on the plastic capacities of the adult brain, mainly training- or practice-based interventions. The mechanisms of brain plasticity interact with psychological processes and behavior and together provide a number of considerations for the conceptualization of interventions.

3.1. Injury-Induced Plasticity. Injury to the peripheral or central nervous system changes receptive field characteristics of neurons and neural representations through deprivation of the original afferent inputs these neurons receive [85, 86]. The key mechanisms driving this change are the disinhibition of silent synapses, and the loss of inhibitory or excitatory inputs from lesioned neural populations connected to nonelesioned regions, including homologous areas in the two hemispheres [87]. In both cases, it is important to appreciate the effects of functional changes in nonlesioned areas and their influence on the control of the impaired behavior. As a consequence, rehabilitation efforts should not only focus on the impaired function per se, for example, the affected upper-limb in the case of hemiplegia, but also consider the effects of use or nonuse of the lesser-affected extremities. This is particularly relevant for patients with poor recovery as they will most likely entirely rely on the less-affected extremity in everyday behavior. This might, at least in theory, increase the interhemispheric inhibition exerted by the nonlesioned hemisphere.

3.2. Use-Related Reorganization. Sensory stimulation and practice shapes neural representations [88]. These changes are most likely driven through Hebbian mechanisms as well as dendritic and axonal processes [89]. Critically, use-related reorganization is not driven by increased neural activation alone but heavily depends on the behavioral relevance of the activity [90–92]. This association of sensory stimulation and consequential changes in neural representations and receptive field parameters has been demonstrated most elegantly in monkeys who received auditory and tactile simulation within the same protocol. Behaviorally, the animals were only rewarded for responses in one of the two stimulation modalities, and subsequent changes in the brain were only observed for the rewarded modality. Thus this data indicates that neural representations are only susceptible to stimulation-induced reconfigurations if this stimulation is attended to and of behavioral significance. Therefore, we argue that interventions aiming to enhance recovery through the induction of practice-induced plasticity not only need to focus on the actual practice element of the intervention but also consider how the intervention characteristics enforce attention and provide tangible and motivating feedback.

3.3. Generic Effects of Information Processing Influencing Motor Cognition. Motor control is a complex behavior that goes far beyond motor execution and the processes typically associated with primary motor cortex function. Cognitive processes such as motor planning, error-monitoring and attention can heavily influence motor performance. Motor rehabilitation research, however, typically conceptualizes motor function as the ability to execute a movement with little consideration being given to the cognitive processes that might influence this ability. For example, few studies have investigated how much patients with hemiplegia benefit from advanced movement preparation. Anticipatory processes and motor planning modulate motor performance. The respective behavioral costs or benefits result from perceptual, cognitive, and motoric components of the stimulus-response cascade, such as stimulus-response mapping and response selection. Few studies have investigated advanced movement preparation in patients. A study by Verleger et al. [93] suggests that well-recovered patients show little difference to controls in a motor priming task. Using a similar paradigm in patients with poor recovery, our group found marked behavioural and electrophysiological difference between patients and matched control. Most strikingly, the data suggests that patients are more sensitive to advance information (manuscript submitted). Thus, it appears that visual precues can facilitate or hinder apparent affected arm abilities, and that the magnitude of this effect is modulated by the severity of the motor deficit. While more research is needed to fully understand the interaction of cognitive processes, stroke severity, and motor performance, the findings summarised previously suggest that using advance movement information in a cognizant and explicit manner may be a beneficial addition to rehabilitation interventions.

3.4. Behavior Modification. In order to translate improvements in motor ability into real-world benefits, treatments have to obtain not only better motor control over the affected arm, but also a transfer of these newly acquired abilities into the curriculum of everyday behaviors. This translation essentially requires a modification of behavior. Behavior change can be facilitated through a number of measures falling under the CBT (cognitive behavioral therapy) umbrella. These measures use not only learning principles, which in themselves are likely to facilitate use-related plasticity processes, but also tools that enhance motivation,

adherence, and coping. The latter, again, are likely to increase the patient's engagement with the intervention, which in turn is likely to improve outcome. Conceptualizing the rehabilitation of motor function as changing motor behavior rather than improving motor ability represents a significant shift in theoretical perspective. It implies that practice-based interventions should include treatment strategies that actively support sustained learning and behavior change, through the explicit use of learning principles and CBT elements. The latter facilitates not only real-world benefit but also enhances the processes of use-related functional reorganization that drive improvements in motor control.

3.5. Psychological Barriers. Interview data (unpublished) from patients with severe chronic hemiplegia indicates that these patients experience disproportionate psychological and service-related barriers. For example, statements such as "I have lost my hand," "I hate it (the hand) and want to make it invisible", and "it (the hand) looks horrible and is no good; I'd cut it off if I could" suggest that patients do not only face the actual physical impairment but also face psychological barriers to using any residual ability. This aspect is particularly important for interventions that rely on motor practice because the patient's engagement with the intervention is directly linked to their ability to cope with their disability. However, more often than not physiotherapy is provided without considering the psychological barriers associated with the use of the hemiplegic hand. We therefore argue that in order to improve the prospects for patients with low-functioning hemiparesis it is necessary to better understand the psychology of poor recovery and build that knowledge into motor rehabilitation interventions.

In addition to the psychological barriers low-functioning patients seem to experience, our interview data suggests a strong perception amongst these patients that the care system is presumptuous and does not provide for them. This is illustrated by comments such as "my doctors gave up on me after 3 month," "my GP said that my hand will not get better," "my physio tried to work with my hand initially but soon gave up," "the OT only taught me how to manage things (with my good hand), I guess this was because she knew that my (paretic) hand would be no good," and "there is nothing they can do for me because I cannot move." These comments highlight not only the need to understand the patient perspective and a holistic approach to long-term care of these patients, but also a critical need to develop motor rehabilitation treatments that help patients to enhance their residual motor ability and enhance its real world benefit.

3.6. Tiredness, Fatigue, and Daytime Sleepiness. Tiredness and fatigue are a common concern in patients after stroke. This affects not only the patients' general levels of activity but, of course, also the level of engagement with the therapy process. Not a lot can be gained in a therapy session with a tired patient! Moreover, tiredness and fatigue are linked to sleep, and sleep is likely to be a modulating factor of recovery. For example, Terdouzi et al. [94] has shown that poorer sleep is associated with poorer long-term outcome. Moreover, patients with chronic low-functioning hemiparesis seem to suffer from sleep difficulties at least as frequently as the general population [95]. This is an important point for a number of reasons. Firstly, poor sleep is often associated with higher daytime sleepiness. As a consequence, patients may be more sleepy and hence less active during the day [96]. Secondly, poor sleep negatively affects daytime performance and information processing. It is therefore likely to further aggravate the difficulties patients already have with activities of daily living and to reduce the benefit patients can get from therapy and other activities. Finally, an increasing body of literature suggests that sleep enhances brain plasticity in general and procedural learning specifically (e.g., [97–100]). Assuming that brain plasticity is the main driver for the recovery of function, good and sufficient sleep is likely to facilitate and probably enhance the rehabilitation effort. Support for this assumption is provided by a series of studies suggesting that motor learning can be positively influenced by sleep [101, 102].

The issues raised previously are relevant to all patients but probably have greater significance in patients with poorer recovery. Therefore, treatments for these patients in particular should incorporate measures to counter tiredness and fatigue and monitor the quality of nocturnal sleep as well as daytime sleepiness.

4. Overt and Covert Movement: Alternative Ways of Stimulating the Motor System

Jeannerod's theory of neural simulation [103] suggests a shared neural network for the control of overt and covert movement modalities such as movement observation and motor imagery. This theoretical framework provides a powerful tool for research in patients with poor recovery.

Generally, evidence from behavioral, neuroimaging, and psychophysiological studies confirms Jeannerod's notion of equivalence in healthy populations. For example, several fMRI studies have shown comparable activations in the cortical motor regions when participants observe or imagine hand movements (e.g., [104–107]). Thereby, these activities are similar to the activations obtained when the same movements are actually performed in the scanner. Typically, these studies use tasks that can be practiced prior to scanning and can be performed in the scanner. While this approach yields interesting and important insights, it lacks ecological validity, particularly with regard to the rehabilitation context. Taking these considerations on board, Szameitat and colleagues [108, 109] studied motor imagery of complex actions, such as eating with knife and fork or running. Using an fMRI paradigm, they successfully demonstrated that imagery of such complex movements is feasible in the scanner environment and leads to meaningful activations in the motor system. These findings are not trivial because complex everyday actions cannot be practiced prior to the scanning. The person will therefore rely on their motor memory rather than the experience obtained through practicing the actual task (e.g., finger tapping) immediately before the scanning begins. In this sense, the imagery

of complex movements, by default, affords less stringent experiment control. However, if motor imagery is to be used as a study tool for patients with poor recovery, their inability to move will prevent practice prior to scanning, and therefore, these patients will also perform the task by relying on their motor memory. Evidence showing the feasibility and suitability of a paradigm that omits practice is therefore particularly relevant for the application in patients with poor residual recovery. Moreover, the study of complex actions with fMRI opens the door to the investigation of the representation of activities of daily living and the alteration of those representations throughout recovery and/or treatment.

As mentioned previously, the cognitive processes involved in advance movement preparation are likely to play an important part in the person's ability to function in everyday life but might also enhance or hinder the rehabilitation effort. Understanding to what extend the principle of equivalence also holds for the higher cognitive processes involved in motor planning is therefore important. In a series of EEG experiments, Kranczioch and colleagues [110, 111] directly compared execution, imagination, and observation of finger movements in an advanced motor preparation paradigm. These studies firstly showed that the EEG-derived ERPs provide a good tool for the study of covert movements. This is important because the high temporal resolution of EEG typically requires precisely timed stimuli, which is a challenge for the imagery condition. At the same time, not all patients can part-take in MRI scanning (e.g., because of metal in their body) and EEG can therefore provide an alternative method to study motor processes.

Covert movements not only provide a good vehicle to study the reorganized motor system of those patients unable to execute the kind of controlled hand movements used in experimental paradigms requiring overt responses, but can also be employed to induce enhanced neural activation of motor circuitries which aids functional reorganization and recovery. Coined by Sharma and colleagues as "a backdoor to the motor system after stroke" [112], therapeutic approaches using covert movement modalities have recently been tested [7, 113–116]. While initial evidence is promising, there are a number of questions that need to be answered in due course. For example, literally all our knowledge on covert movement has been obtained in younger persons, typically University students. Aging is known to affect the motor system (e.g., [117–119]); in fact, the way a person moves is quite indicative of older age and frailty. It is therefore not inconceivable that motor-specific mechanisms of covert movement, determined in younger populations, are differentially affected by age. Similarly, the ability to imagine, or to focus on stimuli during observation, relies heavily on cognitive and perceptual processes [120] and may therefore, again, be modulated by age. The latter may of course also be affected by the stroke [121, 122]. More research that characterizes covert movement in healthy older persons is therefore needed to help tailor treatment development. In addition, it is presently unclear whether imagery and observation provide equally suitable treatment pathways, and how this interacts with lesion location. While several studies have explored the effects of mental practice on recovery [115], there is, to the best of our knowledge, no direct comparison between these methods. Pilot data from our group [123] suggests that motor imagery is best able to activate the reorganized motor system in patients with chronic sever hemiparesis.

5. Concluding Remarks

Poor long-term recovery of motor function after stroke is a major public health issue and a big problem for patients and their families. But treatment provision is not satisfactory, research in this area is limited, and (at least some) patients feel abandoned by the health care system. A deeper understanding of the complexities involved in motor control and their interaction with the mechanisms of brain plasticity as well as psychological aspects of recovery is needed not only to maximize the treatment outcome for patients but also to tailor health service provisions and support infrastructures accordingly. Despite the incredible advancements in brain imaging and rehabilitation research, and the growth of knowledge on brain plasticity over the last 20 years, there is little we can offer to patients with minimal recovery at present. A targeted and interdisciplinary research effort is required to meet the need for research and treatment development. This is necessary for the sake of the individuals affected as well as those who fund the health and welfare systems.

Acknowledgment

The authors gratefully acknowledge Miss Emma Walter for editorial assistance.

References

[1] E. Taub, "Harnessing brain plasticity through behavioral techniques to produce new treatments in neurorehabilitation," *American Psychologist*, vol. 59, no. 8, pp. 692–704, 2004.

[2] J. Liepert, H. Bauder, W. H. R. Miltner, E. Taub, and C. Weiller, "Treatment-induced cortical reorganization after stroke in humans," *Stroke*, vol. 31, no. 6, pp. 1210–1216, 2000.

[3] S. L. Wolf, P. A. Thompson, C. J. Winstein et al., "The EXCITE stroke trial: comparing early and delayed constraint-induced movement therapy," *Stroke*, vol. 41, no. 10, pp. 2309–2315, 2010.

[4] E. V. Cooke, K. Mares, A. Clark, R. C. Tallis, and V. M. Pomeroy, "The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: a systematic review and meta-analysis," *BMC Medicine*, vol. 8, article 60, 2010.

[5] L. V. Gauthier, E. Taub, C. Perkins, M. Ortmann, V. W. Mark, and G. Uswatte, "Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke," *Stroke*, vol. 39, no. 5, pp. 1520–1525, 2008.

[6] M. H. Bowman, E. Taub, G. Uswatte et al., "A treatment for a chronic stroke patient with a plegic hand combining CI therapy with conventional rehabilitation procedures: case report," *NeuroRehabilitation*, vol. 21, no. 2, pp. 167–176, 2006.

[7] 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.

[8] G. A. Donnan, M. Fisher, M. Macleod, and S. M. Davis, "Stroke," *The Lancet*, vol. 371, no. 9624, pp. 1612–1623, 2008.

[9] M. Thorngren and B. Westling, "Rehabilitation and achieved health quality after stroke. A population-based study of 258 hospitalized cases followed for one year," *Acta Neurologica Scandinavica*, vol. 82, no. 6, pp. 374–380, 1990.

[10] J. Bogousslavsky, G. Van Melle, and F. Regli, "The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke," *Stroke*, vol. 19, no. 9, pp. 1083–1092, 1988.

[11] A. Lipsanen and J. Jolkkonen, "Experimental approaches to study functional recovery following cerebral ischemia," *Cellular and Molecular Life Sciences*, vol. 68, no. 18, pp. 3007–3017, 2011.

[12] F. Liu and L. D. McCullough, "Middle cerebral artery occlusion model in rodents: methods and potential pitfalls," *Journal of Biomedicine and Biotechnology*, vol. 2011, Article ID 464701, 2011.

[13] I. MacRae, "Preclinical stroke research—advantages and disadvantages of the most common rodent models of focal ischaemia," *British Journal of Pharmacology*, vol. 164, no. 4, pp. 1062–1078, 2011.

[14] T. J. Hudzik, A. Borrelli, P. Bialobok et al., "Long-term functional end points following middle cerebral artery occlusion in the rat," *Pharmacology Biochemistry and Behavior*, vol. 65, no. 3, pp. 553–562, 2000.

[15] J. Sharkey, I. M. Ritchie, and P. A. T. Kelly, "Perivascular microapplication of endothelin-1: a new model of focal cerebral ischaemia in the rat," *Journal of Cerebral Blood Flow and Metabolism*, vol. 13, no. 5, pp. 865–871, 1993.

[16] R. L. Roof, G. P. Schielke, X. Ren, and E. D. Hall, "A comparison of long-term functional outcome after 2 middle cerebral artery occlusion models in rats," *Stroke*, vol. 32, no. 11, pp. 2648–2657, 2001.

[17] K. Miyake, S. Takeo, H. Kaijihara, and E. P. Wei, "Sustained decrease in brain regional blood flow after microsphere embolism in rats," *Stroke*, vol. 24, no. 3, pp. 415–420, 1993.

[18] M. Walberer, M. A. Rueger, M. Simard et al., "Dynamics of neuroinflammation in the macrosphere model of arterio-arterial embolic focal ischemia: an approximation to human stroke patterns," *Experimental and Translational Stroke Medicine*, vol. 2, no. 1, article 22, 2010.

[19] R. L. Zhang, M. Chopp, Z. G. Zhang, Q. Jiang, and J. R. Ewing, "A rat model of focal embolic cerebral ischemia," *Brain Research*, vol. 766, no. 1-2, pp. 83–92, 1997.

[20] C. Orset, R. Macrez, A. R. Young et al., "Mouse model of in situ thromboembolic stroke and reperfusion," *Stroke*, vol. 38, no. 10, pp. 2771–2778, 2007.

[21] H. Yao, H. Sugimori, K. Fukuda et al., "Photothrombotic middle cerebral artery occlusion and reperfusion laser system in spontaneously hypertensive rats," *Stroke*, vol. 34, no. 11, pp. 2716–2721, 2003.

[22] D. W. Howells, M. J. Porritt, S. S. J. Rewell et al., "Different strokes for different folks: the rich diversity of animal models of focal cerebral ischemia," *Journal of Cerebral Blood Flow and Metabolism*, vol. 30, no. 8, pp. 1412–1431, 2010.

[23] M. Fisher, "Recommendations for standards regarding preclinical neuroprotective and restorative drug development," *Stroke*, vol. 30, no. 12, pp. 2752–2758, 1999.

[24] W. Hacke, M. Kaste, E. Bluhmki et al., "Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke," *The New England Journal of Medicine*, vol. 359, no. 13, pp. 1317–1329, 2008.

[25] N. Wahlgren, N. Ahmed, A. Dávalos et al., "Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study," *The Lancet*, vol. 369, no. 9558, pp. 275–282, 2007.

[26] A. Furlan, R. Higashida, L. Wechsler et al., "Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial," *Journal of the American Medical Association*, vol. 282, no. 21, pp. 2003–2011, 1999.

[27] C. A. Molina and J. Alvarez-Sabín, "Recanalization and reperfusion therapies for acute ischemic stroke," *Cerebrovascular Diseases*, vol. 27, no. 1, pp. 162–167, 2009.

[28] W. Muangpaisan, J. L. Hinkle, M. Westwood, J. Kennedy, and A. M. Buchan, "Stroke in the very old: clinical presentations and outcomes," *Age and Ageing*, vol. 37, no. 4, pp. 473–475, 2008.

[29] A. Di Carlo, M. Lamassa, G. Pracucci et al., "Stroke in the very old: clinical presentation and determinants of 3- month functional outcome: a European perspective," *Stroke*, vol. 30, no. 11, pp. 2313–2319, 1999.

[30] M. C. Zurrú and G. Orzuza, "Epidemiological aspects of stroke in very old patients," *Cardiovascular and Hematological Disorders*, vol. 11, no. 1, pp. 2–5, 2011.

[31] A. Popa-Wagner, S. T. Carmichael, Z. Kokaia, C. Kessler, and L. C. Walker, "The response of the aged brain to stroke: too much, too soon?" *Current Neurovascular Research*, vol. 4, no. 3, pp. 216–227, 2007.

[32] K. Asplund, J. Karvanen, S. Giampaoli et al., "Relative risks for stroke by age, sex, and population based on follow-up of 18 european populations in the MORGAM project," *Stroke*, vol. 40, no. 7, pp. 2319–2326, 2009.

[33] K. Uchino, D. Billheimer, and S. C. Cramer, "Entry criteria and baseline characteristics predict outcome in acute stroke trials," *Stroke*, vol. 32, no. 4, pp. 909–916, 2001.

[34] J. I. Rojas, M. C. Zurrú, M. Romano, L. Patrucco, and E. Cristiano, "Acute ischemic stroke and transient ischemic attack in the very old-risk factor profile and stroke subtype between patients older than 80 years and patients aged less than 80 years," *European Journal of Neurology*, vol. 14, no. 8, pp. 895–899, 2007.

[35] B. Manwani, F. Liu, Y. Xu, R. Persky, J. Li, and L. D. McCullough, "Functional recovery in aging mice after experimental stroke," *Brain, Behavior, and Immunity*, vol. 25, no. 8, pp. 1689–1700, 2011.

[36] A. M. Demchuk, D. Tanne, M. D. Hill et al., "Predictors of good outcome after intravenous tPA for acute ischemic stroke," *Neurology*, vol. 57, no. 3, pp. 474–480, 2001.

[37] H. T. H. Tu, B. C. V. Campbell, S. Christensen et al., "Pathophysiological determinants of worse stroke outcome in atrial fibrillation," *Cerebrovascular Diseases*, vol. 30, no. 4, pp. 389–395, 2010.

[38] P. Coyle, "Outcomes to middle cerebral artery occlusion in hypertensive and normotensive rats," *Hypertension*, vol. 6, no. 2, pp. I-69–I-74, 1984.

[39] A. Reza Noorian, R. G. Nogueira, and R. Gupta, "Neuroprotection in acute ischemic stroke," *Journal of Neurosurgical Sciences*, vol. 55, no. 2, pp. 127–138, 2011.

[40] R. P. Allred, C. H. Cappellini, and T. A. Jones, "The "good" limb makes the "bad" limb worse: experience-dependent interhemispheric disruption of functional outcome after

cortical infarcts in rats," *Behavioral Neuroscience*, vol. 124, no. 1, pp. 124–132, 2010.

[41] R. J. Nudo, G. W. Milliken, W. M. Jenkins, and M. M. Merzenich, "Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys," *Journal of Neuroscience*, vol. 16, no. 2, pp. 785–807, 1996.

[42] R. J. Nudo, B. M. Wise, F. SiFuentes, and G. W. Milliken, "Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct," *Science*, vol. 272, no. 5269, pp. 1791–1794, 1996.

[43] E. Taub, G. Uswatte, V. W. Mark, and D. M. Morris, "The learned nonuse phenomenon: implications for rehabilitation," *Europa Medicophysica*, vol. 42, no. 3, pp. 241–255, 2006.

[44] S. L. Wolf, C. J. Winstein, J. P. Miller et al., "Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial," *The Lancet Neurology*, vol. 7, no. 1, pp. 33–40, 2008.

[45] H. Nhan, K. Barquist, K. Bell, P. Esselman, I. R. Odderson, and S. C. Cramer, "Brain function early after stroke in relation to subsequent recovery," *Journal of Cerebral Blood Flow and Metabolism*, vol. 24, no. 7, pp. 756–763, 2004.

[46] N. S. Ward, M. M. Brown, A. J. Thompson, and R. S. J. Frackowiak, "Neural correlates of outcome after stroke: a cross-sectional fMRI study," *Brain*, vol. 126, no. 6, pp. 1430–1448, 2003.

[47] N. S. Ward, M. M. Brown, A. J. Thompson, and R. S. J. Frackowiak, "Neural correlates of motor recovery after stroke: a longitudinal fMRI study," *Brain*, vol. 126, no. 11, pp. 2476–2496, 2003.

[48] N. S. Ward, J. M. Newton, O. B. C. Swayne et al., "Motor system activation after subcortical stroke depends on corticospinal system integrity," *Brain*, vol. 129, no. 3, pp. 809–819, 2006.

[49] S. Bestmann, O. Swayne, F. Blankenburg et al., "The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI," *Journal of Neuroscience*, vol. 30, no. 36, pp. 11926–11937, 2010.

[50] F. E. Buma, E. Lindeman, N. F. Ramsey, and G. Kwakkel, "Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review of the literature," *Neurorehabilitation and Neural Repair*, vol. 24, no. 7, pp. 589–608, 2010.

[51] N. Murase, J. Duque, R. Mazzocchio, and L. G. Cohen, "Influence of interhemispheric interactions on motor function in chronic stroke," *Annals of Neurology*, vol. 55, no. 3, pp. 400–409, 2004.

[52] 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.

[53] M. Ameli, C. Grefkes, F. Kemper et al., "Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke," *Annals of Neurology*, vol. 66, no. 3, pp. 298–309, 2009.

[54] D. A. Nowak, "The impact of stroke on the performance of grasping: usefulness of kinetic and kinematic motion analysis," *Neuroscience and Biobehavioral Reviews*, vol. 32, no. 8, pp. 1439–1450, 2008.

[55] N. Takeuchi, T. Chuma, Y. Matsuo, I. Watanabe, and K. Ikoma, "Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke," *Stroke*, vol. 36, no. 12, pp. 2681–2686, 2005.

[56] C. G. Mansur, F. Fregni, P. S. Boggio et al., "A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients," *Neurology*, vol. 64, no. 10, pp. 1802–1804, 2005.

[57] Y. H. Kim, S. H. You, M. H. Ko et al., "Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke," *Stroke*, vol. 37, no. 6, pp. 1471–1476, 2006.

[58] E. M. Khedr, M. R. Abdel-Fadeil, A. Farghali, and M. Qaid, "Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke," *European Journal of Neurology*, vol. 16, no. 12, pp. 1323–1330, 2009.

[59] T. H. Emara, R. R. Moustafa, N. M. Elnahas et al., "Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke," *European Journal of Neurology*, vol. 17, no. 9, pp. 1203–1209, 2010.

[60] S. T. Pendlebury, A. M. Blamire, M. A. Lee, P. Styles, and P. M. Matthews, "Axonal injury in the internal capsule correlates with motor impairment after stroke," *Stroke*, vol. 30, no. 5, pp. 956–962, 1999.

[61] A. Sterr, S. Shen, A. J. Szameitat, and K. A. Herron, "The role of corticospinal tract damage in chronic motor recovery and neurorehabilitation: a pilot study," *Neurorehabilitation and Neural Repair*, vol. 24, no. 5, pp. 413–419, 2010.

[62] R. Pineiro, S. Pendlebury, H. Johansen-Berg, and P. M. Matthews, "Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke: evidence of local adaptive reorganization?" *Stroke*, vol. 32, no. 5, pp. 1134–1139, 2001.

[63] H. Johansen-Berg, M. F. S. Rushworth, M. D. Bogdanovic, U. Kischka, S. Wimalaratna, and P. M. Matthews, "The role of ipsilateral premotor cortex in hand movement after stroke," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 22, pp. 14518–14523, 2002.

[64] E. A. Fridman, T. Hanakawa, M. Chung, F. Hummel, R. C. Leiguarda, and L. G. Cohen, "Reorganization of the human ipsilesional premotor cortex after stroke," *Brain*, vol. 127, no. 4, pp. 747–758, 2004.

[65] J. L. Hinkle, "Variables explaining functional recovery following motor stroke," *The Journal of Neuroscience Nursing*, vol. 38, no. 1, pp. 6–12, 2006.

[66] G. Kwakkel, "Impact of intensity of practice after stroke: issues for consideration," *Disability and Rehabilitation*, vol. 28, no. 13-14, pp. 823–830, 2006.

[67] G. Kwakkel, J. M. Veerbeek, E. E. H. van Wegen, R. Nijland, B. C. Harmeling-van der Wel, and D. W. J. Dippel, "Predictive value of the NIHSS for ADL outcome after ischemic hemispheric stroke: does timing of early assessment matter?" *Journal of the Neurological Sciences*, vol. 294, no. 1-2, pp. 57–61, 2010.

[68] K. Hilari, S. Northcott, P. Roy et al., "Psychological distress after stroke and aphasia: the first six months," *Clinical Rehabilitation*, vol. 24, no. 2, pp. 181–190, 2010.

[69] G. M. S. Nys, M. J. E. van Zandvoort, H. B. van der Worp et al., "Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke," *Journal of the Neurological Sciences*, vol. 247, no. 2, pp. 149–156, 2006.

[70] K. Narasimhalu, S. Ang, D. A. De Silva et al., "The prognostic effects of poststroke cognitive impairment no dementia and domain-specific cognitive impairments in nondisabled ischemic stroke patients," *Stroke*, vol. 42, no. 4, pp. 883–888, 2011.

[71] A. Karl, N. Birbaumer, W. Lutzenberger, L. G. Cohen, and H. Flor, "Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain," *Journal of Neuroscience*, vol. 21, no. 10, pp. 3609–3618, 2001.

[72] 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.

[73] T. Elbert, C. Pantev, C. Wienbruch, B. Rockstroh, and E. Taub, "Increased cortical representation of the fingers of the left hand in string players," *Science*, vol. 270, no. 5234, pp. 305–307, 1995.

[74] P. Ragert, A. Schmidt, E. Altenmüller, and H. R. Dinse, "Superior tactile performance and learning in professional pianists: evidence for meta-plasticity in musicians," *European Journal of Neuroscience*, vol. 19, no. 2, pp. 473–478, 2004.

[75] O. Collignon, G. Vandewalle, P. Voss et al., "Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 11, pp. 4435–4440, 2011.

[76] 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," *Journal of Neuroscience*, vol. 18, no. 11, pp. 4417–4423, 1998.

[77] B. Röder, W. Teder-Sälejärvi, A. Sterr, F. Rösler, S. A. Hillyard, and H. J. Neville, "Improved auditory spatial tuning in blind humans," *Nature*, vol. 400, no. 6740, pp. 162–166, 1999.

[78] T. Elbert, A. Sterr, B. Rockstroh, C. Pantev, M. M. Müller, and E. Taub, "Expansion of the tonotopic area in the auditory cortex of the blind," *Journal of Neuroscience*, vol. 22, no. 22, pp. 9941–9944, 2002.

[79] D. Caplan, "Language-related cortex in deaf individuals: functional specialization language or perceptual plasticity?" *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 25, pp. 13476–13477, 2000.

[80] J. Rouger, S. Lagleyre, J. F. Démonet, B. Fraysse, O. Deguine, and P. Barone, "Evolution of crossmodal reorganization of thevoice area in cochlear-implanted deaf patients," 2011, *Human Brain Mapping*. In press.

[81] K. Debas, J. Carrier, P. Orban et al., "Brain plasticity related to the consolidation of motor sequence learning and motor adaptation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 41, pp. 17839–17844, 2010.

[82] A. Galván, "Neural plasticity of development and learning," *Human Brain Mapping*, vol. 31, no. 6, pp. 879–890, 2010.

[83] D. J. Ostry, M. Darainy, A. A. G. Mattar, J. Wong, and P. L. Gribble, "Somatosensory plasticity and motor learning," *Journal of Neuroscience*, vol. 30, no. 15, pp. 5384–5393, 2010.

[84] J. Zhang and Z. Kourtzi, "Learning-dependent plasticity with and without training in the human brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 30, pp. 13503–13508, 2010.

[85] M. Tinazzi, G. Zanette, A. Polo et al., "Transient deafferentation in humans induces rapid modulation of primary sensory cortex not associated with subcortical changes: a somatosensory evoked potential study," *Neuroscience Letters*, vol. 223, no. 1, pp. 21–24, 1997.

[86] T. D. Waberski, A. Dieckhöfer, U. Reminghorst, H. Buchner, and R. Gobbelé, "Short-term cortical reorganization by deafferentation of the contralateral sensory cortex," *NeuroReport*, vol. 18, no. 11, pp. 1199–1203, 2007.

[87] F. C. Hummel and L. G. Cohen, "Drivers of brain plasticity," *Current Opinion in Neurology*, vol. 18, no. 6, pp. 667–674, 2005.

[88] W. M. Jenkins, M. M. Merzenich, and G. Recanzone, "Neocortical representational dynamics in adult primates: implications for neuropsychology," *Neuropsychologia*, vol. 28, no. 6, pp. 573–584, 1990.

[89] A. Wolters, F. Sandbrink, A. Schlottmann et al., "A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex," *Journal of Neurophysiology*, vol. 89, no. 5, pp. 2339–2345, 2003.

[90] G. H. Recanzone, M. M. Merzenich, and W. M. Jenkins, "Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a," *Journal of Neurophysiology*, vol. 67, no. 5, pp. 1057–1070, 1992.

[91] G. H. Recanzone, M. M. Merzenich, W. M. Jenkins, K. A. Grajski, and H. R. Dinse, "Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency-discrimination task," *Journal of Neurophysiology*, vol. 67, no. 5, pp. 1031–1056, 1992.

[92] G. H. Recanzone, C. E. Schreiner, and M. M. Merzenich, "Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys," *Journal of Neuroscience*, vol. 13, no. 1, pp. 87–103, 1993.

[93] R. Verleger, S. Adam, M. Rose, C. Vollmer, B. Wauschkuhn, and D. Kömpf, "Control of hand movements after striatocapsular stroke: high-resolution temporal analysis of the function of ipsilateral activation," *Clinical Neurophysiology*, vol. 114, no. 8, pp. 1468–1476, 2003.

[94] A. Terzoudi, T. Vorvolakos, I. Heliopoulos, M. Livaditis, K. Vadikolias, and H. Piperidou, "Sleep architecture in stroke and relation to outcome," *European Neurology*, vol. 61, no. 1, pp. 16–22, 2008.

[95] A. Sterr, K. Herron, D. J. Dijk, and J. Ellis, "Time to wake-up: sleep problems and daytime sleepiness in long-term stroke survivors," *Brain Injury*, vol. 22, no. 7-8, pp. 575–579, 2008.

[96] M. M. Siccoli, N. Rölli-Baumeler, P. Achermann, and C. L. Bassetti, "Correlation between sleep and cognitive functions after hemispheric ischaemic stroke," *European Journal of Neurology*, vol. 15, no. 6, pp. 565–572, 2008.

[97] T. P. Brawn, K. M. Fenn, H. C. Nusbaum, and D. Margoliash, "Consolidating the effects of waking and sleep on motor-sequence learning," *Journal of Neuroscience*, vol. 30, no. 42, pp. 13977–13982, 2010.

[98] M. A. Nitsche, M. Jakoubkova, N. Thirugnanasambandam et al., "Contribution of the premotor cortex to consolidation of motor sequence learning in humans during sleep," *Journal of Neurophysiology*, vol. 104, no. 5, pp. 2603–2614, 2010.

[99] C. A. Rieth, D. J. Cai, E. A. McDevitt, and S. C. Mednick, "The role of sleep and practice in implicit and explicit motor learning," *Behavioural Brain Research*, vol. 214, no. 2, pp. 470–474, 2010.

[100] M. P. Walker, T. Brakefield, J. Seidman, A. Morgan, J. A. Hobson, and R. Stickgold, "Sleep and the time course of motor skill learning," *Learning and Memory*, vol. 10, no. 4, pp. 275–284, 2003.

[101] C. Siengsukon and L. A. Boyd, "Sleep enhances offline spatial and temporal motor learning after stroke,"

Neurorehabilitation and Neural Repair, vol. 23, no. 4, pp. 327–335, 2009.

[102] C. F. Siengsukon and L. A. Boyd, "Sleep to learn after stroke: implicit and explicit off-line motor learning," *Neuroscience Letters*, vol. 451, no. 1, pp. 1–5, 2009.

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

[104] B. D. Berman, S. G. Horovitz, G. Venkataraman, and M. Hallett, "Self-modulation of primary motor cortex activity with motor and motor imagery tasks using real-time fMRI-based neurofeedback," *NeuroImage*, vol. 59, no. 2, pp. 917–925, 2012.

[105] B. Lorey, S. Pilgramm, M. Bischoff et al., "Activation of the parieto-premotor network is associated with vivid motor imagery-A parametric fMRI study," *PLoS ONE*, vol. 6, no. 5, article e20368, 2011.

[106] E. Raffin, P. Giraux, and K. T. Reilly, "The moving phantom: motor execution or motor imagery?" *Cortex*. In press.

[107] J. Majdandić, H. Bekkering, H. T. Van Schie, and I. Toni, "Movement-specific repetition suppression in ventral and dorsal premotor cortex during action observation," *Cerebral Cortex*, vol. 19, no. 11, pp. 2736–2745, 2009.

[108] A. J. Szameitat, S. Shen, and A. Sterr, "Motor imagery of complex everyday movements. An fMRI study," *NeuroImage*, vol. 34, no. 2, pp. 702–713, 2007.

[109] A. J. Szameitat, S. Shen, and A. Sterr, "Effector-dependent activity in the left dorsal premotor cortex in motor imagery," *European Journal of Neuroscience*, vol. 26, no. 11, pp. 3303–3308, 2007.

[110] C. Kranczioch, S. Mathews, P. J. A. Dean, and A. Sterr, "On the equivalence of executed and imagined movements: evidence from lateralized motor and nonmotor potentials," *Human Brain Mapping*, vol. 30, no. 10, pp. 3275–3286, 2009.

[111] C. Kranczioch, S. Mathews, P. Dean, and A. Sterr, "Task complexity differentially affects executed and imagined movement preparation: evidence from movement-related potentials," *PLoS ONE*, vol. 5, no. 2, article e9284, 2010.

[112] N. Sharma, V. M. Pomeroy, and J. C. Baron, "Motor imagery: a backdoor to the motor system after stroke?" *Stroke*, vol. 37, no. 7, pp. 1941–1952, 2006.

[113] M. Ietswaart, M. Johnston, H. C. Dijkerman et al., "Mental practice with motor imagery in stroke recovery: randomized controlled trial of efficacy," *Brain*, vol. 134, no. 5, pp. 1373–1386, 2011.

[114] S. J. Page, P. Levine, and A. Leonard, "Mental practice in chronic stroke: results of a randomized, placebo-controlled trial," *Stroke*, vol. 38, no. 4, pp. 1293–1297, 2007.

[115] R. E. Barclay-Goddard, T. J. Stevenson, W. Poluha, and L. Thalman, "Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke," *Cochrane Database of Systematic Reviews*, vol. 5, article CD005950, 2011.

[116] D. M. Nilsen, G. Gillen, and A. M. Gordon, "Use of mental practice to improve upper-limb recovery after stroke: a systematic review," *American Journal of Occupational Therapy*, vol. 64, no. 5, pp. 695–708, 2010.

[117] R. Camicioli, M. M. Moore, G. Sexton, D. B. Howieson, and J. A. Kaye, "Age-related brain changes associated with motor function in healthy older people," *Journal of the American Geriatrics Society*, vol. 47, no. 3, pp. 330–334, 1999.

[118] A. Sterr and P. Dean, "Neural correlates of movement preparation in healthy ageing," *European Journal of Neuroscience*, vol. 27, no. 1, pp. 254–260, 2008.

[119] M. Shinohara, "Adaptations in motor unit behavior in elderly adults," *Current Aging Science*, vol. 4, no. 3, pp. 200–208, 2011.

[120] C. M. Saucedo Marquez, T. Ceux, and N. Wenderoth, "Attentional demands of movement observation as tested by a dual task approach," *PLoS ONE*, vol. 6, no. 11, article e27292, 2011.

[121] C. A. Roller, H. S. Cohen, K. T. Kimball, and J. J. Bloomberg, "Effects of normal aging on visuo-motor plasticity," *Neurobiology of Aging*, vol. 23, no. 1, pp. 117–123, 2002.

[122] S. de Vries et al., "Recovery of motor imagery ability in Stroke patients," *Rehabilitation Research and Practice*, vol. 2011, pp. 283–840, 2011.

[123] A. J. Szameitat, S. Shen, and A. Sterr, "Cortical activation during executed, imagined, observed, and passive wrist movements in healthy volunteers and stroke patients—a within-subject fMRI study," *Neuroimage*. In press.