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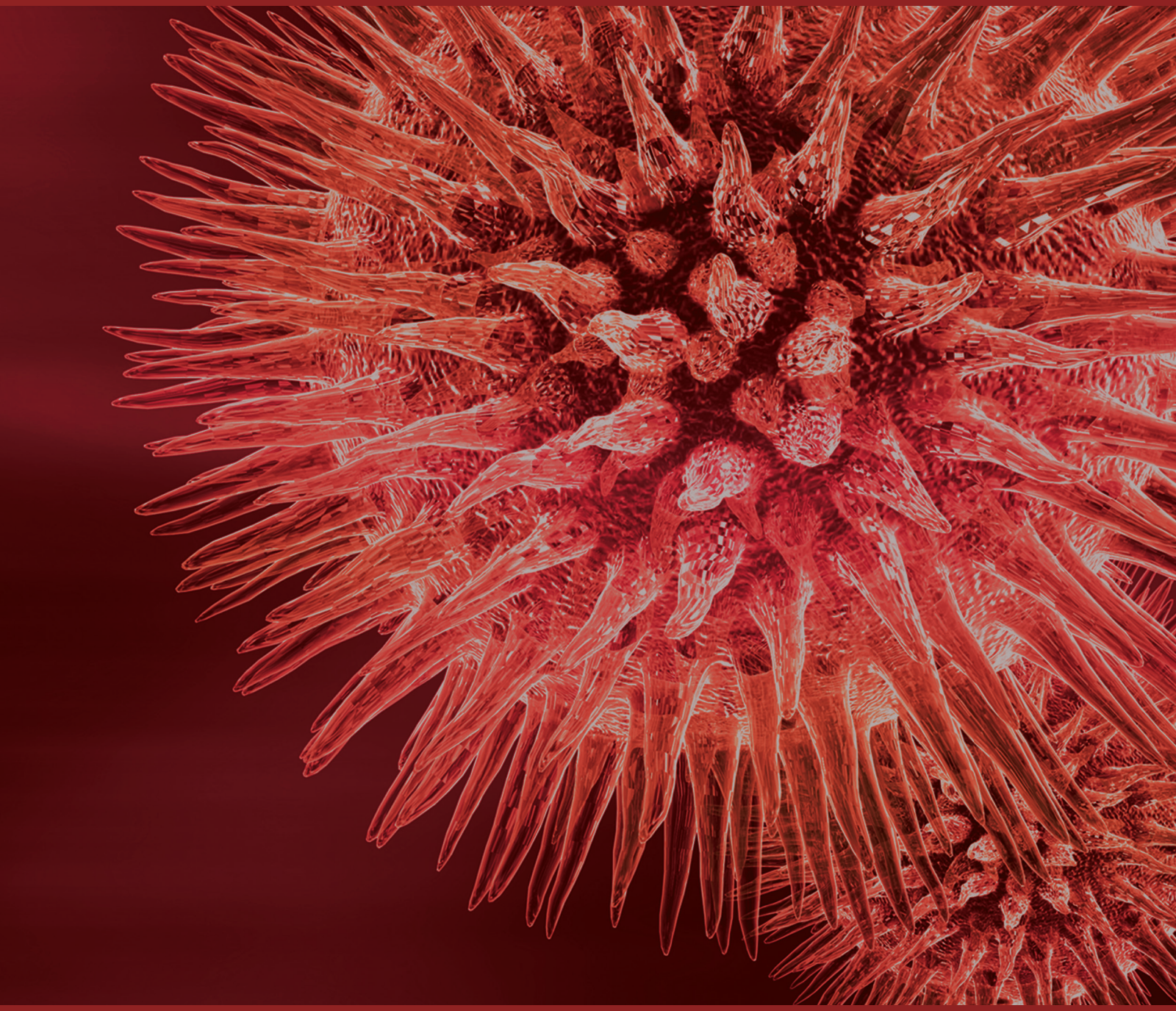
Advances in Neuromotor Stroke Rehabilitation

Guest Editors: Giovanni Morone, Stefano Masiero, Cordula Werner, and Stefano Paolucci



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Editorial

Advances in Neuromotor Stroke Rehabilitation

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Stroke is the second leading cause of death and the third leading cause of disability-adjusted life-years (DALYs) worldwide [1]. In the past two decades, the absolute number of people who have a stroke every year and stroke survivors and the overall global burden of stroke have been increasing [2]. This was the consequence of an increase in life expectancy and reduced mortality in the acute phase in stroke care. The public health systems and the scientific communities should seriously take into account the "pandemia" of stroke survivors [3]. From the other side, a big amount of economic resources, needed for the rehabilitation of people after stroke, is related to the increasing prevalence of patients affected by stroke sequelae. It transforms this ethical duty in an utopistic mission. There is the need of increasing rehabilitation and, at the same time, reducing its costs. New technologies for neurorehabilitation can provide modern tools for increasing efficiency. Despite the extraordinary possibilities of these new approaches, there is a lot of work for integrating them into the routinary rehabilitation programs. These devices should be considered as tools in the hands of neurorehabilitation teams usable in the framework of a rehabilitative program and not only rehabilitative per se. In fact, they should be integrated in a complex model in which the aim and the actual patients conditions concur to tailor training with multimodal conditions integrating classical and well-known conventional therapy with the new approaches, including new technological devices [4].

This complex model includes strategies for motor recruitment control, increasing performance during a task, the enhancement of patients' motivation and engagement, and trainings to empower cognitive functions, to increase cardiorespiratory fitness, to increase quality of movement, and to improve balance and motor control. Each of these specific endpoints should be addressed and concur in a different manner to the rehabilitation user-tailored program in stroke.

The efficacy of the robotic training in arm and walking neurorehabilitation after stroke has been proven in several trials; furthermore, the debate has still been open and there is no possibility at the moment to perform only machine aided training [5]. It should be noted that the machines provide the basics and the therapist's task is to implement these basics into more complex tasks; thus, no machine can replace the experienced therapists. From the other side, the high costs of such robots limit their diffusion, but the possibility that more robots can be used to treat more patients at the same time with only one physiotherapist monitoring all of them should decrease the cost of each therapy [6]. In this special issue, S. Masiero et al. analyzed the costs of the 5 years experiments on arm robotic training in hospital setting in subacute stroke, reaching this conclusion "*Robotic upper limb rehabilitation after acute stroke by NeReBot: evaluation of treatment costs.*" The increase of the rehabilitation offers in terms of number of therapies provided without increasing the costs is mandatory. In this line telerehabilitation is

an important strategy when coupled to an early discharge. M. Agostini and colleagues showed us the feasibility and the efficacy of a home telerehabilitation protocol in poststroke anomia "*Telerehabilitation in poststroke anomia.*"

Video game-based therapy and the virtual reality system are playing an important role in reducing costs, especially, using commercial gaming systems, and augmenting the involvement of patients' attention and participation to the exercise/game. A paper in this special issue for the first time has shown that the balance training performed using a commercial console is more effective than the conventional therapy: "*The efficacy of balance training with video game-based therapy in subacute stroke patients: a randomized controlled trial.*" Furthermore, the development of a patients' tailored system with specific exercises and specific augmented feedback as described in the paper of P. Kiper et al. "*Reinforced feedback in virtual environment for rehabilitation of upper extremity dysfunction after stroke: preliminary data from a randomized controlled trial*" provides a next step toward this aim.

Quantitative assessment is also important for providing a tailored rehabilitation. The study of M. Manca et al. identified five clusters characterizing the gait dysfunction of patients with stroke "*Gait patterns in hemiplegic patients with equinus foot deformity.*" Similarly, I. Aprile et al. have identified an upper limb kinematic analysis for assessing alterations in reaching function, providing more chances to train each patient in a specific tailored way "*Kinematic analysis of the upper limb motor strategies in stroke patients as a tool towards advanced neurorehabilitation strategies: a preliminary study.*"

Among the novel rehabilitation approaches, the action observation is another one of interest. The observation of actions performed by other people activates in the perceiver the same neural structures responsible for the actual execution of the same actions exploiting the neurophysiological mechanism for the recovery of motor impairment as shown in the paper of P. Sale and colleagues "*Action observation therapy in the subacute phase promotes dexterity recovery in right-hemisphere stroke patients.*"

The complex model for treating patients with stroke, in the last years, involved also cardiovascular fitness, in chronic [7], as well as in subacute, phase [8]. The energy cost of walking assessed by a breath to breath method could be expensive involving machines with high costs and not easy to use; conversely, the physiological cost index is easy to use and of low cost. A. S. DeLussu and colleagues have proved the validity of the physiological cost index for assessing the energy cost during walking training on floor and on robotic gait training in subacute stroke "*Concurrent validity of physiological cost index in walking over ground and during robotic training in subacute stroke patients.*"

Finally, the attention to the sleepiness problems and the correlation with the disabilities is increasing after stroke, but little is known about the sleep and daytime sleepiness of chronic stroke patients as an important factor conditioning patients' ability in activity of daily living. The paper of K. Herron et al. explored the sleep and sleepiness in a chronic stroke population with sustained physical deficits "*Quantitative electroencephalography and behavioural correlates of daytime sleepiness in chronic stroke.*"

All the studies reported in this special issue showed the complexity of the neurorehabilitation of people who suffered from stroke and the consequent need of a complex tailored rehabilitation that is not only an economic burden but also an ethical issue. The way a nation cares for people with disabilities is an indicator of its progress.

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Clinical Study

Action Observation Therapy in the Subacute Phase Promotes Dexterity Recovery in Right-Hemisphere Stroke Patients

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The clinical impact of action observation (AO) on upper limb functional recovery in subacute stroke patients is recent evidence. We sought to test the hypothesis that training everyday life activities through AO coupled with task execution might activate the left hemisphere different from the right one. Sixty-seven first-ever ischemic stroke subjects were randomly assigned to receive upper limb training coupled with AO tasks or standard rehabilitation. The groups were matched by age and gender, Bamford category, and interval from stroke and lesion side. Fugl-Meyer (FM) and Box and Block Test (BBT) were used to measure hand function recovery at the end (T1) and 4-5 months after the treatment (T2). At T1, FM was increased by 31% (±26%), of maximum achievable recovery, whereas BBT was increased by 17% (±18%); at T2, FM had reached 43% (±45%) of maximum recovery, while BBT had reached 25% (±22%). Combining the effects of treatment to those of lesion side revealed significantly higher gains, in both FM and BBT scores, in left hemiparetic subjects when exposed to AO as compared to standard rehabilitation alone ($P < .01$). The findings lead to recommend the use of AO in addition to motor training in left hemiparetic patients.

1. Introduction

The most common and disabling motor deficit following stroke is the loss of upper limb function [1]. Functional recovery is known to be influenced by the size, type, and site of brain damage [2], as well as by the quality and intensity of the rehabilitation intervention. The current views on rehabilitation effectiveness advise to pursue the relearning of basic skills concerned with activities of daily living (ADL) and to practice ADL in an intensive manner in order to optimize the upper limb function [3].

Over the last few years, several approaches have been tested with respect to their efficacy at promoting hand dexterity recovery after stroke. Among them, task-oriented therapy, robot-assisted rehabilitation, and action observation were paid the greatest attention [4–7].

Action observation (AO) is defined as a dynamic state during which an observer can understand what other people are doing by simulating the actions and the outcomes that are likely to follow from the observed motor act [8]. In particular, the systematic observation of daily actions followed by their imitation represents a novel rehabilitation approach; AO exploits a well-known neurophysiological mechanism by which the brain matches an observed action to its motor counterpart [9]. This phenomenon is supposed to occur via the activation of the mirror neuron system (involving the inferior parietal lobule, the premotor cortex, and the superior frontal gyrus) [10]. Fadiga et al. [11] suggested that observation of action has a direct influence on primary motor cortex and muscle activity, thus supporting the idea that observation can prime movement execution by activating common neural processes. A research conducted by Buccino et al. [12] revealed that the mirror neuron system is especially active during the observation of actions which are part of the motor repertoire of the observer. In studies where AO was applied as a tool for promoting motor relearning, stroke patients were asked to observe everyday life actions (i.e., actions of high ecological value), of which they had motor competence and experience. The hypothesis that such aspects of the observed actions could trigger brain areas belonging

to the mirror neuron system was strengthened by the finding that the motor improvement observed in patients undergoing an AO treatment, compared to controls undergoing standard rehabilitation, paralleled an increased activation in a network comprising bilateral ventral premotor and inferior parietal areas (supposedly containing the mirror neuron system) plus bilateral superior temporal gyrus, supplementary motor area (SMA), and contralateral supramarginal gyrus [13].

Gatti et al. showed that AO is better than motor imagery as a strategy for learning a novel complex motor task, at least in the early phase of motor learning, thus emphasizing its role in neurorehabilitation [14]. In a recent paper, we showed the clinical impact induced by 4 weeks of structured AO rehabilitation treatment at enhancing the upper limb functional recovery in subacute stroke patients. In particular, we demonstrated a persistently higher improvement in the Box and Block Test scores in the experimental group as compared to the controls [5].

In the present research, we combined AO with the direct effects of action execution to promote dexterity recovery in subacute stroke patients, with moderate to severe upper limb paresis. Based on the finding that the mirror neuron system is mostly activated by the observation of tasks of whom the observer has motor experience, we sought to test the hypothesis that training everyday life activities through AO coupled with task execution might activate the left hemisphere (i.e., the hemisphere contralateral to the dominant hand) to a different extent from the right hemisphere (i.e., the hemisphere contralateral to the nondominant hand).

Therefore, we designed a trial where right-handed people, surviving their first-ever ischemic stroke, were randomly assigned to receive either AO coupled with action execution or standard rehabilitation for 4 weeks.

2. Material and Methods

This is a randomized controlled observer-blind trial aimed at discriminating the effectiveness of AO, in left versus right hemiparetic subjects, receiving AO as an add-on treatment to the standard physical therapy in the early phase of stroke onset.

Eligible patients had moderate to severe upper limb paresis, following their first-ever ischemic stroke. According to our previous study protocol [5], we enrolled patients 30 days (±7) after the event (Figure 1). All patients were right handed prior to stroke and exhibited unilateral brain lesions.

The following exclusion criteria were identified: (1) posterior circulation infarction; (2) subarachnoid hemorrhage; (3) severe forms of neglect and anosognosia; (4) impaired comprehension or dementia; (5) history of endogenous depression or serious psychiatric disorders; (6) severe visual deficits; (7) bilateral motor impairment; (8) severe sensory deficits in the paretic upper limb; (9) refusal or inability to provide informed consent; and (10) other concomitant severe medical problems.

Diagnosis was confirmed by means of a CT scan and/or an MRI. The baseline assessment included the Canadian Neurological Scale (CNS), the Mini-Mental State Examination (MMSE), the Bell Barrage Test, and the ideomotor apraxia test (Spinnler-Rognoni).

Furthermore, the following functional evaluations were performed at the beginning (T0), at the end of the 4-week treatment period (T1), and 4-5 months from treatment conclusion (T2): the Fugl-Meyer Test (FM), with respect to the upper limb items [15], and the Box and Block Test (BBT) [16].

The Fugl-Meyer assessment is one of the most widely used quantitative measures of motor impairment. It has been applied in both the clinical and research setting to evaluate recovery in poststroke hemiplegic patients. Items are scored on a 3-point ordinal scale (0 = cannot perform; 1 = performs partially; 2 = performs fully). The five domains assessed include motor function (upper limb maximum score = 66; lower limb maximum score = 34), sensory function (maximum score = 24), balance (maximum score = 14), joint range of motion (maximum score = 44), and joint pain (maximum score = 44). Subscales can be administered without using the full test.

The BBT was devised to assess unilateral gross manual dexterity in stroke subjects. It requests patients to seat at a table, facing a rectangular box that is divided into two square compartments of equal dimension by means of a partition: one of the two compartments contains one hundred and fifty, 2.5 cm, colored, wooden cubes. The individual is instructed to move as many blocks as possible, one at a time, from one compartment to the other for a period of 60 seconds. The final score is computed by counting the number of blocks moved during the one-minute trial period. Healthy adults aged 20 and up have been found to move around 75 cubes ±9,1, within one minute, without any significant differences between the dominant and nondominant hand [16]. The interrater reliability and validity of FM and BBT are excellent [17].

All assessments were performed by a trained occupational therapist (OT) who was not aware of the research aims and treatment content. The local ethical committee approved the study. All patients gave informed consent to the investigation.

2.1. Subjects. The studied sample was made of 67 subjects (26 women), aged 66.5 ± 12.7 years (range: 28–87); the interval from stroke was 29.6 ± 4.5 days (range: 23–37); the left hemisphere was involved in 30 cases. Subjects were moderately disabled, their average Barthel index being 43.1/100 ± 20.6; the upper limb function (on the paretic side) was severely impaired as measured by a mean BBT of 8.9 ± 11.9 on the paretic side, compared to 69.1 ± 8.2 on the healthy side.

The subjects were randomly assigned either to the experimental treatment (EG, 33 cases) or to the control treatment (CG, 34 cases).

2.2. Random Group Allocation. The random allocation to treatment was concealed and based upon a custom computerized system, using dedicated software. Each participating center was provided with client software through which the local participant could ask the server, for any eligible

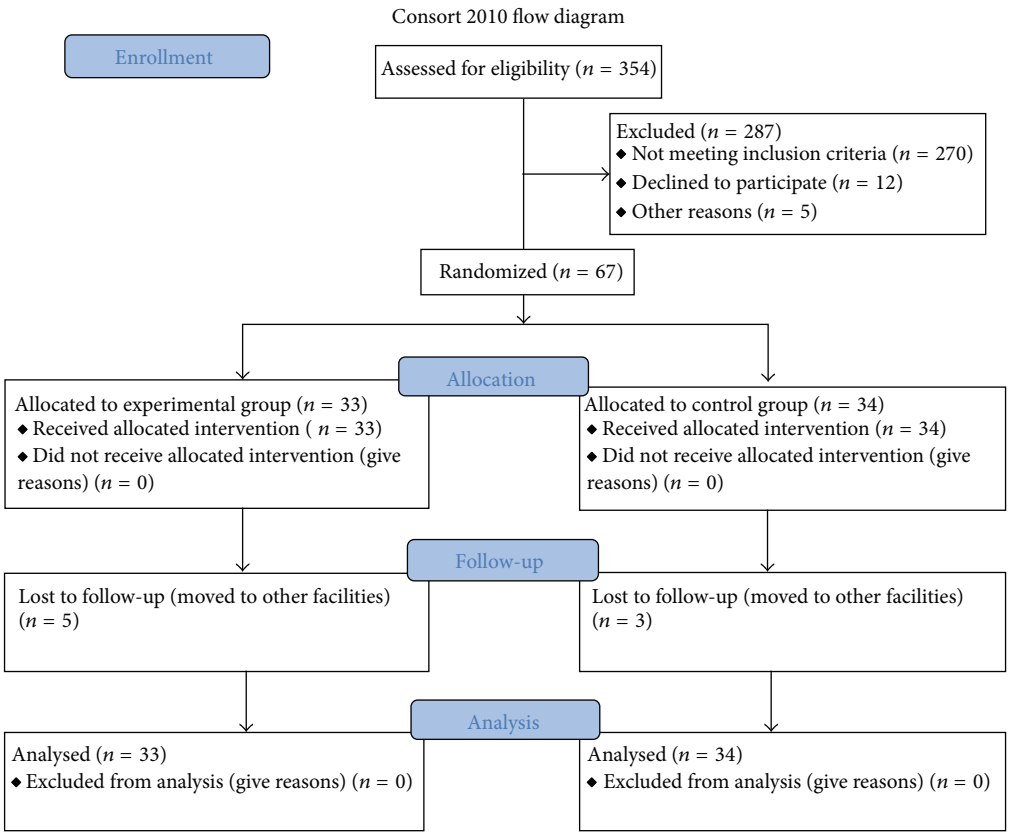

Figure 1: Consort 2010 flow diagram.

subject, for the group allocation by simply entering his/her age, gender, and brain lesion side. The server could be solely accessed through the client software and an HTTPS Internet protocol. In order to allow for a balanced subject allocation into EG and CG groups, the Lehmer algorithm was applied. Therapists were randomly assigned to patients within each group, by using the same procedure.

All subjects underwent in-patient rehabilitation consisting of at least 3 hours/day of physiotherapy (60-minute practice of trunk control and standing, gait and balance training, and breathing exercise), occupational therapy (60-minute training of wheelchair locomotion and practice of activities of daily living), and speech and swallow therapy (60-minute practice of activities to enhance speech, articulation, fluency, and safe swallowing). No differences were admitted between right and left hemiparetic subjects with respect to the daily amount of formal upper limb training.

In addition to standard rehabilitation, eligible patients received two 15-minute daily sessions, 5 days/week, for 4 consecutive weeks, of either experimental (EG) or control treatment (CG), according to the random allocation outcome.

2.3. Experimental Treatment. Every day, before starting physical training, EG patients were asked to carefully watch footages showing 20 different daily routine tasks (actions) carried out with the upper limb [6]. The patient was presented only one task per day, starting from the easiest and ending with the most complex action throughout 20 sessions, the whole treatment period lasting 4 weeks (5 sessions/week). Each action consisted of three different meaningful motor sequences displayed in order of ascending difficulty and lasting 3 minutes each. Tasks were based on some relevant ADLs such as drinking from a glass, combing hair, opening a box, eating an apple, and more, all actions being object- and goal-directed. For example, take and drink a cup of coffee was divided into 3 acts: (1) reach and grasp the handle of the cup with the affected arm and return to the starting point; (2) reach and grasp the handle of the cup with the affected arm; rise the cup towards the mouth; return to the starting point; (3) reach and grasp the handle of the cup with the affected arm; rise the cup towards the mouth and drink; then, return to the starting point. There were unimanual and bimanual tasks. Unimanual tasks required the use of only the affected limb. The actions were observed from a first-person perspective. Actors in the videos were young nondisabled people, either men or women, different from video to video. During each daily session, the patient had to watch the video under OT supervision. In particular, subjects were asked to carefully observe the video, in order to prepare to imitate the presented action, whereas the OT consistently held high

the patient's attention with verbal feedback. At the end of each sequence, the OT prompted the patient to perform the same movement over a time period of 2 minutes, providing help when needed. The patients were asked to perform the observed action with their paretic upper limb at their best convenience, as many times as they could. They received verbal instructions by the OT as follows: "slowly put the hand of your affected arm to the top of your head. You may use your unaffected arm to help guide if needed," or "extend your affected arm to the wall in front of you. You may use your unaffected arm to help guide if needed." The OT judged whether patients could accomplish the task themselves or should be assisted in the task of imitating the observed action. In the last case, the OT provided patients with physical help (limb support or passive mobilization) to help them perform the action. No interaction with object was allowed; patients had only to imitate the motor sequence they had observed. No movements in free space or manipulation were requested. Each session had to last about 15 minutes (3-minute sequence observation and 2-minute action performance for 3 motor sequences) and was repeated twice per day, in two separate sessions, at least 60 minutes apart; during the interval, the patient was requested to rest.

2.4. Control Treatment. Different from the experimental treatment, a "sham" action observation was used for CG patients. Subjects were shown 5 static images displaying objects, without any animal or human being, for 3 minutes [6]. The displayed objects were not manipulable and consisted of pictures of buildings, trees, cruise ships, mountains, beach umbrellas, beds, and tables. A cognitive task was required in order to keep the patient's attention at high concentration: for a 3-minute sequence, images were separately displayed, each for 30 seconds, and then overlapped all together during the last 30 seconds, as an intrusive image (interloper) that the patient was asked to identify so that his attention span could be checked in real time by the OT. For example, the images regarded seascapes, but, inside the sequence, there was an image with mountains. The subject had to identify the image with mountains. Subjects were then asked to perform limb movements (at their best convenience) for 2 minutes according to a standard sequence, simulating those performed by the EG, in what refers to shoulder and elbow joint mobilization. They received verbal instruction by the OT such as the following: "starting with your elbow flexed at an angle of 90° and your shoulder adducted, please abduct your shoulder and extend your elbow as far as you can. You may use your unaffected arm to help guide if need." They did never interact with objects nor did they see the OT perform the movement. Movement was actively performed to the best of each subject's ability. As for EG, OT provided patients with physical help (limb support or passive mobilization) to help them accomplish the motor sequence. For each session, 3 different 3-minute sequences were displayed (each including 5 new images), thus leading to a 15-minute total duration of the rehabilitation session.

Both EG and CG received two treatment sessions/day at 60-minute interval apart. Every missed session was retrieved. Subjects who did not retrieve sessions and interrupted treatment for more than 5 consecutive days were excluded from the study.

2.5. Statistical Methods. The BBT was the primary outcome measure applied. It was chosen due to its validity and reliability as a dexterity measure in poststroke hemiplegic patients, whereas FM was deemed to assess upper limb gross motor function. Given the multiple endpoints measured in the study, the sample size was calculated according to the BBT, that is, to the parameter expected to benefit the most from the experimental treatment. We used the unpaired t-test to assess the homogeneity of the 2 groups at baseline for age, interval from stroke, and primary outcome measures. Moreover, in order to take into account both within-group and between-group changes at each time point, the "T1–T0" and "T2–T0" differences in FM and BBT scores were analyzed in a 2×2 repeated-measures analysis of variance (ANOVA); post hoc between-group comparisons were performed using the Mann-Whitney U test. In order to adjust the assessment of function improvement by score severity at entry, we applied a rehabilitation "effectiveness index," which was computed for each outcome measure, at each time point, as follows: (score T f-up-score T0.)/(max. achievable score-score T0). The formula describes observed improvements as percentages of maximum achievable gains, thus balancing the observed score changes across subjects showing different neurological impairment at baseline, with an effort towards emphasizing the achievement of optimal scores [18]. The maximum achievable score for BBT was set, for each patient, upon the healthy upper limb performance.

3. Results

The distribution of the patients by age, gender, and main clinical characteristics, at baseline, did not significantly differ between the EG and the CG. All subjects completed the 4-week treatment period and fulfilled the assessment protocol at T1. Subsequently, five patients from EG and 3 from CG moved to a different rehabilitation facility and declined the invitation to the follow-up visit.

The assessment performed at both T1 and T2 showed a significant improvement in arm function, in the whole sample. The observed changes (computed as percentages of the maximum recovery potential) were as follows: 31% (±26%) for the Fugl-Meyer at T1, 43% (±45%) for the Fugl-Meyer at T2, 17% (±18%) for the Box and Block Test at T1, and 25% (±22%) for the Box and Block Test at T2. No effects of age, gender, and stroke aetiology on upper limb function recovery were ascertained. The comparison between groups revealed a significantly higher gain for the EG than the CG, with respect to functional measures taken at both T1 and T2. An interaction analysis combining the effects of treatment to those of lesion side revealed that left, though not right, hemiparetic subjects achieved significantly greater benefits, in both FM and BBT scores, when exposed to AO, compared to standard rehabilitation alone (Table 1).

Table 1: Outcome measure score changes are displayed as percentages of recovery potential (effectiveness indices) at the end of the treatment (T1) and 4-5 months afterwards (T2).

	EG Mean ± SD (percentages of the maximum recovery potential)		CG Mean ± SD (percentages of the maximum recovery potential)		EG versus CG comparison *P* value
	T1	T2	T1	T2	
FM score change					
All subjects	40% ± 24% (33)		22% ± 25% (34)		**,003**
		56% + 32% (28)		30% ± 51% (31)	**,023**
RH subjects	42% ± 25% (15)		30% ± 29% (15)		n.s.
		64% ± 28% (12)		52% ± 39% (13)	n.s.
LH subjects	38% ± 24% (18)		15% ± 18% (19)		**,003**
		50% ± 35% (16)		15% ± 54% (18)	**,029**
RH versus LH comparison *P* value	n.s.	**,027**	n.s.	**,042**	
BBT score change					
All subjects	23% ± 21% (33)		11% ± 14% (34)		**,012**
		31% ± 22% (28)		19% ± 21% (31)	**,031**
RH subjects	18% ± 21% (15)		15% ± 12% (15)		n.s.
		29% ± 2/% (12)		28% ± 18% (13)	n.s.
LH subjects	27% ± 20% (18)		8% ± 14% (19)		**,005**
		33% ± 23% (16)		13% ± 20% (18)	**,008**
RH versus LH comparison *P* value	n.s.	n.s.	n.s.	**,042**	

The results of between-group comparisons, by treatment and by lesion side, are reported. EG: experimental group; CG: control group; FM: Fugl-Meyer; BBT: Box and Block Test. RH: right hemiparetic; LH: left hemiparetic.

4. Discussion

This study shows that action observation can stimulate and enhance the beneficial effects of motor training in left hemiparetic patients undergoing intensive rehabilitation in the subacute phase of ischemic stroke.

In agreement with previous studies [4–6, 19], our data suggests that observation of action, with the intention to imitate movements, can increase the excitability of the brain motor areas and, in doing so, can stimulate the recovery of motor control. Moreover, in addition to what has been already described by others, we hypothesized and observed that action observation, coupled with action execution, induces a higher improvement in right hemispheric compared to left hemispheric strokes.

It is fair to acknowledge that we did not carry out any electrophysiological or functional imaging studies to investigate the neural correlates of our clinical findings. The greater susceptibility of left, compared to right, hemiparetic strokes, to achieve functional benefits from a rehabilitation treatment implementing AO, cannot be easily explained. Recently, some researchers showed that the perception of tools, though not of other objects, activates the left premotor and somatosensory cortex, representing object affordances [20]. According to these authors, viewing tools automatically activates mental representations associated with their manipulation, independent of the kind of object and the type of grip (unimanual or bimanual). The left premotor cortex has been found to be involved with any kind of object and grip, as early as 200 milliseconds after stimulus presentation, thus supporting the hypothesis of a left hemisphere asymmetry in the neural representation of grasping, within this region. It may be hypothesized that right-handed people develop an asymmetrical representation of motor skills leading to a greater involvement of the left hemisphere during the observation of everyday life actions. Hamzei et al. recently proposed a connectivity model where the illusion of bimanual hand movement during mirror training (MTr) promoted functional coupling between each premotor region and the supplementary motor area (SMA) ipsilateral to the untrained hand, which in turn showed an increased functional interaction with the ipsilateral sensory motor cortex (SMC) [21]. More specifically, they proved that right hand training, in healthy subjects, led to performance improvement of the untrained left hand and that this finding was made possible by the involvement of the left SMA. They did not test their hypothesis in the reversed setup (i.e., trying to increase right hand performance via left hand training); therefore, they cannot exclude the assumption that left hemisphere is especially activated, during action observation, this being the key factor that prompts the achievement of motor practice effects, when movement is just observed. The emphasis on the role played by the left hemisphere networks in AO tasks, as can be inferred from the findings by Hamzei et al. [21], could provide a neurophysiological basis to our empirical findings of a selective improvement of left hemiparetic stroke subjects undergoing motor training coupled with AO; in fact, it could be hypothesized that daily tasks are especially represented

in the left hemisphere of right-handed people and that the activation of the mirror neuron system of this side (which is spared in left hemiparetic subjects) is a key factor to the increase of activity of cortical motor areas. Of course, this hypothesis needs to be confirmed by the reverse finding of a greater benefit achieved through AO in right hemiparetic, left-handed subjects.

Study Limitations. The interpretation of group differences is only based on clinical measures and this methodological choice represents the main limitation of this research. Future studies combining electrophysiological recording or functional neuroimaging with data acquired using experimental psychology will hopefully provide a more comprehensive understanding of how action observation modulates the brain activity and the recovery of motor performance.

Nonetheless, the randomized and controlled design of this study, coupled with the blindness of assessments and the random allocation of therapists, supports the reliability of study findings. In fact, although our results concern subjects in the subacute phase of stroke, where spontaneous recovery is still expected, this possible source of bias was taken into account, by comparing the functional evolution of a moderate-severe upper limb paresis exposed either to an AO treatment or a "sham" treatment. Since the subjects in the EG and CG were matched with respect to clinical, functional, and demographic characteristics at baseline, spontaneous recovery might have equally concerned both groups, and, therefore, any further between-group difference should be regarded as treatment-related. The amount and kind of training received by each patient in the EG has possibly had its counterpart in the training received by a matched patient in the CG.

The choice of applying an effectiveness index, which describes observed improvements as percentages of maximum achievable gains, was aimed at adjusting motor recovery by score severity at entry, thus controlling for interindividual differences in the functional state before treatment. This kind of data processing may have helped to compensate the effects of the unavoidable differences in the amount and type of motor training undertaken by subjects showing different degrees of motor impairment at enrolment.

5. Conclusion

The results obtained in this research endorse the use of AO in addition to motor training in first-ever stroke survivors with left hemiparesis following right hemisphere damage. The positive findings obtained in subjects with moderate to severe upper limb paresis, the simplicity of treatment, and the lack of side effects strongly recommend extending the use of AO, in association with physiotherapy, to the early stage of stroke care. Larger future trials could be conducted enhancing the application of AO by the use of novel technology, in telerehabilitation protocols. Finally, further clinical trials exploiting fMRI to locate cortical reorganization following stroke, in a heterogeneous population, could challenge our hypothesis and define the real role of the left hemisphere network in brain-injured subjects.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Concurrent Validity of Physiological Cost Index in Walking over Ground and during Robotic Training in Subacute Stroke Patients

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Physiological Cost Index (PCI) has been proposed to assess gait demand. The purpose of the study was to establish whether PCI is a valid indicator in subacute stroke patients of energy cost of walking in different walking conditions, that is, over ground and on the Gait Trainer (GT) with body weight support (BWS). The study tested if correlations exist between PCI and ECW, indicating validity of the measure and, by implication, validity of PCI. Six patients (patient group (PG)) with subacute stroke and 6 healthy age- and size-matched subjects as control group (CG) performed, in a random sequence in different days, walking tests overground and on the GT with 0, 30, and 50% BWS. There was a good to excellent correlation between PCI and ECW in the observed walking conditions: in PG Pearson correlation was 0.919 ($p < 0.001$); in CG Pearson correlation was 0.852 ($p < 0.001$). In conclusion, the high significant correlations between PCI and ECW, in all the observed walking conditions, suggest that PCI is a valid outcome measure in subacute stroke patients.

1. Introduction

In stroke survivors cardiorespiratory reconditioning represents a challenge to improve patients' mobility and quality of life, especially for those who regain deambulation in the community [1].

The stroke survivor reduction of cardiovascular fitness is a real problem limiting patients' return in community life. This problem comes out because more than 75% of patients affected by a stroke have a cardiovascular disease [2] and because after a stroke patients reduce their mobility. As recommended by the American Heart Association, moderate aerobic training is useful in subacute stroke condition to avoid deconditioning [3], and several authors during the last 10 years documented the importance of an aerobic training in stroke survivors in terms of reducing insulin resistance, improving lipid profile and glucose tolerance, and improving cognitive function [4–6].

For these reasons electromechanical assisted and robotic machines providing body weight support (BWS) were made to train nonambulatory patients, with less demand for the physiotherapist, and should be useful for increasing the amount of walking exercise avoiding deconditioning. In fact Chang et al. demonstrated that more than two weeks of Lokomat training improved cardiovascular fitness early after stroke [7].

The Gait Trainer (GTII, Rehastim, Berlin) [8, 9] is one of these machines and its positive effect on walking ability was well documented [10] especially in more severe patients [11, 12]. During GT exercise it is important to know patients' cardiac demand and oxygen consumption to train patients in a safe manner to improve the reconditioning across the therapy session.

Oxygen consumption and energy cost of walking (ECW) have been widely used in the literature investigating the efficacy of interventions for improvement of walking capability.

It has been reported that gas exchange analysis is a reliable method after stroke [13, 14]; nevertheless ECW measurement is generally impracticable in clinical settings due to unavailability of dedicated instrumentations and expert physicians. Another method used to assess gait demand is the Physiological Cost Index (PCI), proposed by MacGregor [15, 16]. The PCI is calculated as follows: (heart rate during steady state exercise minus heart rate at rest) divided by walking speed; PCI is expressed in beats/meter and indicates the increased heart rate (HR) necessary for exercise (walking). The PCI theory has been based on the fact that, for submaximal effort, a correlation exists between HR and $V'O_2$. Based on this correlation, PCI has the potential to represent an easy and cheap index of ECW for a given subject, useful for clinicians that have no other more expensive and sophisticated devices as, for example, portable gas analyzer.

The correlations between PCI and $V'O_2$ have been investigated in amputees (children and adults) [17, 18], children with cerebral palsy [19], adults with spinal cord injuries [20], and healthy adults [21]. Also PCI has been reported as outcome measure, in several studies, after interventions in persons with cerebral palsy [22], spinal cord injury [23, 24], rheumatoid arthritis [25], stroke [26–28], and acquired brain injury [29].

A few and conflicting data are reported in the literature about validity and reliability of PCI in stroke population: Danielsson et al. concluded that the PCI showed limited reliability and validity as a measure of energy cost after stroke, even if it would be useful as a simple measure for patients in clinical situation [30]; Fredrickson et al. reported that the PCI can be used as a proxy index for the oxygen cost of walking in subjects after stroke [31]; in a more recent work Danielsson et al. [32] estimated the ECW of subjects with motor impairment late after stroke by means of PCI.

It has to be considered that heart rate measurement could be affected by altered vagal or sympathetic regulation, secondary to brain injury [33–36] or medication. Nonetheless, it would be of clinical interest to assess the PCI method in a sample of persons with (subacute) stroke to test its suitability as a simple, inexpensive measure of energy cost.

Concerning validity, correlations between the PCI and ECW were reported by Bowen et al. [19] in a study on children with cerebral palsy, where a correlation coefficient of 0.50 was found. An extremely high correlation ($r = 0.99$) was found between HR and $V'O_2$ by Rose et al. [37] in two-minute walk tests conducted at different speeds. Engsberg et al. [17] reported that the vertical displacement of the pelvis, the PCI, and HR were adequate tools in the assessment of energy expenditure. In a study on patients with spinal cord injury, Ijzerman et al. [20] concluded that the ability of the PCI to detect changes (longitudinal validity) was good ($r = 0.86$). To our knowledge there are no studies about assessment of ECW, during overground walking or during walking on the GT, by means of PCI in subacute stroke patients. Thus, in the present study the aim was to establish whether PCI is a valid indicator in subacute stroke patients, and in healthy age- and size-matched subjects, of ECW in different walking conditions, that is, over ground and on the GT with BWS. To accomplish the aim, the study tested if correlations exist between PCI and ECW, indicating validity of the measure and, by implication, validity of PCI. Finally, in order to provide information regarding energy demand during robotic training with BWS oxygen consumption data in different GT BWS walking conditions have been quantified in MET.

2. Methods

Patients with stroke in a rehabilitation department were asked to volunteer for the study (patients group (PG)). The inclusion criteria were first time stroke at least 6 months previously, 18 to 65 years of age, hemiparesis, stable heart condition, and walking ability without assistance for 5 minutes (or, if necessary, with a walking aid or orthosis). Exclusion criteria were severe cardiac disease or arrhythmia, pain during walking, walking impairment other than stroke-induced, and inability to understand information or follow instructions. An age- and body-size-matched healthy control group (CG) was also recruited. The study was approved by the local ethics committee. All participants were informed before they signed the consent form to take part in the study. All study participants performed an overground walking test (OGWT) and 3 walking tests on the GT with three different percentages of body weight support (BWS), namely, 0% BWS, 30% BWS, and 50% BWS (GTWT-0% BWS, GTWT-30% BWS, and GTWT-50% BWS). Each participant performed one test per day in four consecutive days in a random sequence. For the OGWT, participant had to walk forth and back along a 20 m linear course at a self-selected walking speed. Patients were allowed to use their walking aids (e.g., cane) if necessary. Also on the GT, walking speed was self-selected during the first minute of walking and then remained unchanged until the walking test end. During all tests participants wore a portable breath by breath gas analyzer $K4b^2$ (Cosmed, Italy) to assess oxygen consumption ($V'O_2$) and a heart rate monitor (Polar Electro Oy, Finland) to collect heart rate (HR) data. Each WT (OGWT and GTWT) lasted at least 5 minutes to allow reaching and maintaining a cardiac and metabolic steady state (SS).

As baseline data the mean values of the last 3 minutes of a 10-minute resting condition recording were considered while the SS phase data were calculated as the mean value of the data collected in the last two minutes of data recording during each walking test.

Mean walking speed during OGWT was calculated as the ratio of distance to time; thus, the walking speed obtained in the last 2 min of data collection was considered.

The PCI was calculated as follows:

$$\mathrm{PCI} = \frac{\mathrm{SSHR}\ \ (\mathrm{beats/\,min}) - \mathrm{Resting\ HR}\ \ (\mathrm{beats/\,min})}{\mathrm{walking\ speed}\ (\mathrm{m/\,min})}. \tag{1}$$

2.1. Statistical Analysis. Mean and standard deviation were computed for all the measured parameters. We choose to use repeated measure analysis of variance because the measurements were continuous and because this analysis allows for comparing at the same time within- and between-subjects

factors. A repeated measures ANOVA was carried out to assess differences within (walking conditions: over ground, GTWT-0% BWS, GTWT-30% BWS, and GTWT-50% BWS) and between (group: PG, CG) subjects factors. Walking conditions and group were considered as main factors in this analysis; thus the comparison between walking conditions was performed by including all subjects in the two groups; the group comparisons were performed by including all walking conditions. The level of significance for the ANOVA analysis was set at $p < 0.05$. When ANOVA revealed statistically significant results, post hoc comparisons were carried out with Bonferroni correction. To assess correlations between PCI and ECW a Pearson correlation was calculated.

3. Results

Six patients with hemiplegia due to stroke (age: 66 ± 15 y; time since stroke: 8 ± 3 weeks; four men) and 6 healthy age- and size-matched subjects as CG (age: 76 ± 7 y; six men) were enrolled in the study. PG and CG mean body mass and stature were 66 ± 6 kg and 164 ± 7 cm, 76 ± 7 kg, and 173 ± 3 cm, respectively. Only one stroke subject needed aid for OGWT; all patients were able to reach and maintain SS phase, as described in the protocol.

The mean self-selected walking speed of PG during OGWT was 1.25 ± 0.51 km/h; in the same WT CG walked at 3.60 ± 0.44 km/h, a speed significantly higher than that chosen by PG ($p < 0.001$). On the GT the mean self-selected walking speeds of PG for GTWT-0% BWS, GTWT-30% BWS, and GTWT-50% BWS were 1.53 ± 0.18, 1.50 ± 0.17, and 1.51 ± 0.17 km/h, respectively. CG mean self-selected walking speeds during GTWT-0% BWS, GTWT-30% BWS, and GTWT-50% BWS were 1.57 ± 0.16, 1.54 ± 0.12, and 1.62 ± 0.22 km/h, respectively. No differences were observed between groups in the GTWTs speeds. Within-group analysis showed that OGWT PG speed did not differ significantly from that on the GT, while for CG the OGWT speed was significantly higher than that reached at each GTWT, $p < 0.001$.

Figures 1 and 2 show PCI and ECW data of PG and CG, respectively, in all the observed walking conditions. PG PCI mean values accounted for abnormally elevated values in OGWT compared to CG (1.45 ± 0.87 versus 0.35 ± 0.06 beats/m); the difference between groups was statistically significant ($p = 0.012$, with Bonferroni correction). Also ECW PG data of OGWT were higher than those of CG (0.66 ± 0.37 versus 0.21 ± 0.02 mL/kg/m), with statistical significance ($p = 0.015$, with Bonferroni correction). Further, it has to be noted that for PG OGWT has the significantly highest values for both PCI and ECW, while for it CG is the contrary ($p < 0.02$).

As can be seen in Figures 1 and 2, for both groups on the GT the improvement in BWS is paralleled by a decrease of PCI and ECW. On the GT, for all the observed walking conditions (i.e., with the several percentages of BWS), there were no differences between groups. At the within- group analysis PG showed statistical differences between GTWT-30 and -50% BWS versus GTWT-0% BWS, $p < 0.02$, while

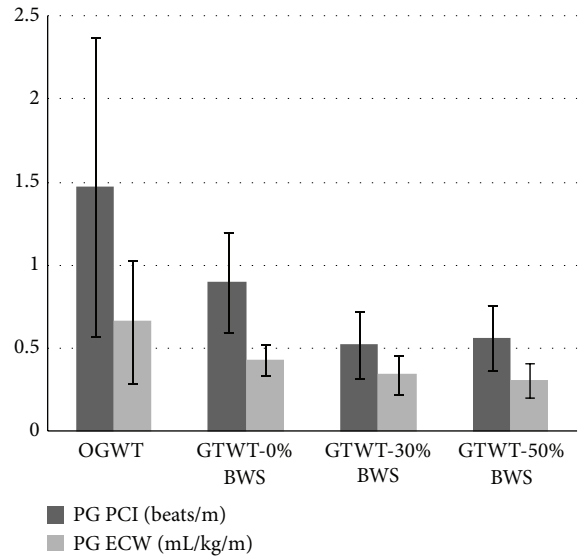

Figure 1: PCI and ECW of PG in the observed walking conditions.

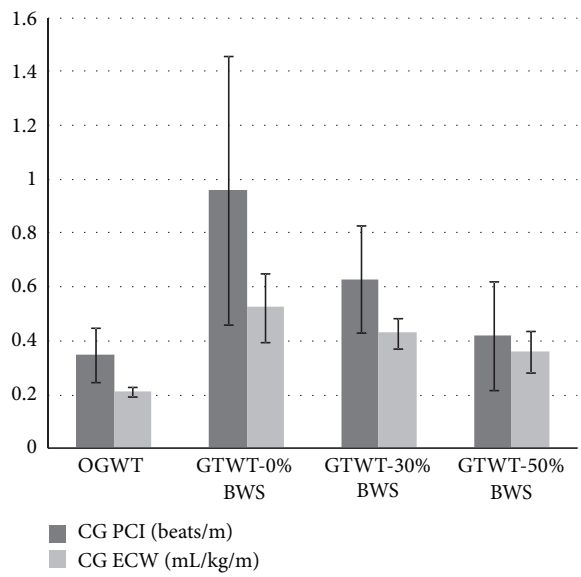

Figure 2: PCI and ECW of CG in the observed walking conditions.

CG showed significantly higher values between GTWT-0, -30, and -50% BWS versus OGWT ($p < 0.02$). Further, due to the reduced sample size, we have also used nonparametric statistics (Friedman's analysis) for confirming (or not) the results of parametric one.

As reported in Figure 3, there is a good to excellent correlation between PCI and ECW, in the observed walking conditions: in PG Pearson correlation was 0.919 ($p < 0.001$); in CG Pearson correlation was 0.852 ($p < 0.001$). Furthermore, the two fitting lines based on a first-order polynomial model resulted to be very similar in the two groups. Conversely, although quadratic regressions improved the fitting of data in terms of adjusted R^2, the curve for healthy subjects diverged from that of patients, for which

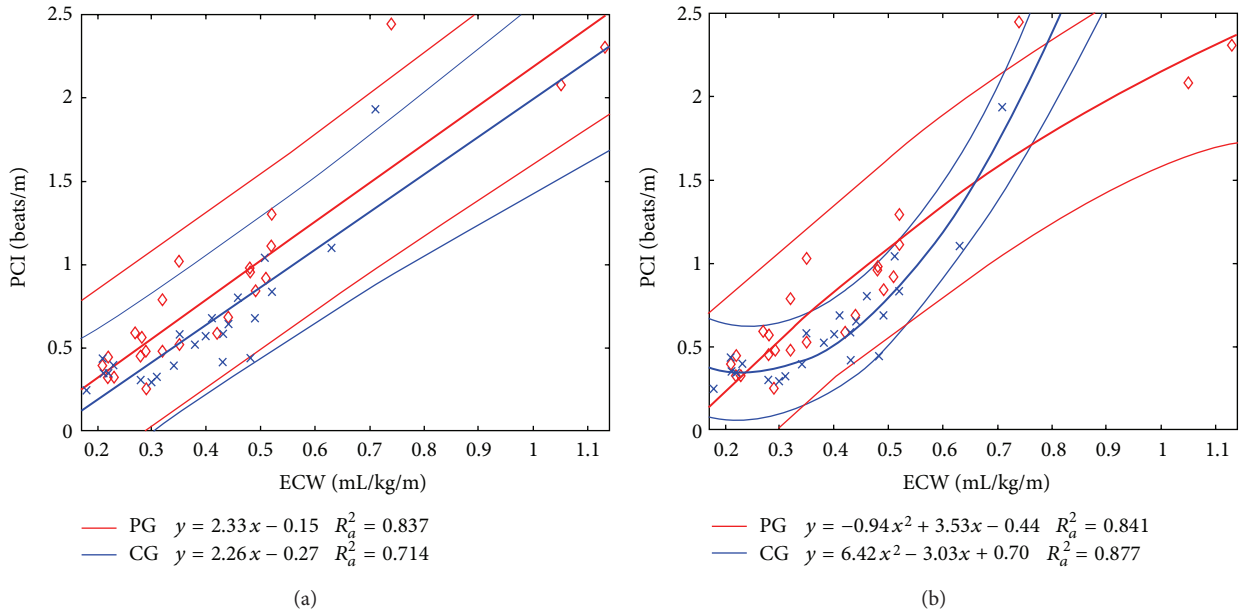

Figure 3: Correlations between PCI and ECW, in all the observed walking conditions (over ground, on the GT with 0, 30, and 50% BGWS), of PG (red diamonds) and CG (blue crosses). On the left (a) are first-order polynomial fitting lines and on the right (b) second-order polynomial fitting lines (with the same color of data). Thin lines represent the 95% confidence interval for all the fits. Equations of fits and values of adjusted R^2 are also reported.

Table 1: MET of PG and CG in the observed walking conditions.

	REST	OGWT	GTWT-0% BWS	GTWT-30% BWS	GTWT-50% BWS
PG	0.80 ± 0.27	3.3 ± 0.8	3.1 ± 0.8	$2.4^{*\S} \pm 0.9$	$2.2^{*\S} \pm 0.9$
CG	1.05 ± 0.21	3.6 ± 0.6	3.9 ± 1.2	$3.1^{*\S} \pm 0.5$	$2.7^{*\S} \pm 0.6$

Data are reported as mean and standard deviation. Significant difference of post hoc analysis: *with respect to overground and §with respect to GTWT-0% BWS.

the increment of the polynomial fit order slightly varied the adjusted R^2.

Table 1 reports energy expenditure data, expressed as MET, and p values, of both groups in all the observed conditions.

PG had the highest MET values at OGWT, while CG had the highest value at GTWT-0% BWS. On the GTWT both groups showed a decrease of energy expenditure with the increase of BWS. As can be noted the CG always showed values higher than PG; no statistical differences were observed between groups. According to work classification, for both groups, OGWT and GTWT-0% BWS accounted for a moderate intensity work, while GTWT-30% and GTWT-50% BWS resulted as light job [38].

4. Discussion

The lack of sophisticated and expensive instrumentations and of ad hoc trained physicians/physiotherapists in clinical settings determines the need of cheap and easy methods to obtain valid outcome measures. The widely diffused possibility to collect heart rate may allow for the implementation of outcome measure based on heart rate data. Thus the present study aimed at verifying the validity of PCI as cheap and easy outcome measure in subacute stroke patients. Further, the increasing diffusion of robotic machines providing BWS [7, 11, 39], like the GT, induced us to investigate the validity of PCI also during training on the GT.

To accomplish this aim, the PCI and the ECW in a PG and in an age- and size-matched CG were determined in several walking conditions, namely, OGWT, GTWT-0%, GTWT-30%, and GTWT-50% BWS; then the correlation between PCI and ECW data was determined.

The high significant correlation for PG ($r = 0.9191$, $p < 0.001$) and for CG ($r = 0.852$, $p < 0.001$) suggests the possibility of using PCI as valid outcome measure in subacute stroke patients. Further, related to OGWT, PCI was able to discriminate stroke patients from healthy subjects (1.45 ± 0.87 versus 0.35 ± 0.06 beats/m, $p = 0.012$), similarly to ECW (0.66 ± 0.37 versus 0.21 ± 0.02 mL/kg/m, $p = 0.015$). Our PG OGWT data are in line with those reported by Mossberg [29] for PCI, while their ECW data were lower than ours (0.374 ± 0.203 mL/kg/m) for stroke subjects. Further, also Mossberg [29] found a significant good correlation between PCI and ECW in stroke patients during walking on treadmill. PCI and ECW data reported by Stein et al. [28] are lower than our PG OGWT data, probably because in the study protocol of Stein et al. for walking test a treadmill was used provided with hand support, and the protocol allowed for a light hand support during walking. This could have reduced the energy and cardiac demand in comparison to our study protocol.

As reported in Figure 1, for PG OGWT had the highest values for both PCI and ECW; besides, on the GT the improvement in BWS was paralleled by a decrease of PCI and ECW. On the GT the same trend of PCI and ECW was observed for CG, but CG, differently from the PG, had the lowest PCI and ECW data in OGWT, as can be seen in Figure 2. This last result is due to the fact that CG had no limitations in performing OGWT, considering that CG was healthy and OGWT represented a habitual motor task, while for PG OGWT represented something to be regained, hard to perform in comparison to GTWTs. It has to be noted that CG had on the GTWTs walking speed values close to those of the PG, because GT permits a maximal walking speed of 2 Km/h [8].

The similarity of PCI and ECW trends on the GTWTs, with the different BWSs, between PG and CG is more evident in Figure 3, where the correlation between PCI and ECW is reported for both groups. The PCI has a high correlation with ECW that indicates its validity either on the OGWT or on the GT with different BWS. As ECW, also PCI is able to detect differences between PG and CG (1.45 ± 0.87 versus 0.35 ± 0.06 beats/m, $p = 0.012$). On the GT for all walking conditions (i.e., with 0, 30, and 50% BWS) neither ECW nor PCI revealed differences between groups. This fact could be due to the light intensity [36] of the job performed, particularly at GTWT-30% and GTWT-50% BWS. Nevertheless both ECW and PCI, at the within-group analysis, revealed statistical significant differences among GTWT BWS conditions: PG showed statistical differences between GTWT-30 and 50% BWS versus GTWT-0% BWS, $p < 0.02$, while CG showed significantly higher values between GTWT-0, -30, and -50% BWS versus OGWT ($p < 0.02$).

As a further result, as reported in Table 1, PG and CG had the highest MET values at OGWT and GTWT-0% BWS, respectively, and on the GTWTs both groups showed a decrease of energy expenditure with the increase of BWS. Besides, for both groups, OGWT and GTWT-0% accounted for a moderate intensity work, while GTWT-30% and GTWT-50% resulted as light job. This last result, in accordance with PCI and ECW data, further confirms that training on the GT with 30–50% of BWS is less energy demanding and suggests that it could be a safer walking rehabilitation tool with respect to the traditional one conducted over ground.

4.1. Study Limitation. The main limitation of the study was small sample size. This also limited the possibility to take into account possible confounding factors such as age or basic gait speed. It has to be considered that it is hard to convince patients who have yet a lot of problems and discomfort to be engaged in a study like ours. Not so many people are prone to be engaged in several measures that are not invasive but fastidious and that need patients' active participation. However, our data adds information to previous findings, useful in clinical settings.

5. Conclusion

The high significant correlations between PCI and ECW, in all the observed walking conditions, suggest that PCI is a valid outcome measure in subacute stroke patients. Also, PCI is comparable to ECW in its ability to discriminate between stroke patients and healthy subjects in overground walking test.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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Clinical Study

Quantitative Electroencephalography and Behavioural Correlates of Daytime Sleepiness in Chronic Stroke

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Sleepiness is common after stroke, but in contrast to its importance for rehabilitation, existing studies focus primarily on the acute state and often use subjective sleepiness measures only. We used quantitative electroencephalography (qEEG) to extract physiological sleepiness, as well as subjective reports, in response to motor-cognitive demand in stroke patients and controls. We hypothesised that (a) slowing of the EEG is chronically sustained after stroke; (b) increased power in lower frequencies and increased sleepiness are associated; and (c) sleepiness is modulated by motor-cognitive demand. QEEGs were recorded in 32 chronic stroke patients and 20 controls using a Karolinska Drowsiness Test protocol administered before and after a motor priming task. Subjective sleepiness was measured using the Karolinska Sleepiness Scale. The findings showed that power density was significantly increased in delta and theta frequency bands over both hemispheres in patients which were not associated with subjective sleepiness ratings. This effect was not observed in controls. The motor priming task induced differential hemispheric effects with greater increase in low-frequency bands and presumably compensatory increases in higher frequency bands. The results indicate sustained slowing in the qEEG in chronic stroke, but in contrast to healthy controls, these changes are not related to perceived sleepiness.

1. Introduction

Daytime sleepiness is commonly experienced in the acute phase of stroke [1, 2] which becomes a chronic problem in 34% of patients sustaining beyond six months [3–7]. Poststroke sleepiness is associated with lower quality of life [5], affects the ability to return to work [8], impacts cognitive functioning [9, 10], and hinders rehabilitation participation and outcome [7, 11–13]. Furthermore, the increased number of accidents committed by persons with a history of stroke has been attributed to sleepiness and fatigue [14, 15]. Several factors may contribute to sleepiness in stroke patients including neurological damage per se [16], depression [17], low social interaction [3], medication side effects [18–20], insomnia [21], sleep disordered breathing [17], and general poor health [5]. Strokes that affect the motor cortex may result in partial, or full, paralysis of the limbs. These limitations in motor functioning require increased effort for most activities of daily living, resulting in a greater level of exhaustion and sleepiness [22].

Sleepiness is complex construct to quantify and measure. Sleepiness describes an increased drive to sleep [23] which is distinct from fatigue. Fatigue refers to exhaustion as a result of physical or mental strain but this does not necessarily require sleep to be reversed [24]. Sleepiness can be measured subjectively using questionnaires; however, this only captures perceived sleepiness which can be influenced by other factors such as experimenter bias, mood, motivation, and poor introspection [25–27]. The latter has been particularly observed in those with brain injury and sleep problems [4, 17, 28]. Therefore, the objective measurement of physiological arousal is more accurate for detecting sleepiness levels. This requires the recording of neural activity in real time, and therefore, more sophisticated technology, that

is, electroencephalography (EEG). Decreased physiological arousal, or sleepiness, is indicated by EEG frequency changes. Frequencies can be grouped into four distinct frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (>12 Hz). The EEG in the normal waking adult consists primarily of beta and alpha rhythms. When arousal decreases, the rhythm becomes dominated by alpha and eventually lower frequencies when transitioning to sleep (>8 Hz). EEG methods have been incorporated into protocols for measuring sleepiness with a greater level of accuracy compared to questionnaire approaches alone.

A commonly used protocol is the Multiple Sleep Latency Test (MSLT) [29]. The MSLT aims to quantify sleepiness propensity by recording the EEG whilst the participant is given an opportunity to sleep in a laboratory. Sleep onset is determined by visual scoring of the EEG when the criteria for stage 1 sleep are met for 90 seconds [29]. A shorter sleep onset latency, measured in minutes, indicates higher the sleep propensity.

The MSLT protocol does not provide additional information about the characteristics of the EEG per se. But through offline analysis of the frequency composition of the raw EEG at a particular time point, the power in the slower frequencies associated with increased sleepiness (>12 Hz) can be determined to provide important indicators for how sleepy a person is whilst awake. This process is known as quantitative EEG (qEEG). Karolinska Drowsiness Test (KDT) [30] utilises qEEG to quantify sleepiness [31]. In the KDT protocol, the EEG is recorded whilst participants are awake and qEEG analyses are applied offline. Studies have shown that increased power in the lower frequency bands, mostly alpha and theta, correlates with subjective ratings of sleepiness across multiple time points in healthy adults [32–34]. Slowing of the waking EEG is generally recognised as a physiological indicator of subjectively experienced sleepiness, and indeed, increased sleep propensity [33].

Although sleepiness is often reported after stroke which brings additional problematic consequences, the majority of studies rely on subjective reports thus rendering our understanding of sleepiness in this population as limited which has implications for effective patient management. Objective neurophysiological methods, such as qEEQ [31–35], are lacking in this population but could help to improve the quantification of the level of severity of sleepiness problems in this population.

To the best of our knowledge, qEEG has not yet been used as a tool to investigate sleepiness in chronic stroke patients with chronic deficits. Several studies have used qEEG in acute stroke patients in the context of identifying neurological abnormalities and reported slowing in the delta and theta frequency ranges [36–39]. The concept of subjective alertness state was not addressed in these studies. Therefore, we do not know if qEEG correlates of sleepiness are present in stroke patients, in the same way as has been observed in nonbrain injured populations, nor to what degree this method can be used to measure sleepiness in this population.

In light of this gap in the literature, the present experiment therefore examined the qEEG in relation to subjective ratings of sleepiness in stroke patients with chronic hemiparesis. We hypothesised that the slowing of the daytime EEG, observed in the early stages of recovery, might be sustained in the chronic phase. Based on findings in healthy controls, we further predicted that increased power in the lower frequency bands is indicative of greater perceived sleepiness. Moreover, we hypothesised that these sleepiness parameters would be modulated by motor cognitive demand, and that this effect would be stronger in the presence of hemiparesis. Therefore, we applied a motor task in this study to facilitate motor cognitive demand.

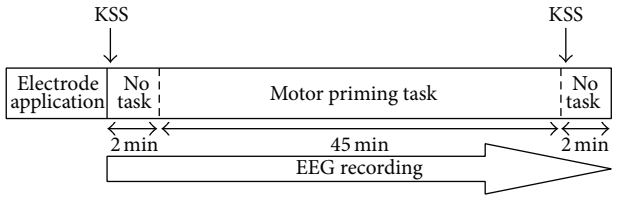

Figure 1: Study protocol.

2. Methods

2.1. Design and Protocol. This study employed a mixed within and between participant design. Each participant followed the protocol as outlined in Figure 1. After electrode application, waking EEGs were recorded for two minutes before and after the motor priming task with eyes open. During this time, participants were instructed to focus on a black dot in the centre of the screen as described in Karolinska Drowsiness Test [33]. A subjective sleepiness rating (Karolinska Sleepiness Scale; KSS) was recorded at the beginning of each two minute EEG recording at pre- and posttask (Figure 1).

2.2. Participants. Thirty-two community dwelling patients with first ever unilateral cortical or subcortical stroke >12 months were recruited via local general practitioner surgeries, hospitals, and online support communities. Average time since stroke was 69.1 months (±45.59, range 12–210). Eighteen patients had right, and 14 had left hemispheric strokes. Patients' mean age was 53.94 (±12.16 years, range 28–73) and 56% of the sample were male. All patients had approval from their general practitioner prior to taking part in the study. Exclusion criteria comprised a seizure within the past six months, severe balance difficulties, uncorrected visual impairment, uncontrolled comorbid illnesses or psychological disturbance, and diagnosed sleep disorders. The Mini Mental State Exam (MMS) [40] was applied in order to exclude those with cognitive deficits. The MME assesses orientation, immediate and short-term memory, attention, calculation, language, and spatial awareness. Total scores ≥25 are considered normal [40] and formed the exclusion criteria for this study.

The control group comprised twenty neurologically healthy participants recruited from the general population via flyers and posters. Exclusion criteria comprised presence of a brain injury or other serious health condition, diagnosed

Table 1: Participant information: data presented as mean, ± 1 standard deviation, range, or percent.

Demographical variables	Stroke patients (n = 32)	Controls (n = 20)
Gender (M : F)	18 : 14	10 : 10
Age (Years)	53.97 ± 12.16 (28–73)	54.10 ± 13.21 (33–72)
BMI	24.10 ± 2.56 (18.20–28.90)	24.56 ± 3.64 (18–30.80)
MMSE	29.10 ± 1.06 (26–30)	—
ESS	6.69 ± 4.41 (0–17)	5.45 ± 4.52 (0–15)
Chronicity	60.91 ± 45.59 (12–210)	n/a
Stroke hemisphere (Left : Right)	14 : 18	n/a
Medication (frequency of participants on medications)	Antidepressant (4) Cardiac control (4) Antiepileptic (5) Sleep hypnotics (1)	n/a
Alcohol (units per week)	8.98 ± 10.75 (0–45)	3.66 ± 8.12 (0–35)
Caffeine (servings per day)	4.36 ± 2.73 (0–12)	3.31 ± 2.74 (0–10)
Nicotine (cigarettes per day)	0.97 ± 3.90 (0–20)	0.50 ± 2.24 (0–10)

sleep disorder, and clinically significant psychological disturbance. Mean age was 54.1 years (±13.21, range 33 to 72) and 50% of the sample was male.

No participants were diagnosed with clinically significant sleepiness. The Epworth Sleepiness Scale (ESS) [23] was used as a measure of average sleepiness levels. ESS scores ≥10 are suggestive of significant problem with sleepiness. According to the ESS criteria, 28% of patients and 20% of controls reported significant sleepiness. Two out of five patients taking antiepileptic medication were above the ESS criteria. One out of four patients taking antidepressants was above ESS criteria. Mean ESS scores did not significantly differ between groups. Patients did not differ from controls apart from alcohol consumption where patients consumed significantly more than controls ($z = -2.62$, $P < .01$). Further analyses revealed no differences between patients with left or right hemispheric stroke. The demographics of the two groups are summarised in Table 1.

The study protocol was approved by the Surrey Research Ethics Committee (National Health Service UK) and the University of Surrey Research Ethics Committee. Written informed consent was obtained prior to participation. All procedures adhered to the ethical guidelines outlined by the Declaration of Helsinki [41].

2.3. Measures. Subjective sleepiness was measured with Karolinska Sleepiness Scale (KSS) [33], a one-dimensional scale to assess sleepiness at a particular time point. Scores ranged from 1 (very alert) to 9 (very sleepy). The KSS has shown good correlation with objective measures of alertness including EEG and vigilance tests [30], and in sleep deprivation paradigms [33, 42].

Waking EEG was used to record physiological indicators of sleepiness using a 64-channel QuickAmp system (Brain Products GmbH Munich, Germany) and Ag/AgCl electrodes using the standardised 10-10 montage [43]. Impedances were kept below 5 kOhm. Data was recorded in DC mode with a sampling rate of 500 Hz, and against average reference.

The motor task used Rosenberg's motor priming paradigm to facilitate motor cognitive demand in patients with chronic motor deficits poststroke [44].

One of four precues (left ≪, right ≫, either right or left <> or noresponse ><) were presented within an empty line drawn circle. Precues were immediately followed by one of three response cues represented by a black semicircle filled in white appearing within the line drawn circle: left half (left button press), right half (right button press), or bottom half circle (no response).

Participants were instructed to respond to the cues using the button press as quickly as possible. Precue presentations were randomised and were 100% predictive of the response cue. Following the response, a feedback screen was displayed for 500 ms and indicated either of the following: correct response ("correct") or incorrect response ("wrong"; "not responded to response cue"; "a response was required!") and responses within 200 ms of response cue ("too early!"). Sixty trials were presented approximately in 6 blocks. The response window was 1830 to 4000 milliseconds. Responses were executed with the left or right index finger, hand or arm, dependent on ability of patients who have some level of chronic hemiparesis. All participants first completed a training block to familiarise themselves with the procedure. Stimulus presentation was delivered using Neurobehavioural Systems Presentation Software (http://www.neurobs.com/).

2.4. Analysis. EEG signals were analysed offline using the Brain Analyzer Software (Brain Products GmbH Munich, Germany). A digital 0.5 Hz high pass and 30 Hz low pass phase shift-free Butterworth filter was applied as well as a 50 Hz notch filter. The two-minute segments of raw data were inspected manually for artefacts and further subdivided into two-second epochs. Frequency composition was determined through the Fast Fourier Transformation (FFT) module embedded in Visual Analyser. FFT criteria were set to full spectrum, resolution 0.5 Hz, power density output (μV^2/Hz), and a Hanning window (10%) was applied. The FFT values

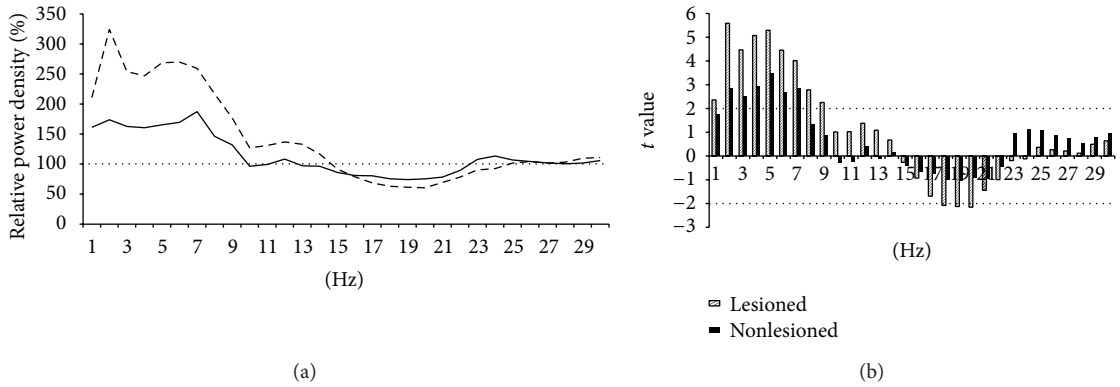

Figure 2: Difference in the EEG between patients and controls: (a) power density for the central derivation per 1 Hz for patients expressed as a percentage above or below controls at 100%; (b) between group t values with the dashed line to cut off point for significance.

were averaged and exported in 0.5 Hz bins ranging from 1 to 30 Hz. These data were further subdivided into discrete, nonoverlapping frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz). Power density values were transformed using log base 10 (Log 10).

Differences in frequency composition between patients and controls were calculated for central electrodes (C3 and C4). Task and sleepiness effects were examined using central electrodes plus additional derivations including frontal (F3/F4), parietal (P3/P4), and occipital (O1/O2). Topographical distributions of discrete frequency bands were spline-interpolated [45] to create cortical maps for visual inspection.

To visualise group differences, geometric mean calculations were performed to express power density values of patients as a percentage of controls, a method previously used in nonbrain injured samples [46–48]. This was achieved by (1) transforming power density values using Log10, (2) averaging data across participants, (3) subtracting patient data from controls, (4) antilogging these values, and (5) multiplying by 100.

Performance on the motor task was measured as reaction time (ms), defined as time between response cue onset and button press, and the number of correct responses to the cue (%). For stroke patients, performance results were drawn from responses of the nonlesioned hand to minimise the impact of the motor deficit on performance. Reaction time and correct responses were averaged across blocks for all participants.

Statistical analysis was conducted using SPSS (SPSS Inc.; version 15.0). Between-group demographic variables were compared using t-tests or the Mann-Whitney U Test for nonnormal data. EEG data was log transformed using Log10. T-tests were used to directly compare the EEG of patients and controls for each 1 Hz bin between 1 and 30 Hz. Topographical maps of difference between patients and controls were plotted using the P values drawn from t-tests between groups per frequency band. Mixed-model ANOVAS with the repeated measures factors of task (pre-, post-) and hemisphere (left/right for controls; lesioned/nonlesioned for patients) and one between factor (group) were calculated to test for group and task effects on the KSS and EEG per frequency band. Significant findings were further examined using one-sided Fisher's protected t-tests with alpha set to $P \leq .05$. For multiple comparisons, the Bonferroni correction was applied. Pearson's correlation coefficients were used to examine associations between KSS and EEG parameters. Correlations were Fisher's z transformed to allow the calculation of Z_{obs} score as described in Steiger [49]. Z_{obs} larger than 1.96 are statistically significant.

3. Results

3.1. QEEG Characteristics in Patients versus Controls. Figure 2 presents the power density values where patient data are expressed as a percentage above or below control data. Patients showed greater power in the delta and theta ranges compared to controls (Figure 2), with significant increases between 1 and 9 Hz in the lesioned hemisphere and between 2 and 7 Hz in the nonlesioned hemisphere. At the same time, power in the higher frequency bands (18 to 20 Hz) was significantly decreased in the lesioned hemisphere. When correcting for multiple comparisons, this pattern remains the same whereby the cutoff for significance is a t value of 2.45, with the exception of increases at 1 and 9 Hz in the lesioned hemisphere.

Topographic maps were calculated for patients with either left or right side stroke versus controls (Figure 3) by plotting the statistical difference between groups in the EEG power density for all electrodes (P value). Visual inspection shows a wide distribution of increased lower frequencies in both patients groups in comparison to controls. Left-lesioned patients show significantly greater frontal, central, parietal, and occipital slowing within the alpha and theta bands than controls. The right hemispheric group showed predominately frontal and parietal slowing in the delta band, as well as global slowing in the theta band, and increased alpha in frontal, parietal, and occipital regions compared to controls.

3.2. Effects of Motor Task on EEG and KSS. Reaction times in controls were significantly faster with a mean of 433 ms

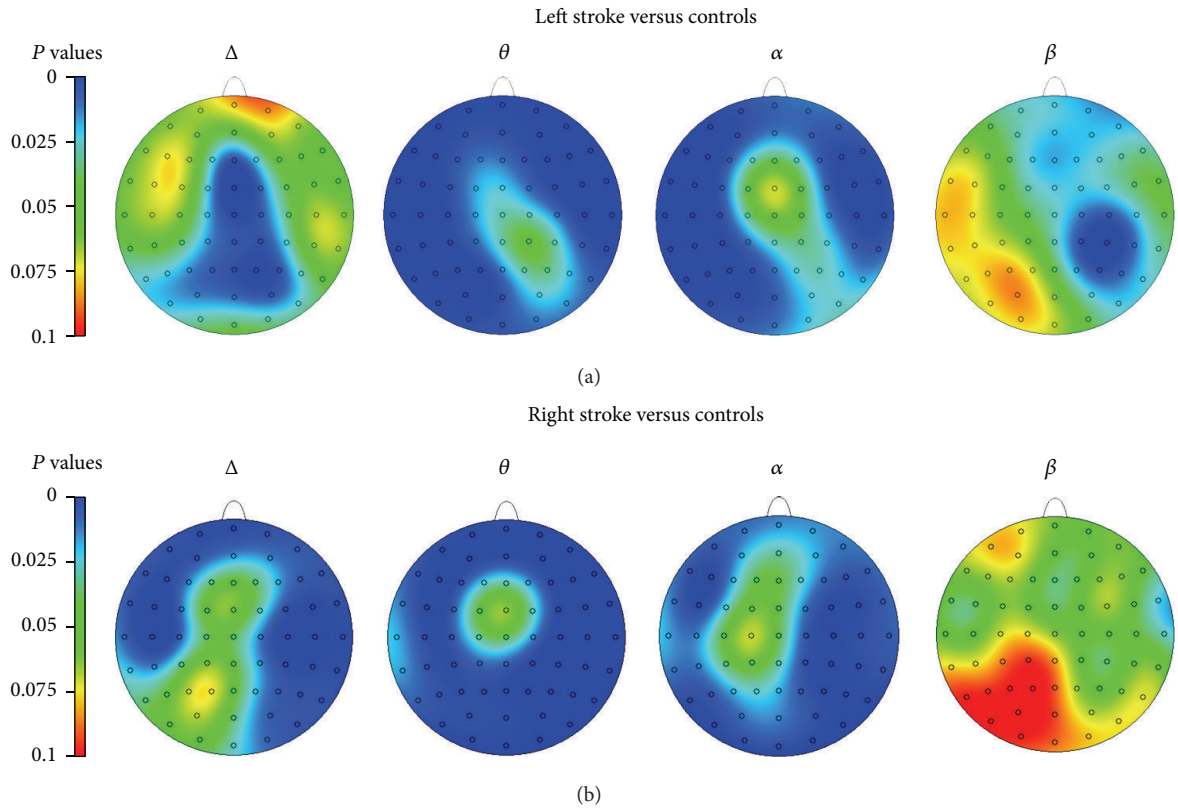

Figure 3: Topographical mapping of group differences in the EEG: level of significance for t-tests between (a) left ($n = 14$) and (b) right ($n = 18$) side stroke compared to controls is presented. When correcting for multiple comparisons of 64 electrodes, alpha level is $P = 0.0008$. This is indicated approximately by the grey line on the axes.

(SD = 67.70, range = 326–601; $z = -3.24$, $P < .001$) compared to 583 ms (SD = 239, range = 291–1664) in patients. The number of correct responses was significantly lower in patients (97.46%; SD = 5.17, range = 70–100) than controls (99.40%; SD = 0.72, range = 97.4–100; $z = -3.20$, $P < .001$).

KSS scores are presented in Figure 4. Most participants scored ≤3, and the distributions for patients and controls do not indicate substantial differences. This is supported by the lack of significant group effect ($F_{1,50} = 0.80$, $P = .37$). A significant main effect task ($F_{1,50} = 49.44$, $P \leq .001$) indicated that the subjectively perceived sleepiness was higher after completion of the task in all participants. Further inspection of KSS scores revealed a significant increase from 3.59 (±2.20) at pretask to 4.97 (±2.02) at posttask for patients ($t = -4.63$, $P \leq .001$) and from 2.95 (±1.64) at pretask to 4.65 (±2.13) at posttask for controls ($t = -6.03$, $P \leq .001$). The group differences at pre- and at post- were not significant.

Within-group task effects were computed separately for frontal, central, parietal, and occipital regions for each frequency band for lesioned and nonlesioned hemispheres in patients and controls (Table 2). Significant posttask increases in delta were revealed for patients in the frontal areas of the lesioned hemisphere. Increased theta was present in the lesioned hemisphere in both patients and controls. In patients, the nonlesioned hemisphere showed significantly increased theta only in the central region. For both groups, alpha power increased significantly with the task in all regions except for the parietal region in controls. In both groups, a significant posttask increase in alpha power was found across all regions apart from the parietal region of controls. Significant posttask increases within the beta band were observed for central and parietal regions in both patients and controls. In addition, controls did show an increase in frontal beta power at posttask. However, there were no changes in the beta band for frontal or occipital regions in patients. When correcting for multiple comparisons, the pattern remains the same when the alpha level is set to $P \leq .0.001$ with the exception of changes from pre- to posttask in the parietal and occipital regions of controls.

The relative change from pre- to posttask in the EEG for all brain regions (frontal, central, parietal, and occipital) between lesioned and nonlesioned hemisphere within patients and controls was compared for each frequency band. A significant group difference was only revealed for alpha in the occipital area ($F_{2,81} = 2.37$; $P < .05$). Further analysis showed less occipital alpha in the lesioned hemisphere compared to controls ($t_{29} = 1.87$; $P < .05$). For the nonlesioned hemisphere, this effect showed a similar trend ($t_{50} = 1.56$; $P = .06$).

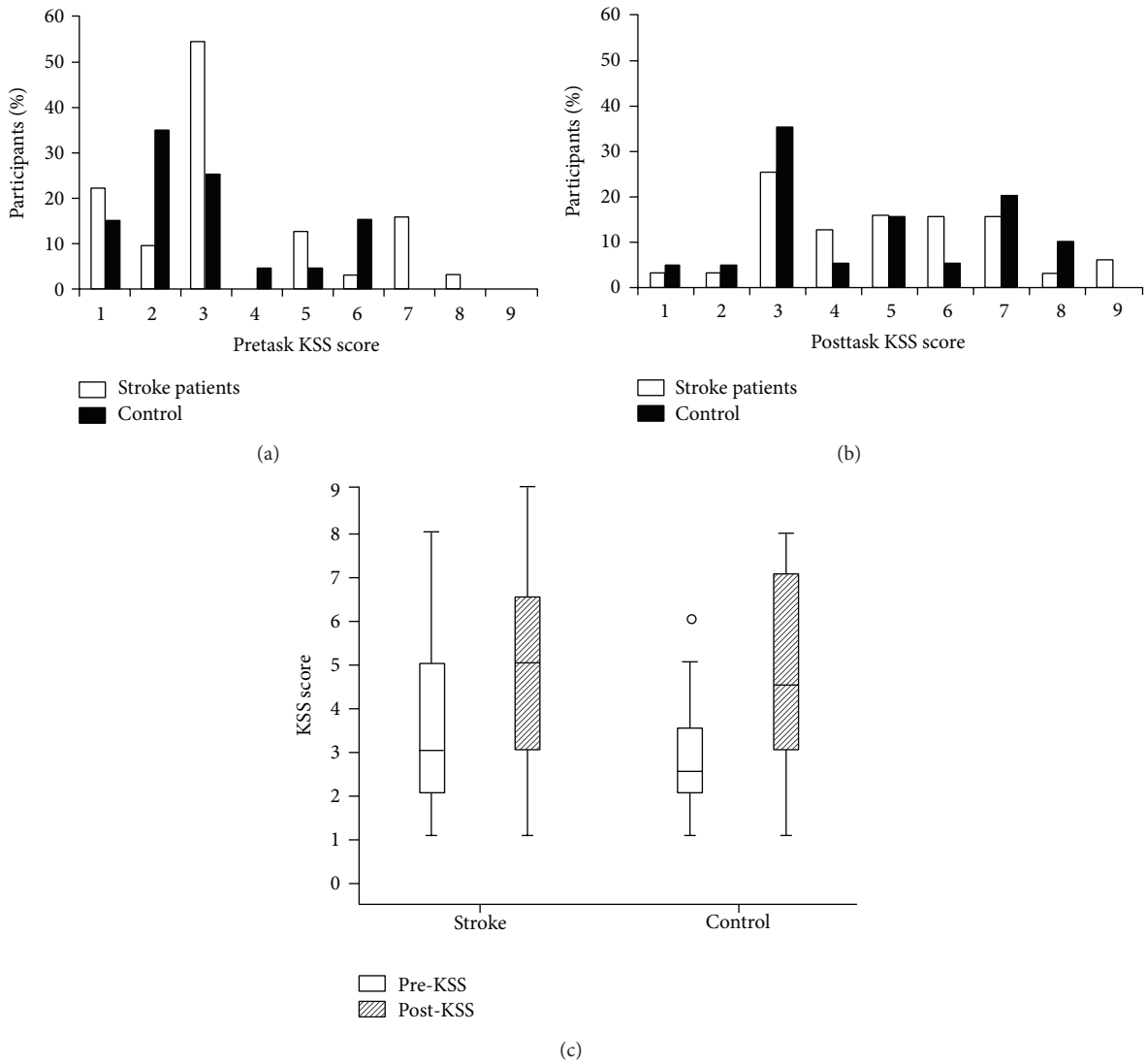

Figure 4: Changes in sleepiness ratings: (a) distribution of KSS scores pre-; (b) posttask; and (c) box plot displaying median KSS scores centrally in the box. Top and bottom values of the box represent the upper and lower interquartile range (H-spread) containing 50% of cases. The whiskers represent the highest and lowest scores which lie within 1.5 times the H-spread. Values >1.5 times the H-spread are outliers, represented by circles.

4. Associations

Correlations were computed for EEG power in each frequency band and the KSS. These correlations are listed for pre- and posttask in Tables 3(a) and 3(b).

At pretask, a significant association between increased KSS and increase central beta and occipital alpha was found for the lesioned hemisphere. For the nonlesioned hemisphere, higher pretask KSS was associated with greater central and parietal beta. In contrast, controls showed a significant association between higher KSS and increased global theta power as well as increased central alpha and higher KSS at pretask.

At posttask (Table 3(b), a relationship between occipital alpha and increased KSS was found for the lesioned he) misphere. In controls, increased posttask KSS was associated with increased theta in all derivations except occipital and increased alpha in the central and parietal areas. After correcting for multiple comparisons, the increase in occipital alpha for pretask patients remained significant as did the frontal and central theta in controls.

Post hoc analysis using Fisher's z transformation revealed that the only difference between controls' and patients' correlation coefficients that approached statistical significance was that for the theta band (Z_{obs} ranged between 1.31 and 1.71).

5. Discussion

The present study used EEG recordings to examine whether patients in the chronic state show alterations in their wake EEG and to investigate how these changes are related to perceived sleepiness. We further sought to determine whether

Table 2: Pre- to Posttask change in EEG power (t values): negative values indicate an increase in EEG power. Significant changes are identified as * ≤0.05, ** ≤0.001, and *** ≤0.0001.

	Delta	Theta	Alpha	Beta
Lesioned hemisphere				
Frontal	**−2.84****	**−3.42****	**−3.60*****	−1.86
Central	−0.73	**−2.73****	**−3.54****	**−3.69****
Parietal	−0.40	−1.58	**−2.50****	**−4.39*****
Occipital	−0.93	**−2.70****	**−2.99****	−0.41
Nonlesioned hemisphere				
Frontal	−0.57	−1.91	**−3.15****	−1.42
Central	−0.64	**−2.34***	**−5.38*****	**−3.68*****
Parietal	−1.62	−1.28	**−3.57****	**−4.72*****
Occipital	−1.60	−1.82	**−3.38****	−0.61
Controls				
Frontal	−0.70	**−4.06*****	**−4.32*****	**−4.96*****
Central	0.79	1.79	**−3.38****	**−4.63*****
Parietal	−0.32	**−2.11***	−1.90	**−2.72****
Occipital	−1.42	**−2.31***	**−3.67****	−1.01

Table 3: Correlations between KSS and EEG power density at pre- (a) and posttask (b): Pearson's r coefficient is presented. Significant correlations are identified as * ≤0.05, ** ≤0.001.

(a)

Pretask	Delta	Theta	Alpha	Beta
Lesioned hemisphere				
Frontal	0.04	0.12	0.20	0.24
Central	0.10	0.09	0.15	**0.31***
Parietal	0.11	−0.03	0.13	0.18
Occipital	0.15	0.07	**0.39****	0.16
Nonlesioned hemisphere				
Frontal	0.07	0.02	0.18	0.16
Central	0.07	0.14	0.24	**0.31***
Parietal	−0.02	0.06	0.15	**0.35***
Occipital	0.07	0.06	0.24	0.19
Control				
Frontal	0.23	**0.51****	0.31	0.04
Central	0.28	**0.56****	**0.44***	0.33
Parietal	0.34	**0.43***	0.24	0.19
Occipital	0.14	**0.44***	0.14	0.26

(b)

Posttask	Delta	Theta	Alpha	Beta
Lesioned hemisphere				
Frontal	0.20	0.18	0.30	0.05
Central	0.15	0.04	0.19	0.13
Parietal	0.05	−0.14	0.05	−0.05
Occipital	0.17	0.10	**0.36***	0.10
Nonlesioned hemisphere				
Frontal	0.13	0.06	0.21	−0.12
Central	0.26	0.18	**0.34***	0.09
Parietal	0.09	0.16	**0.31***	0.06
Occipital	0.17	0.20	0.32	0.13
Control				
Frontal	0.35	**0.39***	0.24	−0.03
Central	0.05	**0.37***	**0.48***	0.41
Parietal	0.25	**0.41***	**0.38***	0.33
Occipital	−0.11	0.27	0.09	0.19

motor cognitive demand would modulate the wake EEG in patients and controls. Overall, the results confirm our initial hypothesis that the prevalence of lower frequencies in the wake EEG, characteristic of the acute and subacute phase of stroke, is sustained in the chronic phase. However, in contrast to our expectations, this slowing of the EEG was not associated with an increase in perceived sleepiness in patients. In other words, the EEG characteristics, commonly accepted as biomarkers for sleepiness in healthy persons, are present in the wake EEG of patients with chronic stroke but do not seem to be associated with greater perceived sleepiness.

To the best of our knowledge, this is the first study using a qEEG-based approach to examine sleepiness in a chronic stroke population with sustained motor deficits. The various findings and their implications are discussed below.

5.1. Wake EEG Characteristics in Patients. Compared to controls, an increase in slow (≤9 Hz) frequencies was observed in both hemispheres. This slowing covered large areas of the cortex including frontal, parietal, and occipital areas as indicated by the topographical maps. The right stroke group showed more delta, particularly in frontal and central regions. These findings are in line with reports of increased global delta and theta during the acute phase of stroke [36, 38, 39]. The only study which examined qEEG in chronic stroke patients beyond one year used a single electrode in the frontal area and showed significantly more delta in patients [50]. The present findings therefore expand existing knowledge on the characteristics of the wake EEG in the chronic state. The data suggests that changes in EEG frequency, in particular the lower frequency bands, are sustained in the chronic phase of stroke and that these changes affect both the lesioned and the nonlesioned hemispheres. Interestingly, significant differences between the hemispheres were observed for frequencies >11 Hz, with greater beta power over the nonlesioned hemisphere, which may reflect a compensatory mechanism. No hemispheric differences were found for controls. In addition to the increased prevalence of low frequencies, earlier stages of recovery are marked by hemispheric dissymmetry [38, 51–53]. The present findings therefore suggest that the wake EEG in the chronic state maintains some key characteristics of the acute phase, namely, a greater prevalence of lower frequencies and a hemispheric dissymmetry in the beta range.

5.2. Effects of the Motor Task. Both patients and controls reported posttask increases in the KSS, suggesting greater sleepiness after the task. Posttask changes were also observed in the EEG, with both groups showing predominantly increased alpha and theta. Theta increases were consistent between the lesioned hemisphere and controls in frontal, central, and occipital regions. In the nonlesioned hemisphere, only the central area reached significance for increased theta. Critically, patients also showed increased frontal delta in the lesioned hemisphere which was not observed in the nonelesioned hemisphere or for controls. In other studies with healthy participants, posttask increases in the alpha range are indicative of mild subjective sleepiness, whereas increased delta activity is suggestive of more severe sleepiness [54, 55].

With regard to between-group effects, there was significantly less posttask change in occipital alpha in the lesioned hemisphere compared to controls and the nonlesioned hemisphere, while controls and the nonlesioned hemisphere did not differ. In this sense, the nonlesioned hemisphere "responded" to the task in a similar fashion as controls, while the lesioned hemisphere responded differently. This suggests that the hemispheric dissymmetry might not just be a physiological epiphenomenon but a characteristic that is functionally important for cognition and behaviour.

In addition to changes in the lower frequency bands, we further observed a posttask increase in beta in patients, in both hemispheres, and controls. Notably, this increase in higher frequencies occurred at the same time as an increase in lower frequencies, an effect also described in studies requiring sustained mental effort in control populations [56, 57]. This effect most likely reflects that the compensatory effort participants have to make in the face of declining vigilance as the time-on-task increases [56]. However, this theory has not been tested directly in chronic stroke patients.

5.3. Associations. The present study has found that subjective sleepiness ratings strongly correlated with increased pre- and posttask theta and alpha in controls, corroborating previous work in this area [33–35]. The finding is in line with the generally accepted assumption that the EEG-derived neurophysiological markers of sleepiness are directly related to the subjective perception of sleepiness and indeed reflect greater sleep propensity [33]. In patients, the relationship between subjective sleepiness and EEG indices was much less prominent, with only near significant correlation coefficients within the theta band. This dissociation between subjective and objective sleepiness markers is an interesting finding and clearly requires further investigation. One possible explanation is that patients habituate to their chronic sleepiness over time and therefore fail to perceive or report it. In this context it is interesting to note that other studies have found poor consistency between self-reported sleepiness and other indicators of sleepiness in patients, including observable report, actigraphy, and indeed the MSLT. Moreover, Sforza et al. [58] found no correlation between EEG and self-reports in patients with sleep disorders and concluded that the wake EEG is not sensitive to sleepiness in this population. The same argument may be put forward for the present study. However, our own observations during the experiment indicated that patients were indeed rather sleepy. This was shown in patients' behavioural characteristics of sleepiness including yawning, eyes closed, and a nodding head, while the electrodes were attached. The subjective sleepiness ratings therefore stand in contrast to the behavioural signs of sleepiness we observed. We therefore conclude that it is likely that patients have greater difficulty with the perception of their sleepiness, a hypothesis which could be explored using the MSLT. In addition, a larger sample size would build on the results from this study.

Increased beta weakly correlated with higher KSS in patients at pretask only and this effect was not observed in controls. This further provides more direct support to the compensation theory as discussed above. We hypothesise that the increased beta is indicative of the allocation of cognitive and behavioural resources, necessary to compensate for the limited attentional capacity [10]. This may signify a sustained compensatory beta enhancement that is necessary for patients to function in everyday life. At posttask, this effect disappears and may reflect an exhaustion of maximum attention capacity.

5.4. Limitations and Further Theoretical Considerations. Even though the results show significantly more slowing of the EEG in patients compared to controls, which is similar to that shown in sleep deprived persons, the cause of sleepiness cannot be identified. It may be the result of several factors including disruption to alertness mechanisms as direct result of lesion location [16], poor sleep [21], low mood [17], and increased effort required in movement and cognition after stroke [22]. It is likely that sleepiness may be the combined effect of several factors. Regardless of cause, the results show that patients are poor at recognising alertness state even though there is clear evidence of EEG slowing in both hemispheres, similar to that seen after sleep deprivation.

The participant sample has some points for consideration. Due to the sample size, the statistical power is small and therefore more studies are necessary to further explore measuring sleepiness in stroke populations. The sample included participants taking medication that may affect the EEG including antiepileptics [59] and antidepressants [60, 61]. Although there are other factors contributing to increased sleepiness as described in the introduction, we cannot decipher the degree to which these factors interact with the EEG and perception of sleepiness. However, had medication significantly affected the patients' EEG, we would expect the effect to be observed in both hemispheres. Furthermore, some antidepressants may even increase vigilance [61]. Overall, we aimed to capture a representative sample of stroke patients which would typically include those who engage in behaviour that can contribute to changes in physiological arousal such as medication usage but are not directly related to their stroke per se. We have shown that regardless of cause of sleepiness, the observed EEG slowing is potentially problematic in patient prognoses after stroke and requires attention.

6. Conclusion

The present study shows long-term changes of the wake EEG in patients with chronic hemiparesis after stroke. The data suggests a general slowing of the EEG that affects the lesioned and nonlesioned hemisphere. This slowing is not associated with subjective sleepiness and this has implications for the recognition and treatment of an aspect of stroke that impacts rehabilitation and safety. Investigating the causes of this dissociation will add to a better understanding of the long-term consequences of stroke and eventually help to improve stroke care.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

The Efficacy of Balance Training with Video Game-Based Therapy in Subacute Stroke Patients: A Randomized Controlled Trial

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The video game-based therapy emerged as a potential valid tool in improving balance in several neurological conditions with controversial results, whereas little information is available regarding the use of this therapy in subacute stroke patients. The aim of this study was to investigate the efficacy of balance training using video game-based intervention on functional balance and disability in individuals with hemiparesis due to stroke in subacute phase. Fifty adult stroke patients participated to the study: 25 subjects were randomly assigned to balance training with Wii Fit, and the other 25 subjects were assigned to usual balance therapy. Both groups were also treated with conventional physical therapy (40 min 2 times/day). The main outcome was functional balance (Berg Balance Scale-BBS), and secondary outcomes were disability (Barthel Index-BI), walking ability (Functional Ambulation Category), and walking speed (10-meters walking test). Wii Fit training was more effective than usual balance therapy in improving balance (BBS: 53 versus 48, $P = 0.004$) and independency in activity of daily living (BI: 98 versus 93, $P = 0.021$). A balance training performed with a Wii Fit as an add on to the conventional therapy was found to be more effective than conventional therapy alone in improving balance and reducing disability in patients with subacute stroke.

1. Introduction

In recent years, the video game-based therapy with commercial consoles was commonly adopted in both research and clinical settings [1]. Video games were originally designed for recreation, but recently some interactive video games have been specifically designed for rehabilitation [2]. Video game-based therapy and virtual reality [3], despite their intrinsic differences [4], provide the subject with multisensory feedback that requires different levels of action from the participant [1]. Although there is a lack of information regarding the efficacy of video game-based therapy and virtual reality training in rehabilitation, the high diffusion and the low cost of the commercial consoles are the main reasons for the increased attention reserved to their use in clinical and research settings [5]. Theoretically, the virtual reality and video game-based therapy offer the advantage of training the patients in some goal-oriented tasks that can be repeated several times [6] in the context of an enriched environment that gives the possibility of solving both cognitive and motor tasks and of learning new skills [7]. Moreover, the difficulties of the tasks of video games and virtual reality can be controlled and modulated rendering these tools [8] usable in clinical and home settings [2]. Benefits from video game-based therapy were initially demonstrated for upper-limb recovery [9], but, at present, the results on balance and mobility are inconclusive [1, 10]. In particular, little evidence is available in patients with residual disability and balance

disturbances after the subacute phase of stroke [11]. In these patients that are seen and treated after the period of maximal functional recovery from a stroke, the presence of a balance disturbance might represent a relevant limit to a further disability recovery.

The aim of this study was to investigate the effect of a video game-based rehabilitative intervention on balance on the functional recovery of patients with subacute stroke.

We hypothesized that, in patients with mild-to-moderate stroke severity, video game- based training for balance could be superior to common rehabilitative interventions targeted at balance and that this could be associated with better relevant outcomes such as general disability, walking, and mobility.

2. Material and Methods

2.1. Participants. We considered for including in our study all the consecutive patients with recent stroke who were admitted to our rehabilitation unit during their first three weeks of hospitalization from April 2011 to October 2013. Inclusion criteria were the following: hemiparesis in the subacute phase (<3 months from onset, see Table 1) with moderate gait deficits (FAC ≥ 2) [12] caused by a first-ever stroke and age between 18 and 85 years. Exclusion criteria were the presence of motor or cognitive sequelae of prior cerebrovascular accidents, other chronic disabling pathologies, orthopaedic injuries that could impair locomotion, spasticity that limited lower extremity range of motion to less than 80%, sacral skin lesions, Mini-Mental State Examination (MMSE) score < 24, [13] and hemispatial neglect, attention or memory deficit as evaluated by a neurophysiologist. At enrolment, patients were randomized and then evaluated. A second evaluation occurred after 1 month at the end of rehabilitative treatment, and a third evaluation occurred at one month after the end of rehabilitation.

Patients enrolled in the Wii group performed 12 sessions of 20 minutes each of balance training performed with Wii Fit, 3 times a week for four weeks, in add-on to a standard physiotherapy. During the intervention, three games were carried out in order to train balance, coordination, and endurance under the supervision of a physiotherapist: hula hoop, bubble blower, and sky slalom [2, 8, 14]. Patients enrolled in the control group added to standard physiotherapy 20 minutes of balance therapy 3 times/week for 4 weeks. In light of the patient's ability, the balance exercises were focused on trunk stabilization, weight transfer to the paretic leg, and exercise with Freeman board for balance and proprioception. The rehabilitative protocol for both the Wii and the control groups was in add-on to the standard physiotherapy focused on the facilitation of movements on the paretic side and upper-limb exercises and improving balance, standing, and transferring. The protocol was approved by the Ethics Committee at Santa Lucia Foundation, and all participants provided written informed consent. The primary outcome measure of the study was balance measured by Berg Balance Scale [15], whereas the remaining outcomes included assessments of walking ability, evaluated by 10 m walk test at a self-selected speed (10MWT) [16] and Functional Ambulatory Category (FAC) [12], and disability measured by Barthel Index (BI) [17]. A physician, blinded to the treatment allocation, assessed patients immediately after random allocation, after 4 weeks of the intervention, and at one-month follow-up. The randomization list was generated by a personal computer from a physician not involved in recruitment.

2.2. Statistical Analyses. Scores of clinical scales were summarized using nonparametric statistics, reporting lower and upper quartiles, median, and the extreme values within 1.5 times the interquartile range from quartiles. These ordinal data have been compared between the two groups using Mann-Whitney U test at baseline (T0) for verifying the homogeneity of the two groups, at the end of treatment (T1) for assessing the potential differences in the improvements, and at follow-up for evaluating if these changes were maintained (T2). Wilcoxon signed ranks test was used for within-subject comparisons for both groups along time (T0 and T1).

Continuous measures were summarized and analyzed using parametric statistics. Mean and standard deviation were computed for each continuous variable. Baseline comparisons of age and time from stroke event were performed by an unpaired t-test. Repeated measure analysis of variance was used to compare the time spent for completing the ten-meter walking test in the two groups using group as the between-subject factor and time as the within-subject factor. For repeated measure analyses, only data at T0 and T1 were taken into account for avoiding the reduction of analyzed data due to the subjects not reevaluated at follow-up.

Pearson's correlation coefficient was computed at T1 between the percentage improvements in scores of BBS, FAC, and 10MWT. The improvements of BBS and FAC were computed as percentages of actual improvement with respect to the maximum potential improvement, {[(discharge score − initial score)/(maximum score − initial score)] × 100} [18].

3. Results

Fifty patients were enrolled in the study; three patients in the control group dropped the study after x, y, z months from enrollment (Figure 1). The two groups were homogenous at baseline for age, distribution of right/left hemiparesis, time from stroke, and level of independency in activities of daily living as assessed by Barthel Index (Table 1).

Figure 2 shows the scores of BI, FAC, and BBS at the three study planned visits. The Wilcoxon signed ranks tests showed an improvement between T0 and T1 for all the three scales scores in both groups ($P < 0.001$ for all of them). Between groups, at enrollment, there were no significant differences in the scores of all the scales administered ($P = 0.330$, 0.148, and 0.366 for BBS, BI, and FAC, resp.). At the end of the treatment, all the scale scores were significantly higher in Wii group, but FAC score was close to the borderline probability value ($P = 0.004$, 0.021, and 0.053, resp.).

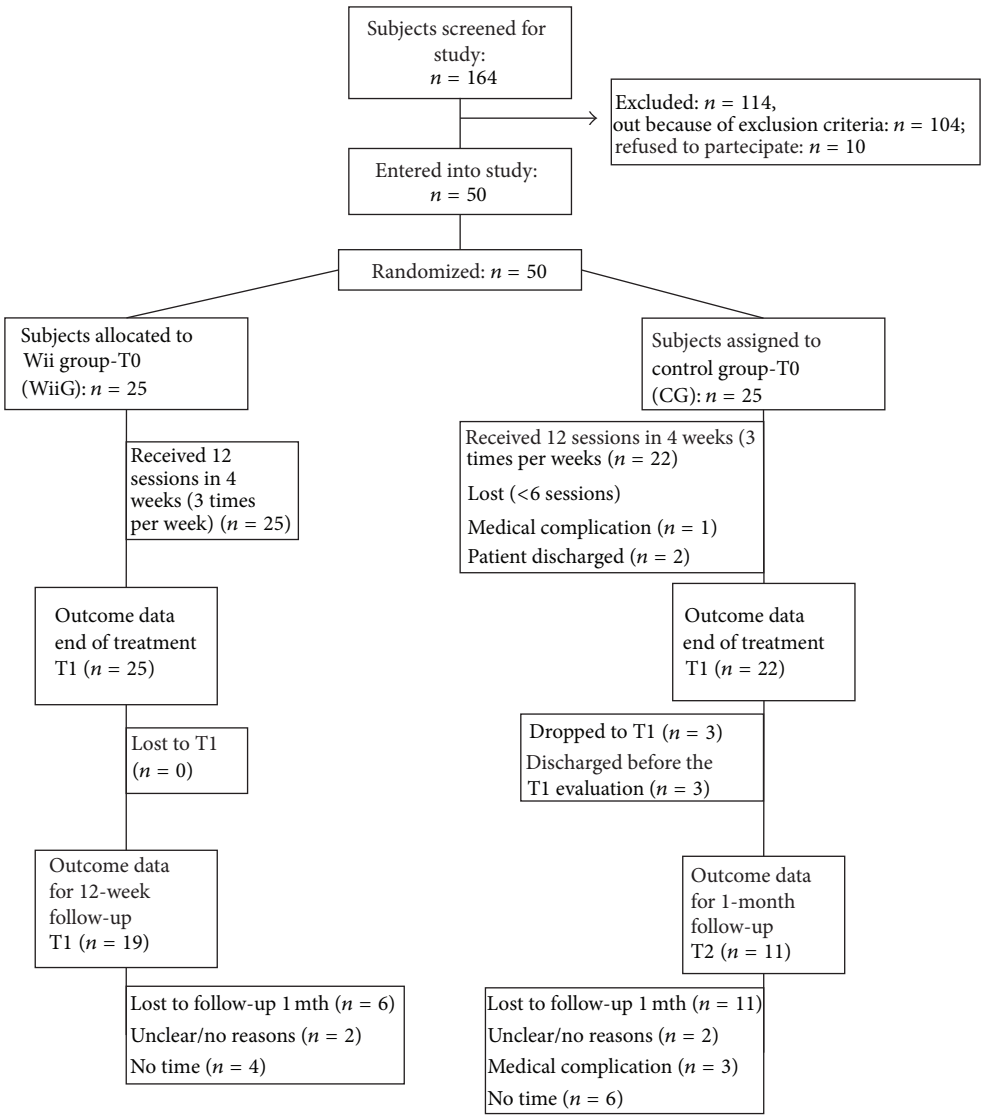

Figure 1: Study flowchart.

Table 1: Demographic and clinical characteristics of the enrolled patients. Mean ± standard deviations are reported for age and time from stroke event, median and interquartile range are reported for Barthel Index, and between the squared brackets the ranges are reported. Statistical comparison for numerical continuous variables was carried out, the t-test and chi-squared test were used to compare frequencies of categorical variables, and the nonparametric Mann-Whitney U test was used to compare the Barthel Index scores.

Groups	Number of patients	Mean age [years] (range)	Time from stroke event [days] (range)	Right/left hemiparesis	Median Barthel Index at admission (interquartile range)
Wii group	25	58.36 ± 9.62 [47–74]	61.00 ± 36.47 [20–155]	11R/14L	87 (27) [37–100]
Control group	25	61.96 ± 10.31 [36–76]	41.65 ± 36.89 [6–124]	18R/7L	78 (32) [39–100]
Total	**50**	**60.16 ± 10.04 [36–76]**	**51.53 ± 37.57 [6–155]**	**29R/21L**	**80 (29) [37–100]**
P value	—	0.208	0.0773	0.239	0.148

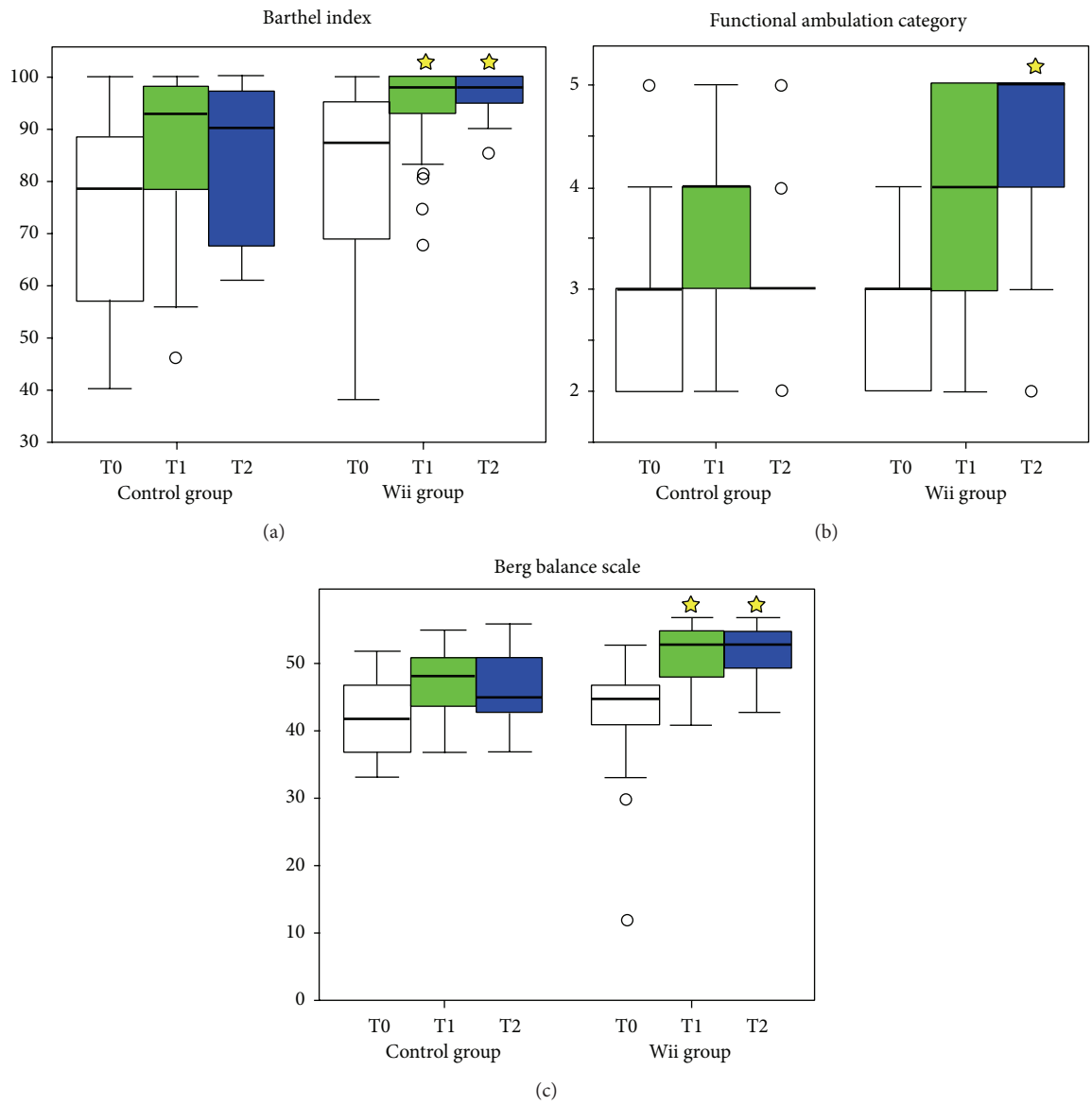

Figure 2: Box-plot of clinical scores at T0 (white), T1 (green), and T2 (blue): the boxes show the lower quartile, median (bold line), and upper quartile values, the whiskers represent the most extreme values within 1.5 times the interquartile range from the ends of the box, and the circles represent the outliers (data with values beyond the ends of the whiskers). Stars indicate the statistically significant differences of the Wii group in respect of the control group.

The difference was maintained (or even increased for FAC score) at follow-up visit three months after enrollment (P = 0.016, 0.025 and P = 0.004, resp.).

Analyzing the 10 MWT, the reduction of time spent to complete the test at T1 in respect of T0 was in mean 35% in the Wii group and 27% in the control group. A repeated measure analysis of variance performed on the time spent to complete this test has found a significant effect of time and hence rehabilitation, independently of which type (P < 0.001), but neither of group (P = 0.373) nor of the interaction between group and time (P = 0.099). At follow-up, the time needed for walking for 10 m was further reduced by about 6% in both groups.

At the end of treatment (T1), the improvement in the equilibrium (in terms of BBS) observed in the Wii group was significantly correlated with the improvement in the functional ambulation FAC (R = 0.696, P < 0.001) but not with the improvement in terms of BI score (R = 0.319, P = 0.121). On the contrary, balance improvement was almost completely independent of the improvement in the ten-meter walking test (R = 0.147, P = 0.484). Analogous analyses performed on the control group showed that

the improvement in the equilibrium was just partially correlated with that of the independent functional ambulation ($R = 0.379$, $P = 0.082$) and with the self-selected walking speed ($R = 0.421$, $P = 0.051$), but it was significantly correlated with that in BI score ($R = 0.452$, $P = 0.035$).

4. Discussion

Our results showed that a video game-based therapy performed using Wii Fit is effective in enhancing balance and independency in activity of daily living in patients affected by subacute stroke. Partial benefits were also observed in walking ability recovery at the follow-up. These results are in accordance with the Cochrane titled virtual reality for stroke rehabilitation reporting for 19 studies, involving 565 patients, significant increments in outcomes related to activity of daily living, but not for gait speed [1]. However, in this Cochrane review [1], no definitive conclusions were carried out regarding balance because of the few studies focused on balance and the lack of studies on subacute phase of stroke. In our randomized controlled trial, we observed an improvement in balance. This improvement in the equilibrium was probably accompanied by progressive more independent walking at the end of treatment, as shown by correlation analyses. In the experimental group, the Wii training on postural balance probably also had positive effects on reducing the need for aids and/or supervision during walking for avoiding the risk of falling. However, these effects were not directly related to an increase of walking speed. In the control group, these correlations were not found statistically significant, but a trend was still evident, also for speed. It was probably due to the fact that the conventional rehabilitation training had more aspects directly focused on walking and less ones focused on equilibrium.

As recently demonstrated [11], active video games involve sensorial and cognitive systems like the selective attention system, visual short-term memory tasks capacity, and spatial, temporal attention for alert task-switching and multitasking. Moreover, active video games incorporate many characteristics of the learning and relearning processes including the ratio of massed versus distributed practice, personalized difficulty levels, and just-right increment steps during learning, fun, and engagement [11]. Also the different types of provided feedback lead to an augmentation and a strengthening of learning mechanisms: auditory feedback [19], visual feedback, scores, performances, and bandwidth feedbacks [19, 20]. Based on this principle, active video game and virtual reality systems are largely utilized in military and police training, flight training, and surgeon training [21]. Despite the fact that we did not focus our study on cognitive and sensorial improvements during video game-based therapy, it is conceivable that the motor control system could benefit from the multitasking training and augmented participation [22] and augmented intensity [23, 24] as specifically demonstrated in another study about balance training [25]. This is in line with the new concept of training patients in fostering learning to learn (or relearn) [26] and could have positively affected the independence in the activity of daily living in patients trained using video games. Their improvement in terms of BI score, in fact, was higher than that of control subjects, but, this improvement was found correlated with the improvement in BBS score only in the control group and not in the Wii group.

So, despite the limited evidence that the use of virtual reality and interactive video gaming may be beneficial in improving balance when compared with the same dose of conventional therapy, video game-based therapy could be used as a suitable add-on for increasing the time spent by patients involved in potential beneficial activities. Despite the fact that video game- based therapy was not developed to address rehabilitation issues, a lot of works and synergies troughs of the neurorehabilitation teams and users' experiences have been realized worldwide and shared with all the community [27]. Further studies have to address several issues, for example, if the improvement is due to the augmentation of repetition or of participation. Another important aspect that needs to be addressed is the evaluation of different cognitive processes enhanced and about different types of learning (i.e., procedural learning [28]) occurring during different types of cognitive tasks performed with video game exercises [29]. Researchers should aim to determine the impact of these variables in exploratory studies.

The main limits of our study were the following: the dropout rate at follow-up, the absence of specific evaluation for assessing potential improvement in cognitive capacities, and the use of Berg Balance Scale for assessing equilibrium that, despite being used worldwide, is less sensitive and objective than quantitative measures of balance such as stabilometry.

5. Conclusions

In conclusion, balance training performed with video game-based therapy performed with Wii Fit and in add-on to the conventional therapy was found to be effective for improving balance and for reducing disability in patients affected by subacute stroke.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Kinematic Analysis of the Upper Limb Motor Strategies in Stroke Patients as a Tool towards Advanced Neurorehabilitation Strategies: A Preliminary Study

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Advanced rehabilitation strategies of the upper limb in stroke patients focus on the recovery of the most important daily activities. In this study we analyzed quantitatively and qualitatively the motor strategies employed by stroke patients when reaching and drinking from a glass. We enrolled 6 hemiparetic poststroke patients and 6 healthy subjects. Motion analysis of the task proposed (reaching for the glass, bringing it to the mouth, and putting it back on the table) with the affected limb was performed. Clinical assessment using the Fugl-Meyer Assessment for Upper Extremity was also included. During the reaching for the glass the patients showed a reduced arm elongation and trunk axial rotation due to motor deficit. For this reason, as observed, they carried out compensatory strategies which included trunk forward displacement and head movements. These preliminary data should be considered to address rehabilitation treatment. Moreover, the kinematic analysis protocol developed might represent an outcome measure of upper limb rehabilitation processes.

1. Introduction

Stroke is the third leading cause of death in Western countries and contributes significantly to the incidence of long-term physical disabilities and handicaps [1]. Up to approximately 85% of stroke survivors experience hemiparesis, resulting in an impairment of an upper limb (UL) immediately after the stroke. Furthermore between 55% and 75% of survivors continue to experience limitations in UL function, which are associated with diminished health-related quality of life, even after 3 to 6 months [2–11]. A good sensorimotor recovery in stroke patients is considered as the capacity of the patient to perform movements in the same way as age-matched nondisabled subjects.

Therefore a good sensorimotor recovery means not only being able to do the movement (quantitative aspect of movement) but also (and more important) knowing how the movement is done (qualitative aspect of movement).

In UL a good sensorimotor recovery may be slower or more complex than in lower limbs. One explanation for poor recovery of arm function may be the greater emphasis placed on retraining gait capability in the effort to mobilize the patient as quickly as possible and to minimize costly hospital stays [12]. Moreover UL movements are also far less stereotypical and more complex than lower limb (LL) movements, involving a wider amount of coordinated multijoint movements, including head, neck, trunk, and shoulder to manipulate objects in the environment.

Clinical outcome scales meant to measure improvement mainly focus on task accomplishment and are often not qualitatively sensitive enough to discriminate improvement in how the task is performed. Instrumental movement analysis can provide more specific information about qualitative movement components and strategies, but this requires special equipment and training and is most applicable in research setting. Kinematics describes movements of the

body through space and time, including linear and angular displacements, velocity, and acceleration, but without reference to the forces involved [13, 14]. Three-dimensional imaging techniques, including optoelectronic systems, can provide a quantitative assessment of movement, but protocols and models for UL analysis are not fully established [15–17].

The focus of stroke rehabilitation is to maximize functional motor ability, such as walking safely from one room to another, or turning a doorknob to open a door, in the limited time available for treatment.

Manual and UL tasks are also difficult to analyze: generally such tasks are not cyclic; they are characterized by a large number of degrees of freedom and, consequently, can be performed adopting different strategies or motor patterns. This accounts for the relatively small number of published studies on instrumented analysis of UL tasks [18], compared to the larger amount of studies on locomotor functions, universally known as Gait Analysis. Drinking from a glass is a very common and important daily life activity. This task is paradigmatic since it includes two relevant phases: a first open-chain movement (reaching for the glass) and a second movement (bringing the glass to the mouth) where a strict coordination among upper limb, trunk, and head movements is required, thus challenging the motor control system even in the presence of UL minimal disability. Interestingly the task of bringing a glass to the mouth in poststroke patients has been considered only in one previous paper reported by Murphy et al. [16]. In Murphy's study [16] patients with subacute and chronic stroke were considered (with a stroke latency from 6 to 64 months). It is known that a long latency from stroke increases the possibility to develop spasticity [19]: this might explain why three of Murphy's patients presented spasticity at the paretic upper limb. Actually, compensatory motor strategies employed by patients can be influenced by UL spasticity and can change over time, depending on when the stroke had actually occurred. Therefore, it is reasonable to expect that motor strategies of upper limb are different between subacute and chronic patients. Moreover, in Murphy's study compensatory movements of shoulder abduction and trunk forward displacement, but not of trunk axial rotation, were considered.

The aim of this study was to analyze, using motion analysis, the quantitative and qualitative UL motor strategies adopted by stroke patients, without spasticity, in reaching for a glass and bringing it to the mouth.

2. Materials and Methods

2.1. Sample. We enrolled 6 hemiparetic poststroke patients (mean age: 78 years; range: 64–84 years; 3 men, 3 women) admitted to our Inpatient Rehabilitation Department.

Inclusion criteria for stroke patients were a subacute status (from 1 month to 6 months after event) following a first unilateral cortical or subcortical stroke and ability to perform the task proposed (reaching for the glass, bringing it to the mouth, and putting it back on the table) with the affected limb.

Exclusion criteria were the presence of musculoskeletal or neurological problems that could affect the function of the arm (trauma, fracture, and peripheral neuropathies) and poststroke spasticity of the affected arm (Ashworth Scale Score ≥ 2).

Two of the 6 patients enrolled had suffered from hemorrhagic stroke, four from ischemic stroke; four had right hemiparesis and two left hemiparesis. The mean value of the Barthel Index was 50 and the mean value of the Fugl-Meyer Assessment for Upper Extremity was 44.

Six healthy subjects (mean age: 64.5 years; range: 52–74 years; 6 women) were used as a control group.

All participants gave written consent to participate in the study, which was approved by our Ethical Committee.

2.2. Clinical Evaluation. The UL motor function was clinically assessed with the Fugl-Meyer Assessment for Upper Extremity (FMA-UE, scale 0–66) [20, 21]. FMA is an efficient and reliable tool useful in monitoring the progress of patients and to analyze comparatively the effectiveness of different therapeutic interventions [22]. Stroke patients included in this study had a moderate arm impairment (FMA-UE scores between 34 and 57; mean: 44.2; SD: 7.7).

The disability was assessed using Barthel Index (BI). It provides a measure of ability, measuring what an individual "can do." The BI ranges from 0 (dependence) to 100 (independence). It is the most widely used measure to assess functional status, having great validity, reliability, and sensitivity. Our sample had a moderate disability (BI values between 34 and 58; mean: 49.5; SD: 9.3).

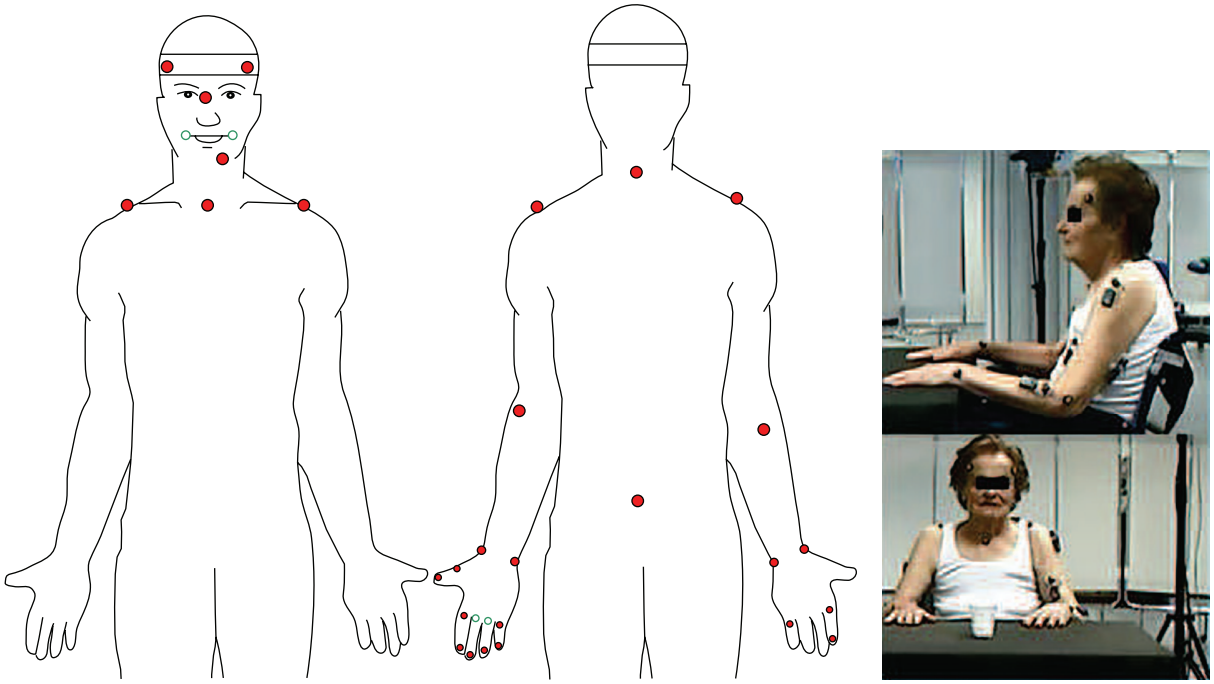
Clinical data of the stroke patients are provided in Table 1.

2.3. Motion Analysis and Motor Task Phases' Identification. The task performance was measured by a SMART motion capture optoelectronic system, able to automatically record 3D trajectories of passive markers by means of stereophotogrammetric methods (BTS S.p.A., Milano, Italy). The experimental protocol included 30 markers on the body (see Figure 1 for detailed listing of markers' positions). The markers had a diameter of 6 mm, except for those placed on the trunk which had a 10 mm diameter (Figure 1). The SMART optoelectronic system was equipped with 8 cameras, working in infrared range and equipped with CCD sensors and appropriate optical filters; whose sampling frequency was 60 Hz (low pass filtered with five point triangular smooth).

The analyzed drinking task required the subject to reach for the glass with his/her affected limb, for subjects belonging to the stoke group, or with the preferred limb, for the control group. The subject was initially seated, with both hands placed on the table and the glass placed at 400 mm from the edge of the table aligned with the subject sagittal plane. The onset of the task (T1) was marked by any motion of the subject body, in particular the hand displacement motion with trunk fixed or the trunk movement with hand still resting on the table. The reaching for the glass with the hand (T2) marked the end of reaching phase and the beginning of bringing-to-mouth phase. The contact of the glass with the lips with a proper glass inclination of approximately 45° (T3) marked the end of bringing-to-mouth and the beginning of drinking phase. The end of drinking (T4) was identified similarly to the previous event T3 and the repositioning of the glass on

Table 1: Clinical data of the sample.

Case	Gender	Age	Latency from stroke	Kind of stroke	Affected arm	Disability and Performance scales	
						Barthel Index (0–100)	Fugl-Meyer Scale (0–66)
Case CR	Male	76	3 months	Hemorrhagic	Right	52	46
Case LG	Male	83	6 months	Ischemic	Left	57	38
Case SF	Female	80	2 months	Ischemic	Right	58	42
Case SFl	Female	64	1 month	Ischemic	Right	56	53
Case CE	Female	81	3 months	Hemorrhagic	Left	34	48
Case SA	Male	84	5 months	Ischemic	Right	41	34



(a) (b)

Figure 1: Markers positioning on the subjects and figure of our patient inside the research setting.

the table (T5) (approximately in its initial position) concluded the task. Therefore, the identified task phases were reaching for the glass (RG, from T1 to T2), bringing the glass to the mouth (BGM, from T2 to T3), drinking from it (DG, from T3 to T4), and putting the glass back on the table (TBGT, from T4 to T5).

Figure 2 shows an example of stick diagrams defining the phases of the motor task, in particular the baseline (a), the reaching for the glass (b), the bringing the glass to the mouth (c), and the putting the glass back on the table (d).

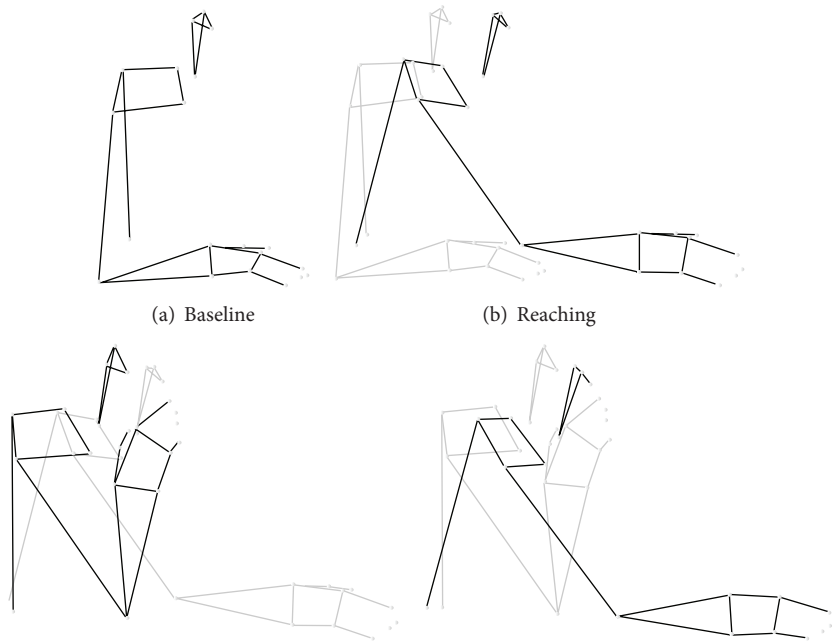
After the patient had practiced the task a few times (2-3 times), we registered three repetitions of the task that were then used for data analysis. Patients were instructed to perform the task at a comfortable self-paced speed after the examiner had announced, "you can start now."

2.4. Quantitative Indexes. The measured markers' trajectories allowed us to compute several kinematic variables, including anatomical landmarks displacements, joints' angles, and body segments' orientations. Those variables supported the computation of scalar indexes concerning phases durations, joint ROM, and relative contribution of specific anatomical subparts to the whole body movement strategy.

In the forward direction, given the forward displacements of the end-effector, the grasping hand, and the forward movement of the proximal points, such as C7 and the shoulder (i.e., the acromion), it is possible to compute specific contribution, expressed in percentage, of the total hand displacement while reaching:

(i) *arm elongation* (AE), relative contribution to reaching (%) as the difference between hand and shoulder forward displacements relative to hand forward displacement;

(ii) *trunk forward inclination* (TF), relative contribution to reaching (%) as the percentage ratio between C7 forward displacement and hand forward displacement;



(a) Baseline (b) Reaching

(c) Bringing to the mouth (d) Put back on the table

Figure 2: Motor task; (a) baseline; (b) reaching; (c) bringing to the mouth; (d) put back on the table.

(iii) *trunk axial rotation* (TA), relative contribution to reaching (%) as the difference between shoulder and C7 forward displacements relative to hand forward displacement.

It is worth noting that, in the implemented model, the sum of AE, TF, and TA accounts for 100% of contributions to hand forward displacement in reaching.

Moreover the range of motion (ROM) of the elbow during reaching for the glass was evaluated.

Another index consisted of the mouth forward displacement during specific phases, that is, the displacement of a marker positioned on the head close to the mouth. This parameter while being largely determined by trunk inclination may be influenced also by neck movements. Given the mouth position (MP) at T1, T2, and T3 events, the following indexes are identified:

(i) MD_{12} = MP (T2) – MP (T1), mouth displacement in mm during reaching;

(ii) MD_{23} = MP (T3) – MP (T2), mouth displacement in mm during bringing-to-mouth;

(iii) MD_{13} = MP (T3) – MP (T1), overall mouth displacement in mm during reaching and bringing to mouth.

Arm contribution was evaluated also in bringing the glass to the mouth and putting it back on the table phases.

Smoothness of movement was quantified by computing the number of movement units (NMUs) during reaching for the glass and bringing the glass to the mouth. The number of movement units (NMU) was defined as the number of hand velocity peaks occurring above a threshold speed of 50 mm/s in the two initial phases (reaching for the glass and bringing the glass to the mouth).

In the present study we have focused on the quantitative indexes of three phases involving upper limb displacements: reaching for the glass (RG), bringing the glass to the mouth (BGM), and putting the glass back on the table (TBGT).

2.5. Statistical Analysis. All statistical analyzes were performed using the STATSOFT (Tulsa, OK, USA) package. Due to the small sample size, nonparametric analyses were performed. We used the Mann-Whitney *U* test for the comparison between two groups (stroke group and control group). Regarding the quantitative motion analysis indexes, for statistical calculations, the mean value of 3 trials was used for each participant.

3. Results and Discussion

Table 1 shows the clinical data of stroke patients.

Figure 3 shows the longitudinal displacements during the task in a stroke patient Figure 3(a) and in a healthy subject Figure 3(b), respectively, of the glass (black line), hand (turquoise line), mouth (red line), shoulder (blue line), and C7 (green line). The dotted line represents the flexion/extension angular displacement of the elbow joint.

The colored panels have been used to highlight the movement phases, which are (i) reaching for the glass (red); (ii) bringing to the mouth (green); (iii) drinking (yellow); and (iv) putting the glass back on the table (grey).

It can be noticed that, in the shown example, the patient took about 7.5 seconds to complete the task, while the healthy subject needed less than 5 seconds.

In Table 2 the comparison between groups (stroke and control group) of the quantitative indexes relative to the

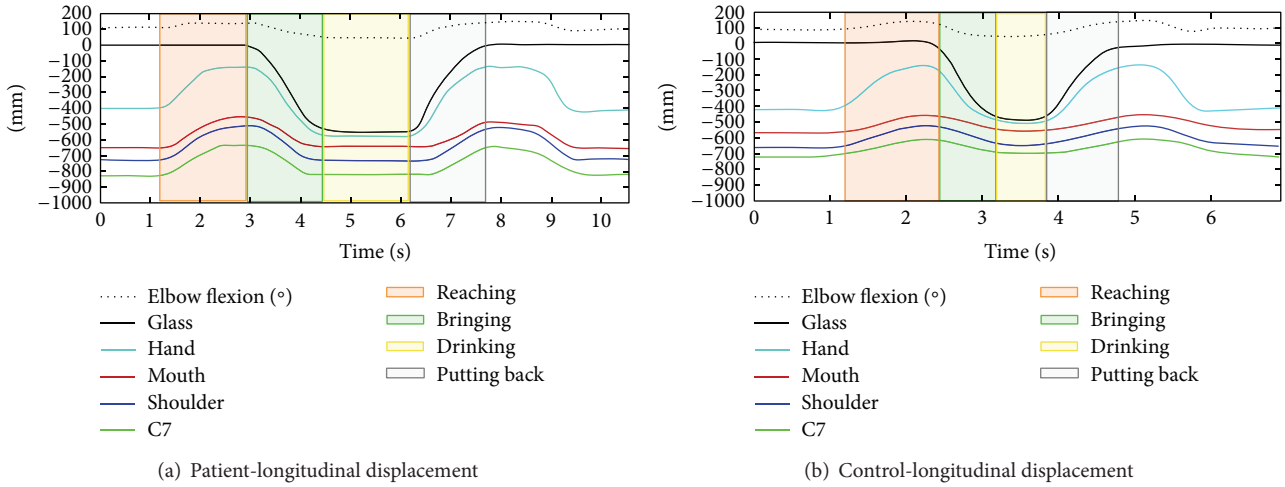


Figure 3: Longitudinal displacements during the whole task in a stroke patient (a) and in a healthy subject (b).

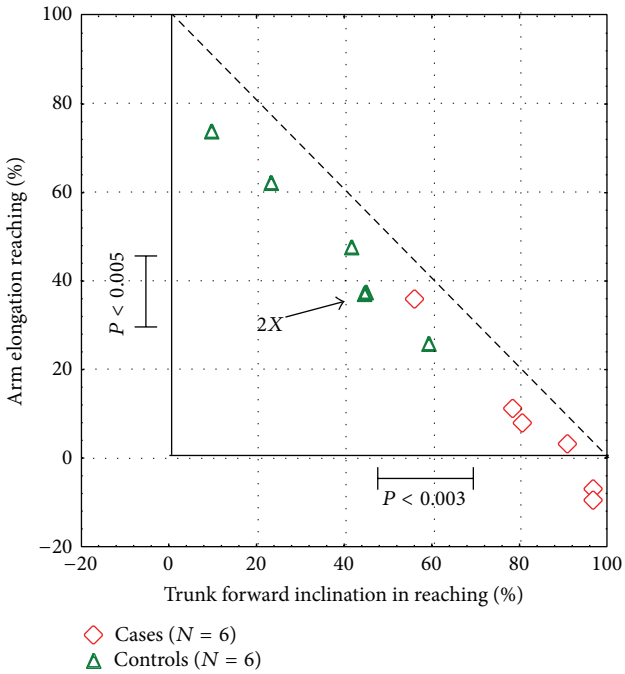


Figure 4: The contribution of the arm elongation and trunk forward inclination in the reaching phase in the two groups (stroke and control group).

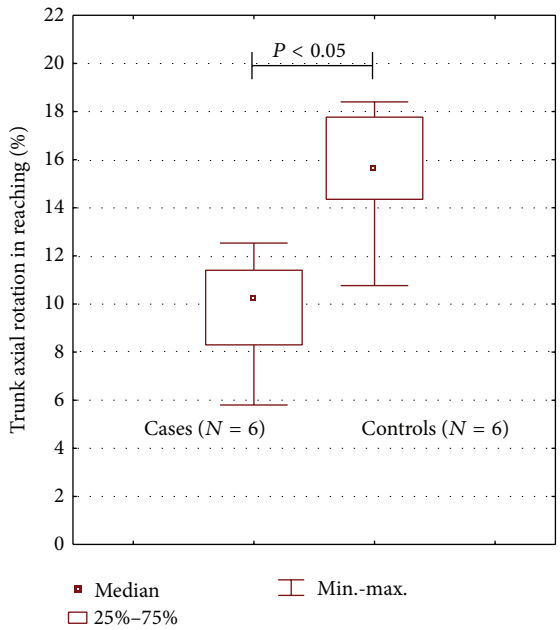


Figure 5: The comparison of the trunk axial rotation in the reaching phase in the two groups (stroke and control group).

phases of the task is reported. In the reaching phase, a significant reduction of the arm elongation ($P < 0.005$, Figure 4), the elbow ROM ($P < 0.003$), and the trunk axial rotation ($P < 0.003$, see Figure 5) was found in stroke patients compared to the control group. In the same phase, a significant increase of the duration ($P < 0.003$), the forward inclination of the trunk ($P < 0.003$, Figure 4), and the mouth forward displacement ($P < 0.003$) was found. A significant increase of duration was found also in the bringing and putting back phases (both $P < 0.003$) in patients in comparison with healthy subjects.

In the graph of Figure 6, the mouth displacement in the bringing phase is plotted versus the mouth displacement in the reaching phase in patients and healthy subjects. Moreover the stick diagrams at the baseline, ending of reaching, and ending of bringing-to-mouth phases are reported for one healthy subject and two representative stroke patients, showing the different motor strategies observed during the task. It can be noticed that, during the reaching phase, the healthy subject in Figure 6(a) showed a wide elongation of the arm with a minimal forward movement of the trunk associated also with an axial rotation of the trunk. Concerning mouth movement of the healthy subjects, we observed (see graph)

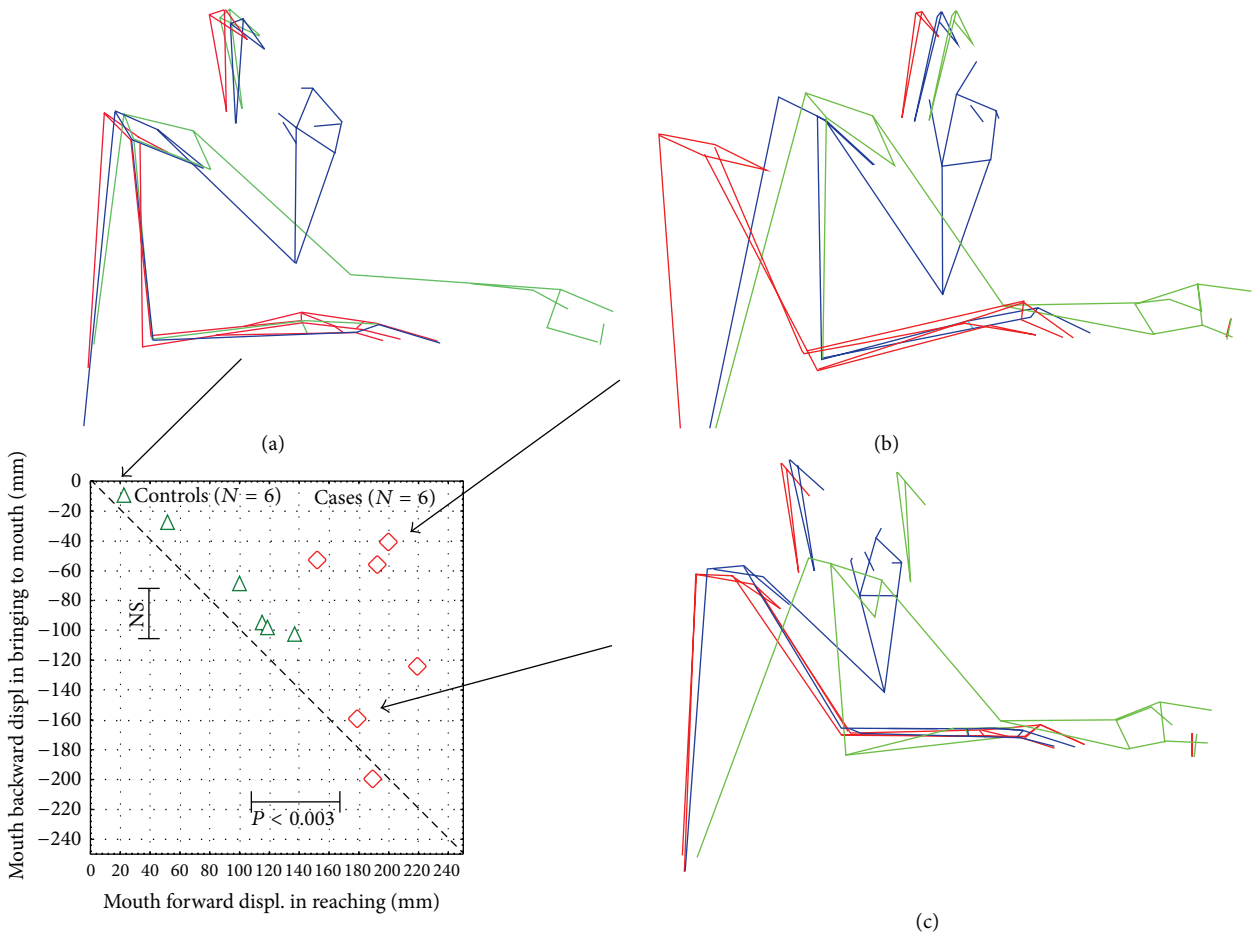


Figure 6: Head-trunk and arm motor strategy during the reaching for the glass and bringing it to the mouth in a healthy subject (a) and in 2 stroke patients ((b) and (c)). The graphic shows the mouth displacement in the bringing phase and the mouth displacement in the reaching phase in the sample.

that the forward displacement in reaching—when present—is comparable to the backward displacement in the bringing phase. On the contrary two different strategies were observed in the patients. The first strategy in Figure 6(b) consisted of an important increase in the forward displacement of the trunk and mouth in the reaching phase but with a reduced arm elongation and without a comparable backward displacement of the trunk and the mouth in the bringing-to-mouth phase. In this case, the patient brings the glass to the mouth remaining in a "forward displaced head and trunk posture." The second strategy in Figure 6(c), conversely, is characterized by an important increase in the forward displacement of the trunk and mouth in the reaching phase, with a reduced arm elongation, but with an equal backward displacement of the trunk and mouth in the bringing phase.

Figure 7 reports the overall mouth displacement during reaching and bringing phases in stroke patients and control group.

The NMU showed statistical differences between the two groups; it ranged from 2 to 3 in healthy participants and from 2 to 26 in stroke patients ($P < 0.0005$).

4. Conclusions

Advanced rehabilitation strategies of the UL in stroke patients should focus on the recovery of the most important daily activities. Usually, with the emphasis on task accomplishment, little attention is given to qualitative aspects of movement and it is hard to distinguish between "primary recovery" and "secondary compensatory strategies" at the level of the basic motor patterns employed. On the other hand, such distinction is valuable given that, while primary recovery could allow patients to perform several motor tasks, compensatory strategies may not generalize to a wide array of tasks. Therefore any method, like the one here proposed, capable of objectifying this distinction is of major importance in the validation of new rehabilitation approaches.

The clinicians should pay attention not only to the ability of the patient to perform a task (which is often possible only using compensatory strategies) but also to how the patient performs the task. In this study we analyzed quantitatively and qualitatively the motor strategies employed by stroke patients when reaching and drinking from a glass.

Table 2: Quantitative Indexes related to the phases of the task: comparison between patients' and controls' group.

Phase	Index	Patients' median	Patients' range	Controls' median	Controls' range	Mann-Whitney P value
Reaching for the glass	Duration (s)	3.09	1.62–3.54	1.24	1.09–1.41	**<0.003**
	Arm elongation (%)	5.63	−9.27–35.83	49.21	34.10–69.50	**<0.005**
	Elbow ROM (°)	10.10	3.37–30.70	48.40	34.20–66.80	**<0.003**
	Trunk forward Inclination (%)	85.77	55.90–96.70	37.84	14.67–52.53	**<0.003**
	Trunk axial rotation (%)	10.20	5.80–12.53	14.15	9.25–17.37	**<0.05**
	Mouth forward displacement (mm)	190.33	152.40–218.75	97.07	31.63–129.75	**<0.003**
	Number of movement units of reaching	5	1–9	1	1-2	**<0.0002**
Bringing the glass to the mouth	Duration (s)	2.59	1.68–4.61	1.46	1.11–1.64	**<0.003**
	Arm contribution (%)	66.37	29.00–72.73	65.85	60.00–82.03	NS
	Mouth backward displacement (mm)	−90.13	−199.47–−39.00	−80.95	−104.35–−16.77	NS
	Number of movement units of bringing	4	1–17	1	1-2	**<0.003**
Putting the glass back on the table	Duration (s)	2.22	1.85–3.89	1.44	1.24–1.52	**<0.003**
	Arm contribution (%)	60.73	29.77–76.77	65.11	61.37–80.57	NS
Number of movement units of reaching and bringing		9.5	2–26	2	2-3	**<0.0005**

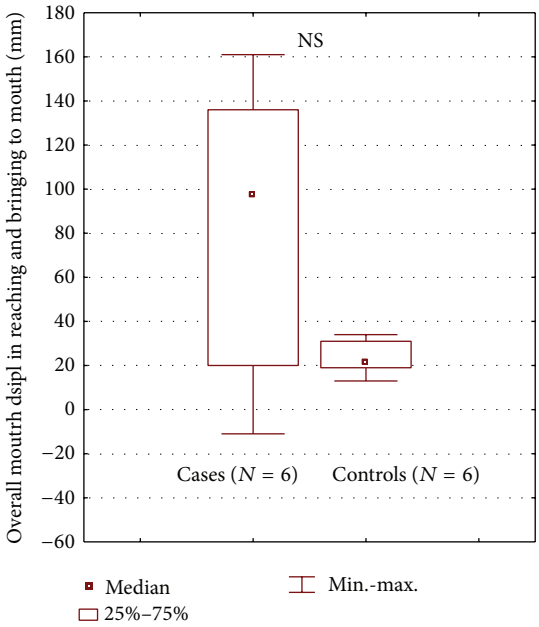


Figure 7: Comparison of the overall mouth displacement in reaching and bringing to the mouth in the two groups (stroke and control group).

During the reaching for a glass the patients showed a reduced arm elongation and trunk axial rotation due to motor deficit. For this reason, as observed, they carried out compensatory strategies which included trunk forward displacement and head movements. In the overall mouth displacement during reaching and bringing phases we observed a trend towards a more advanced mouth position with respect to the initial position in stroke patients than in controls, without statistical significance probably due to the small sample size. However we also observed a higher variability of this parameter in stroke patients probably due to the differences among individual strategies.

In a previous study that Murphy et al. investigated, the authors found that, in stroke patients affected 3 or more months earlier, variables describing movement time, smoothness, and velocity (resp., total movement time, number of movement units, and peak angular velocity of elbow) discriminated best between healthy subjects and patients with stroke (as well as patients with moderate versus mild arm impairment). They also observed that variables describing compensatory movement of the trunk and arm (trunk forward displacement while reaching for the glass and higher shoulder abduction while drinking) discriminated between patients with moderate and mild stroke impairment [16]. Our study shares Murphy's interest for a specific task but we provided a different set of variables.

We considered the reaching task as a global movement of hand forward displacement, of which we quantified the different contributing components: arm elongation, trunk forward inclination, and trunk axial rotation. Differently from Murphy our approach permitted us to show that trunk axial rotation of patients was significantly lower than that of controls. The reduction showed by stroke patients in arm elongation (as also shown by Murphy) and in trunk axial rotation (as only shown in the present study) demonstrated that the trunk forward inclination was of the utmost importance when patients had to reach for the glass.

It is worth noting that, although smaller, our sample of patients was more homogeneous than that of Murphy, who

included both subacute and chronic patients, some of whom with spasticity at upper limb.

As regards the smoothness of movement, quantified by NMUs, it has appeared to be a very important parameter to discriminate movement quality between stroke patients and healthy subjects, as previously observed by Murphy.

These preliminary data need to be confirmed in further studies on a large population of patients with different severity of stroke. The kinematic analysis protocol that we developed and used in the current study might represent an outcome measure of UL rehabilitation processes, also in patients with UL disability due to different diseases/traumas (not only after stroke).

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Robotic Upper Limb Rehabilitation after Acute Stroke by NeReBot: Evaluation of Treatment Costs

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Stroke is the first cause of disability. Several robotic devices have been developed for stroke rehabilitation. Robot therapy by NeReBot is demonstrated to be an effective tool for the treatment of poststroke paretic upper limbs, able to improve the activities of daily living of stroke survivors when used both as additional treatment and in partial substitution of conventional rehabilitation therapy in the acute and subacute phases poststroke. This study presents the evaluation of the costs related to delivering such therapy, in comparison with conventional rehabilitation treatment. By comparing several NeReBot treatment protocols, made of different combinations of robotic and nonrobotic exercises, we show that robotic technology can be a valuable and economically sustainable aid in the management of poststroke patient rehabilitation.

1. Introduction

Stroke has a high social impact because it is a leading cause of motor impairment and disability in ADLs [1]. In 85% of stroke survivors the recovery is partial [2], while in 35% of them a serious disability remains. The 30–60% of patients treated with traditional rehabilitation has a residual functional impairment of the paretic arm and consequently a reduction of ADLs is common [3, 4]. The ageing of population implies that an increasing number of people require rehabilitation after stroke [5, 6]. In the acute and subacute poststroke phases, the robot-assisted rehabilitation of the upper limb may be successfully used in alternative to conventional mobilization: in fact it results as effective as the conventional therapy, especially when it is used in addition to nonrobotic techniques [7–9]. In 2010, the average expense per person for stroke care was estimated at $5455 in the USA while the mean lifetime cost of ischemic stroke was estimated at $140 048 (including inpatient care, rehabilitation, and follow-up care necessary for lasting deficits) [1]. During 2001 to 2005, the average cost for outpatient stroke rehabilitation services and medications the first year after inpatient rehabilitation discharge was $11 145. The corresponding average yearly cost of medication was $3376, whereas the average cost of yearly rehabilitation service utilization was $7318 [1].

Despite the great diffusion of studies on the robotic therapy [10], few data are available about the real costs of robot-aided rehabilitation. Wagner et al. [11] analysed the usual care cost for stroke patients in comparison with additional intensive rehabilitation or additional robotic intervention. They stated that patients in the robot and intensive comparison groups had lower average costs than patients in usual care group, but there were not differences between robotic and intensive groups.

With the present study, we aim to complete our previous studies conducted on the use of the Neuro-Rehabilitation-Robot (NeReBot) for the treatment of poststroke upper limb impairment [7–9, 12], by presenting an evaluation of the costs related to delivering such therapy to patients, with reference to the standard costs of stroke rehabilitation in the Italian

National Health Care System. Further work will be needed to obtain a complete cost-effectiveness evaluation of NeReBot treatment, though, this study allows comparing the costs of such therapy to the control therapies used in the NeReBot clinical trials run so far.

2. Methods

2.1. Description of Robotic Device. Our previous studies were conducted on the clinical utilization of the NeReBot, a device for the treatment of poststroke upper-limb impairment designed and developed at Padua University [13, 14]. This robotic device, unlike the other rehabilitation robots described in the literature, is based on direct-drive wire actuation. This solution can provide many benefits compared with devices characterized by a rigid structure, that is, lower costs, reduced complexity (spatial movements can be obtained despite the limited number of degrees of freedom), compliance by design [15], and a higher degree of reliability and safety. The device can (a) perform spatial movements (flexion and extension, pronation and supination, adduction and abduction, and a circumduction-like movement) of shoulder and elbow, (b) be easily moved to the hospital room and used for early training of the upper limb after stroke, and (c) be used to intervene on patients not only in the sitting but also in the supine position [8].

2.2. Participants. NeReBot was tested in two different clinical trials [8, 9, 12]. Both studies involved hemiparetic subjects in the acute and subacute phases of their stroke, enrolled within 15 days after stroke.

2.3. Study Design. The two randomized controlled trials tested two different robotic protocols in comparison to standard rehabilitation treatment, one using the robot in addition to the traditional treatment [8], one in partial substitution to the standard rehabilitation programme, with a dose-matched approach [9, 12]. Both protocols lasted 5 weeks and included two daily sessions of robotic treatment for five days a week.

2.4. Evaluation of Participants. Muscle tone (Modified Ashworth Scale), strength (Medical Research Council), synergism (Fugl Meyer motor scores), dexterity (Box and Block test and Frenchay Arm test), and ADLs (Functional independence Measure) were measured at all the evaluations (before, at the end of the treatment and at the follow up). As reported in [12], no significant between-group differences were found with respect to demographic characteristics, motor, dexterity, and ADLs, so the substitutive treatment protocol with NeReBot could be considered comparable to the traditional one. On the other hand, the additional protocol yielded greater gains in the robotic group, with respect to controls, both on functional and on motor scales [8]. In other words, patients treated with the Additional Protocol developed a greater recovery of motor function and coordination than patients treated only with the conventional protocol, both at the end of therapy and at follow-up (8 months).

Table 1: Hourly robot cost.

Hourly robot cost	
Robot purchase value	€50.000,00
Annual maintenance (from the 2nd year)	€4.000,00
Amortization period (years)	5
Total robot cost	€66.000,00
Annual robot cost	€13.200,00
Effective days of use per year	260
Daily working hours	8
Annual working hours	2.080
Hourly robot cost	*€6,346*

2.5. Data Considered for Cost Evaluation. To evaluate the costs of robotic and control treatment in the acute and subacute phases poststroke, we considered the hourly cost of a therapist and the daily cost of hospitalization in a Rehabilitation Unit (both referred to the Italian National Healthcare System) and the hourly cost of the NeReBot (Table 1). The latter was derived considering the total purchase cost of the equipment (€50,000) and maintenance costs (8% of the purchase price, from the second year). Such costs were divided by the hours of operation, considering a five-year amortization period and a usage of 2080 hours per year. We assumed a use of the robot within 5 days of the week, 52 weeks per year, and 8 hours per day, for a total of 260 days of use per year (these data refer to the normal organization of the work of a rehabilitation service).

2.6. Intervention Costs (Therapist). The hourly cost of the physiotherapist is obtained by dividing the annual cost of the physiotherapist (gross of social security and tax) for a number of hours actually worked at the rate of 8 hours per day, for 5 days a week, for 44 weeks per year (total: 220 working days).

2.7. Cost for Robotic Session. The hourly cost of a robotic session is given by the sum of two terms: the cost of using the equipment and the cost of the operator (physiotherapist), who makes setting up and supervision during robotic treatment. The last cost depends on the degree of supervision required, which depends on the degree of patient autonomy (greater supervision needed in the early stages of rehabilitation, gradually reduced in the following weeks).

In the case of the NeReBot, based on our clinical experience, we hypothesize that in the first week of treatment a reasonable level of supervision is 1 : 1 (one therapist, one robot), in the second week a level of 1 : 2 (one therapist, two robots), in next three weeks a 1 : 3 level, and a 1 : 4 level from then on. Thanks to the ease of use, the NeReBot requires few minutes to be set up at the beginning of the session (less than 5 minutes) and less time to change the exercise type. Therefore, a single physiotherapist can manage up to four robots, provided these are conveniently located in the same room.

Table 2: Hourly physiotherapist cost.

Hourly physiotherapist cost	
Gross yearly cost	€33.040,00
Effective working days per year	220
Daily working hours	8
Annual working hours	1.760
Hourly physiotherapist cost	*€18,773*

2.8. Cost for Global Therapy. The cost of each protocol is obtained taking the sum of all conventional and robotic treatment sessions. The latter are evaluated on a weekly basis, by multiplying the weekly hours by the hourly cost of robotic therapy for the week in question, in the event of different levels of supervision by the therapist among weeks, as previously assumed.

3. Results

Based on a cost of about €33,000 gross per year, we get an hourly cost of therapist close to €19 (Table 2). Considering 30-minute robotic treatment sessions (to be repeated twice a day), according to the four different levels of supervision (from 1 : 1 to 1 : 4, i.e., 30, 15, 10, and 7.5 minutes per session), we get an hourly treatment cost of robotic therapy ranging between €25 (first week) and €11 (last weeks), according to the different impact of the cost of the operator with respect to the hourly cost of the equipment (Table 3).

3.1. Additional Protocol. The additional Protocol adopted in the first clinical trial [8] consisted of two daily robot-assisted rehabilitation sessions of 25 minutes each, 5 days per week for 5 weeks. The overall treatment consists of approximately 21 hours of robot-assisted exercises, starting during the first week after stroke, in addition to conventional rehabilitation. The additional hours are concentrated in the initial phase (first 5 weeks) of the conventional protocol, which has a total length of 8 weeks on average.

As shown in Table 4, the weekly cost of the additional robotic treatment is obtained by multiplying the weekly additional hours (4,17 hours/week) by the hourly cost of robotic therapy for the week in question, which varies according to the different levels of therapist supervision as previously assumed. By taking the sum of the weekly costs for the whole protocol, we get a total cost per patient just under €330.

Given the greater patient recovery reported in the clinical trial [8], one could expect to make an early dehospitalization of robotic patients, compared to the 8 weeks expected on average. Considering the daily hospitalization cost of €273.64 provided by Diagnosis Related Groups (DRG) in the Autonomous Province of Trento, comparable to the mean Italian DRG value, the recovery of the additional treatment costs could be achieved with an average degree of dehospitalization of 1.2 days per patient (e.g., by reducing the hospitalization of all patients by 1 day and by discharging a patient every five discharged 2 days earlier than the average). Any further reduction of patients' hospitalization would result in money savings for the Healthcare System.

3.2. Mixed Protocol. Another approach could be that of designing a mixed protocol, including some additional robotic sessions with respect to standard rehabilitation treatment and some substitutive robotic sessions in which part of the standard treatment is replaced by robotic treatment. This choice is supported by the result that robotic therapy with NeReBot can be effectively used also in partial substitution of the traditional treatment [9, 12].

Since in the last weeks of treatment the robotic treatment costs are lower than standard treatment, the cost of a mixed protocol may benefit from including additional robotic sessions in the last weeks, whose savings may compensate for the additional costs, with respect to standard treatment, related to the additional robotic sessions. On the other hand, the introduction of additional robotic sessions should lead to faster/greater recovery of patients [8]. As an example, we consider the possibility of modifying the traditional rehabilitative treatment as follows.

(1) During the first period, which represents the phase of the greatest recovery, the protocol could be additional, in order to intensify treatment; this would imply additional costs if compared to conventional treatment alone.

(2) In a second phase, the robotic treatment could be administered in substitution of the portion of conventional treatment dedicated to the upper limb. In this phase, the lower cost of robotic treatment could allow recovering the additional costs generated in the first phase.

Table 5 shows a hypothesis of 2 weeks of addition, with two daily robotic sessions of 25 minutes each, for 5 days per week (125 minutes), yielding a total of more than 8 hours of additional robotic treatment, with a cost per patient of about 170€. This cost is recovered with less than six weeks of substitutive robotic treatment, thanks to a differential (traditional-robotic) hourly cost of approximately €7 on average (Table 6).

4. Discussion

In this paper we provided a quantification of the costs of the additional treatment protocol tested in our first randomized controlled trial of NeReBot [8]. We also calculated the costs of a mixed protocol, including both additional and substitutive robotic training, which has never been tested on patients. In the proposed mixed protocol, without any additional cost with respect to conventional rehabilitation, patients would receive, in the subacute phase, more than 20% additional treatment time (8 hours) with respect to the one normally delivered to the proximal upper limb (40 hours within 8 weeks). The intensification of treatment in the first weeks is expected to bring greater gains on both functional and motor scales, on the basis of the results of the first clinical study [8]. On the other hand, the partial replacement of

Table 3: Hourly robot-aided therapy cost (including physiotherapist cost).

Hourly robot-aided therapy cost (including physiotherapist cost)			
Number of robots per therapist	Length of session (min)	Therapist supervision (min)	Hourly cost (robot + therapist)
1	30	30	€25,119
2	30	15	€15,733
3	30	10	€12,604
4	30	7,5	€11,039

Table 4: Additional Protocol costs. The additional weekly hours are calculated considering two 25-minute daily sessions per 5 days a week (50 min × 2 = 250 min = 4,17 hours).

Additional Protocol costs				
Week (number)	Number of robots per therapist	Hourly cost (robot + therapist)	Additional weekly hours	Additional weekly cost
1	1	€25,119	4,17	€104,74
2	2	€15,733	4,17	€65,61
3	3	€12,604	4,17	€52,56
4	3	€12,604	4,17	€52,56
5	3	€12,604	4,17	€52,56
			Total	**€328,04**

Table 5: Mixed Protocol—phase one. Costs of the additional robotic training sessions delivered in the first two weeks.

Mixed Protocol—phase one	
Additional weeks (no.)	2
Days per week (no.)	5
Sessions per day (no.)	2
Session's length (min)	25
Additional sessions (no.)	20
Additional hours (no.)	8,33
Supervised robot (no.)	1-2
Hourly cost (average)	€20,426
Additional cost	*€170,21*

Table 6: Mixed Protocol—phase two. The number of substitution hours (24,49) has been calculated by dividing the cost of the first two weeks of additional therapy (€170,21) by the hourly saving (€6,95) determined by the substitutive therapy. The so-calculated substitution hours correspond to 58,78 sessions lasting 25 minutes each, which can be delivered (twice a day) in less than 6 weeks to pay back the cost of the additional therapy.

Mixed Protocol—phase two	
Supervised robot (no.)	3-4
Hourly cost (average)	€11,822
Hourly physiotherapist cost	€18,773
Hourly saving	*€6,95*
Substitution hours (no.)	24,49
Substitution sessions (no.)	58,78
Substitution weeks	5,78

conventional treatment with robotic therapy is not going to lead to alterations in motor and functional recovery [9, 12]. Therefore, not only with the Additional Protocol but also with the Mixed Protocol we can expect to be able to anticipate the discharge of patients, which will generate savings for the National Health Care System.

Robotic technology can be a valuable aid in the management of poststroke patient rehabilitation. From the study carried out, we can conclude that the costs of such interventions can be considered easily affordable, if delivered through easy-to-use and moderate-to-low cost devices. Potentially, by implementing adequate rehabilitation protocols, those costs may even be eliminated, while bringing significant economic benefits as well as better clinical outcomes at the same time.

Considering the huge social impact of stroke [1] and the aforementioned benefits and sustainable costs of a robotic treatment, we think that more efforts should be spent to invest in robot-assisted treatment and to study and test novel treatment protocols, also from a cost-effectiveness point of view, in order to well direct the economic resources improving the rehabilitation treatment. The number of people who could take benefit from robotic treatment is expected to grow in the coming years [5, 6], and hospitals that use robotic technology for stroke rehabilitation certainly will have more instruments to answer the growing rehabilitation needs.

Certainly, our model has some limitations, and to be reproduced in other settings requires the availability of more than one robot, adequate working space, and trained physiotherapists. Moreover, a thorough evaluation of cost-effectiveness of our treatment approach needs further work, as we provided so far only clinical evidence and evaluation of treatment costs, which are only part of the story. More in general, some questions still remain open in this field and more studies will be needed in the near future. Hypothetically, reaching a better functional recovery and reduced residual disability should bring also a reduction of the lifetime

cost of stroke, but more research is needed to state it. Further scientific effort should be spent to evaluate if the robotic treatment can be economically advantageous not only in the acute and subacute phases but also in the chronic phase.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Gait Patterns in Hemiplegic Patients with Equinus Foot Deformity

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Equinus deformity of the foot is a common feature of hemiplegia, which impairs the gait pattern of patients. The aim of the present study was to explore the role of ankle-foot deformity in gait impairment. A hierarchical cluster analysis was used to classify the gait patterns of 49 chronic hemiplegic patients with equinus deformity of the foot, based on temporal-distance parameters and joint kinematic measures obtained by an innovative protocol for motion assessment in the sagittal, frontal, and transverse planes, synthesized by parametrical analysis. Cluster analysis identified five subgroups of patients with homogenous levels of dysfunction during gait. Specific joint kinematic abnormalities were found, according to the speed of progression in each cluster. Patients with faster walking were those with less ankle-foot complex impairment or with reduced range of motion of ankle-foot complex, that is with a stiff ankle-foot complex. Slow walking was typical of patients with ankle-foot complex instability (i.e., larger motion in all the planes), severe equinus and hip internal rotation pattern, and patients with hip external rotation pattern. Clustering of gait patterns in these patients is helpful for a better understanding of dysfunction during gait and delivering more targeted treatment.

1. Introduction

A great deal of effort has been made to develop classifications of spastic gait deviations to reduce the complexity of this disorder, improve diagnosis and clinical decision making, and facilitate communication among clinicians [1–7]. Cluster analysis has been frequently applied to detect gait patterns particularly in children with cerebral palsy [8–10]. Over the last ten years, this method has been applied to detect gait patterns or clusters not easily identifiable with standard techniques in stroke patients to classify groups of individuals with similar gait patterns [11–15]. This method has the advantage of taking into account several parameters at the same time rather than a single one for each patient. Dividing data into meaningful groups (clusters) allows capturing the main features of the gait deviation and reflecting homogenous levels of function impairment at each joint [15].

Although most studies have focused on gait clusters of stroke patients, the presence of an equinus foot was not specified; only one study [15] concentrated on equinus deformity using temporal-distance parameters and sagittal joint kinematics during gait. Equinus foot is present in fact in 10–20% of stroke survivors and is considered to be the most detrimental consequence of stroke for gait effectiveness. Appropriate knowledge of its role in stroke gait pattern can provide more targeted and effective rehabilitative treatments.

In these previous studies on cluster analysis of stroke patients, gait velocity was considered a strong determinant for group placement [11]. Furthermore, gait velocity is deemed to be a valid and reliable measure of walking recovery after stroke and has been shown to be a valuable indicator of future health and function [16, 17]. However, the amount of change that is considered to be clinically meaningful and reflective of the level of community ambulation has not been established. In a previous study [18], the present authors showed that correction of equinus foot by surgical intervention, although not determining an increase in the speed of progression, modified ankle-foot kinematics, thus explaining the gains reported by the patients and the subject-specific goals attained through treatment, such as increased stability on the foot, removal

of ankle-foot orthoses, modification of shoes, walking aids, and relief of pain. With regard to this, the assessment of ankle-foot deformity during gait is relevant for appropriate clinical decision making. The attainment of other goals in gait recovery might in fact be relevant even in patients without a chance of improving their velocity. A three-dimensional kinematic approach is furthermore essential in this respect for the complete assessment of this complex deformity [18].

The aim of this study was to focus on the role of foot-ankle complex dysfunction in gait patterns in hemiplegic patients using a gait analysis protocol which allows full assessment of ankle-foot complex kinematics in the three planes of the space. A nonhierarchical cluster analysis based on temporal-distance and kinematics of the whole lower limb joints was applied for this purpose. The hypothesis that ankle-foot complex kinematics plays a major role in gait dysfunction was stated.

2. Material and Methods

2.1. Subjects. The study was carried out retrospectively on a group of subjects who were referred to the Motion Analysis Laboratory of Rehabilitation Medicine Unit in Ferrara for a routine assessment process in the period 2009-2010. Forty-nine consecutive hemiplegic patients with a stabilized clinical condition (30 men and 19 women, 22 with left hemiplegia and 27 with right hemiplegia) and equinus deformity of the foot were enrolled in the study by an experienced clinician (M.M.). The inclusion criteria were hemiplegia at least six months before enrolment in the study, equinus deformity evaluated at the observational analysis and clinical assessment, ability to walk independently for at least 10 m, and absence of previous orthopaedic surgery. Patients were excluded if they had received botulinum injections or a phenol nerve block in the hemiplegic lower limb 6 months before the evaluation and if they had other medical disorders which might have adversely affected their gait pattern.

2.2. Procedures. Gait analysis was performed on a 10 meter walkway with patients walking at a self-selected speed, barefoot, and with or without aid devices (cane).

Three-dimensional kinematics of the lower limbs and time-distance parameters were recorded using a six-camera (Mcam 50, 100 Hz) motion analysis Vicon 460 system (Vicon Oxford Metrics, Oxford, UK). The gait analysis protocol Total3Dgait (T3D) [19], including anatomical-based description of foot joint motion in the three planes of space, already validated on stroke patients [20], was used. Three trials were collected for each subject.

2.3. Statistical Analysis. A set of 38 discrete parameters of amplitude were selected at crucial points of kinematic curves (maximum or minimum values in the stance and swing phase) and values at particular instants of the gait cycle (heel contact, toe-off), according to Benedetti et al. [21]. These variables were, respectively, pelvis maximum rotation, hip flexion at foot contact, hip flexion at toe-off, hip maximum extension in stance, hip maximum flexion in swing, hip total range of movement, knee flexion at foot contact, knee maximum flexion at loading response, knee maximum extension in stance, knee flexion at toe-off, knee maximum flexion in swing, knee total range of movement, ankle flexion at foot contact, ankle plantarflexion at loading response, ankle maximum dorsiflexion in stance, ankle plantarflexion at toe off, ankle maximum plantarflexion in swing, ankle range of motion in the sagittal plane, pelvis minimum rotation, hip maximum adduction in stance, hip maximum abduction in swing, hip range of motion, knee maximum adduction in stance, knee maximum abduction in swing, knee range of motion, ankle maximum abduction in stance, ankle maximum adduction in swing, ankle range of motion in the coronal plane, pelvis minimum rotation, hip maximum internal rotation in stance, hip maximum external rotation in swing, hip total range of motion, knee maximum internal rotation in stance, knee maximum external rotation in swing, knee total range of motion, ankle maximum eversion in stance, ankle maximum inversion in swing, and ankle total range of motion in transverse plane. Stance duration, stride length, cadence, and speed of progression were also included in the cluster analysis. They were normally distributed according to the Kolmogorov-Smirnov test.

As the dataset included 146 gait cycles from 49 patients, a bias due to the patient "effect" was hypothesized. For this reason, a two-step clustering analysis was considered to be reliable and stable for a dataset with continuous variables [22]. This analysis clusters the dataset into many small subclusters, which are then collected into the desired number of clusters using a hierarchical algorithm.

The number of clusters was chosen automatically using both the Akaike's information criterion (AIC) and Bayes information criterion (BIC); the first one generally overestimates and the latter one generally underestimates the number of clusters. The smaller the number is the better the model is. As they converged on the same number of clusters, we accepted that number as a reliable one. The Euclidean distance was applied as measure of distance and the variables were z-standardized. Post hoc analysis of the clusters, corrected for multiple comparisons by the Bonferroni method, was performed to identify the variables characterizing each cluster. Only significant variables for $P < 0.001$ were considered.

The Kruskal-Wallis test was used to explore differences with respect to age, distance from the event, and BMI of patients in the identified clusters ($P < 0.05$).

Statistical analysis was performed using SPSS v.19.0 (IBM Corp., Armonk, NY, USA).

3. Results

147 gait cycles of 49 patients were subdivided by AIC into homogeneous subgroups (clusters). One gait trail corresponding to one patient was excluded as an outlier. Five clusters of parameters representative of gait patterns were identified according to the clustering algorithm: cluster 1 included 34 cycles (23.3% out of the cycles analyzed), cluster 2 included 33 cycles (22.6%), cluster 3 included 26 cycles (17.8%),

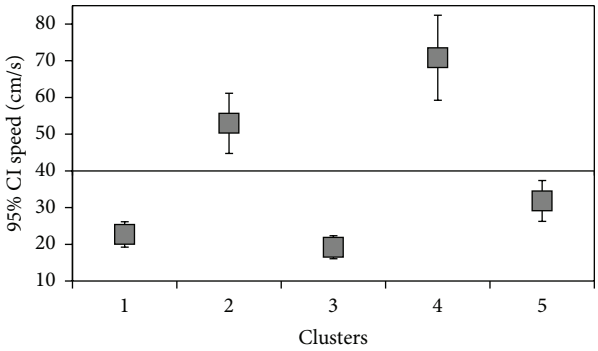

Figure 1: Identification of clusters with respect to speed.

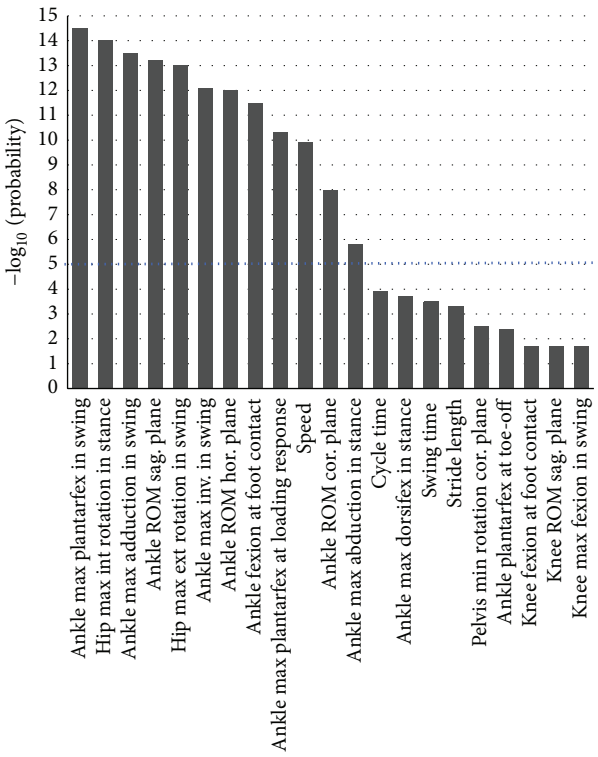

Figure 2: Example of clusters characterization (cluster 1). Above of the dotted line are the variables with statistical significance of $P \leq 0.001$.

cluster 4 included 22 cycles (15.1%), and cluster 5 included 31 cycles (21.2%) (Table 1).

No significant difference was present among clusters in terms of age of patients, time from the event, and BMI (Table 2).

The five clusters identified were different for walking speed: three clusters (1, 3, 5) were characterized by a low walking speed (resp., 34.0, 19.2, 31.8 cm/sec), one (cluster 2) by intermediate walking speed (52.9 cm/sec) and one (cluster 4) by fast walking speed (70.8 cm/sec) (Figure 1).

The kinematic and temporal-distance parameters characterizing the 5 clusters with statistical significance ($P \leq 0.001$) were considered (Figure 2).

The following parameters were not considered as they did not reach statistical significance in any cluster: pelvis maximum rotation in the coronal plane, hip maximum adduction in stance, hip total range of movement in the transverse plane, knee maximum adduction in stance, knee maximum abduction in swing, knee total range of movement in the coronal and transverse planes, and knee maximum internal rotation in stance. All the ankle-foot complex variables were included in the clusters.

Cluster 1 was the most frequently observed (23.3%) and was characterized by low velocity (22.7 ± 9.9 cm/sec) and 11 kinematic variables (Table 3). Nine kinematic parameters referred to the ankle joint whilst two referred to the hip joint. In this cluster, gait pattern was characterized by the greatest plantarflexion at initial contact and loading response phase of the gait with respect to other clusters, reduced abduction through the stance phase and increased plantarflexion, adduction and external rotation of the ankle during the swing phase. The hip joint showed increased internal rotation throughout the stance phase and external rotation throughout the swing phase.

Cluster 2 was characterized by intermediate velocity (52.9 ± 23.1 cm/sec), reduced stride length and 7 kinematic variables. Five kinematic variables in the cluster were relative to the ankle and two to the knee (Table 3).

The gait pattern in this group was characterized by the largest knee flexion at initial contact and during the loading response phase, the smallest ankle swing plantarflexion compared to the other clusters, reduced plantarflexion at initial contact and during loading response phase, reduced ankle adduction in swing phase, and reduced ankle range of motion in the transverse plane.

Cluster 3 was characterized by the slowest velocity among clusters (19.2 ± 7.7 cm/sec), reduced stride length and by 9 kinematic variables. One kinematic variable was relative to the pelvis and 5 referred to the hip and 3 to the ankle (Table 3).

With respect to others, this cluster was characterized by increased pelvic anterior tilt, a reduced hip extension, reduced internal rotation during stance phase, reduced hip abduction during swing phase, and increased hip flexion at initial contact and toe-off. In this cluster, the ankle-foot complex showed the largest reduction of range of motion on the sagittal, frontal, and transverse planes and the largest shortening of stride length.

Cluster 4 was characterized by the highest velocity (70.8 ± 26.1 cm/sec), reduced stride length, cycle time, swing time and 6 kinematic variables. Three kinematic variables were relative to the hip, two to the knee, and one to the ankle joint (Table 3). The hip showed the highest range of motion (38.3 ± 8.9) among clusters, increased hip extension (−6.8 ± 5.6), and reduced hip flexion at toe-off. The knee showed the largest knee range of motion (51.5 ± 14) and hyperextension in stance phase (8.6 ± 3.2). At the ankle, the smallest external rotation among clusters was present during stance. In this cluster, the increased walking speed was associated to the greatest stride length, the shortest gait cycle time, and increased duration of the swing phase.

Table 1: Autoclustering.

Number of clusters	Akaike's information criterion (AIC)	AIC change[a]	Ratio of AIC changes[b]	Ratio of distance measures[c]
1	3873.849			
2	3598.036	−275.814	1.000	1.202
3	3393.501	−204.535	0.742	1.630
4	3325.170	−68.330	0.248	1.255
5	3300.742	−24.429	0.089	1.183
6	3302.954	2.212	−0.008	1.053
7	3312.444	9.491	−0.034	1.153
8	3340.366	27.922	−0.101	1.029
9	3371.712	31.346	−0.114	1.096
10	3413.251	41.540	−0.151	1.103
11	3464.696	51.445	−0.187	1.102
12	3525.088	60.392	−0.219	1.073
13	3591.474	66.386	−0.241	1.122
14	3666.712	75.239	−0.273	1.066
15	3746.426	79.714	−0.289	1.035

[a]The changes are from the previous number of clusters in the table.
[b]The ratios of changes are relative to the change for the two-cluster solution.
[c]The ratios of distance measures are based on the current number of clusters against the previous numbers of clusters.

Table 2: Data on patients.

Cluster	Mean	Confidence interval 95%	
		Lower limit	Upper limit
Age*			
1	44.1	35.5	52.6
2	40.0	21.0	59.0
3	54.2	46.0	62.3
4	53.2	41.4	65.0
5	55.1	48.0	62.3
Months from acute event**			
1	23.5	10.1	36.9
2	120.0	8.0	232.0
3	73.6	32.9	114.3
4	72.8	6.0	140.2
5	81.5	14.9	148.0
BMI***			
1	24.0	21.7	26.3
2	23.4	19.1	27.8
3	25.2	21.6	28.8
4	25.9	23.4	28.3
5	25.2	23.1	27.3

Kruskal-Wallis $^{*}P = 0.157$, $^{**}P = 0.083$, $^{***}P = 0.757$.

Cluster 5 was characterized by slow velocity (31.8 ± 15.2 cm/sec) and 9 kinematic variables. Two kinematic variables were relative to the hip, four to the knee, and three to the ankle (Table 3).

In this cluster, the minimum hip internal rotation in the stance phase and the maximum hip external rotation in swing phase were found. At the knee, hyperextension was present in stance and reduced flexion at toe-off. The ankle joint showed the lowest dorsiflexion in stance, the lowest range of motion on frontal plane, and the greatest abduction during stance phase among all the clusters.

4. Discussion

The gait of hemiplegic patients with equinus foot shows a wide variety of behaviour consistent with the different expressions of the impairment due to muscle spasticity, cocontraction, damaged motor control, extent of the CNS lesion, and structural changes of soft tissues [23]. The categorization of gait pattern by three-dimensional gait analysis provided useful information on the joint dysfunction underlying the gait disability. In particular, the hypothesis of the present study was that the ankle-foot complex plays a major role in gait dysfunction. This was confirmed by the fact that all the ankle selected variables in the three planes of the space were included in all the clusters, although with different statistical significance. Furthermore, clusters were characterized also by walking speed, which has been already reported to be the strongest determinant of group placement in a cluster analysis of stroke patients by Mulroy et al. [11].

According to Perry's classification [24], the patients in the present study presented a walking speed corresponding at a household ambulation (<40 cm/s, clusters 1, 3, 5) or a limited community ambulation (between 40 and 80 cm/s, clusters 2 and 4), whereas only a few patients had a walking speed useful for full community ambulation (>80 cm/s). This sample is very different from that considered by Kinsella and Moran [15], where the "fast" group of patients had a mean walking speed of 42 ± 16 cm/s. This difference of velocity in the two studies, together with the lack of references related to the coronal and transverse planes in Kinsella and Moran study [15], might affect the composition of the individual clusters, making a possible comparison difficult.

Table 3: Summary of gait analysis parameters characteristics of clusters.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Normative[#]
			Time-distance parameters			
Speed of progression (cm/s)	22.7 ± 9.9*	52.9 ± 23.1	19.2 ± 7.7*	70.8 ± 26.1*	31.8 ± 15.2	127.8 ± 11.2
Cycle time (s)	2.7 ± 0.9	1.7 ± 0.4	2.1 ± 0.7	1.4 ± 0.3*	2.1 ± 0.8	1.1 ± 0.1
Stride length (cm)	55.9 ± 14.1	83.1 ± 17.6*	38.6 ± 14.6*	95.1 ± 18.4*	57.5 ± 15.6	141.2 ± 8.7
Swing time (% stride)	30.2 ± 8.1	38.2 ± 4.5	31.3 ± 7.4	41.7 ± 3.7*	39.8 ± 9.3	39.7 ± 1.7
			Kinematic variables (°)			
PELVIS max rotation—Sagittal plane	21.1 ± 8.8	18.2 ± 4.1	23.1 ± 3.1*	15.5 ± 4.7	19.9 ± 4.5	10.3 ± 4.4
PELVIS min rotation—Coronal plane	5.5 ± 2.7	1.7 ± 5.0	6.3 ± 2.6	2.8 ± 3.3	3.9 ± 2.7	−3.9 ± 1.9
PELVIS min rotation—horizontal plane	−19.8 ± 7.9	−13.9 ± 7.4	−24.4 ± 15.0	−10.7 ± 9.3	−21.6 ± 10.9	−5.8 ± 2.5
HIP flexion at initial contact	23.5 ± 9.6	27.3 ± 4.5	35.8 ± 6.4*	23.1 ± 7.1	21.8 ± 4.7	30.9 ± 5.9
HIP flexion at toe-off	15.2 ± 12.5	12.5 ± 6.0	31.2 ± 7.6*	3.6 ± 8.1*	16.9 ± 15.5	−3.1 ± 6.1
HIP max extension in stance	4.35 ± 9.91	4.3 ± 6.3	23.5 ± 6.0*	−6.8 ± 5.6*	7.7 ± 4.1	−9.4 ± 5.7
HIP max flexion in swing	30.90 ± 9.78	30.4 ± 5.1	40.8 ± 9.8	31.4 ± 10.7	29.4 ± 6.1	32.6 ± 5.4
HIP max abduction in swing	−2.8 ± 4.5	−4.9 ± 3.9	1.1 ± 2.4*	−3.4 ± 3.1	−5.3 ± 3.7	−6.6 ± 2.7
HIP max internal rotation in stance	13.0 ± 6.1*	3.6 ± 12.1	−9.2 ± 6.3*	1.2 ± 9.3	−14.2 ± 13.8*	5.5 ± 9.2
HIP max external rotation in swing	8.3 ± 6.6*	−1.4 ± 11.8	−13.4 ± 9.0	−4.5 ± 8.9	−17.8 ± 12.9*	−1.3 ± 9.5
HIP ROM—Coronal plane	9.4 ± 2.9	9.0 ± 4.1	6.4 ± 2.7	12.5 ± 4.1	8.3 ± 3.9	13.7 ± 3.2
HIP ROM—Sagittal plane	27.5 ± 8.3	26.8 ± 7.2	17.8 ± 8.7	38.3 ± 8.9*	38.3 ± 8.9	42.5 ± 4.1
KNEE flexion at initial contact	6.3 ± 7.3	15.9 ± 4.9*	15.9 ± 7.9	7.0 ± 6.6	7.0 ± 6.7*	4.5 ± 3.5
KNEE max flexion at loading response	11.1 ± 10.5	19.4 ± 5.4*	16.6 ± 8.1	7.4 ± 6.7	1.8 ± 5.2*	16.0 ± 5.9
KNEE max extension in stance	−1.2 ± 11.6	5.7 ± 9.9	1.5 ± 6.5	−8.6 ± 3.2*	−9.0 ± 5.9*	4.3 ± 3.8
KNEE flexion at toe-off	18.8 ± 10.2	28.1 ± 11.0	20.3 ± 7.0	22.5 ± 8.3	11.7 ± 7.4*	38.9 ± 6.2
KNEE max flexion in swing	23.1 ± 13.5	33.4 ± 12.0	27.8 ± 8.5	42.8 ± 14.9	19.4 ± 9.9	64.9 ± 5.6
KNEE ROM-Sagittal plane	27.0 ± 11.3	29.7 ± 9.9	26.3 ± 10.5	51.5 ± 14.0*	28.6 ± 10.0	64.8 ± 4.7
ANKLE flexion at initial contact	−26.7 ± 4.4*	−9.0 ± 7.3*	−17.5 ± 13.0	−17.1 ± 5.1	−22.4 ± 4.8	2.6 ± 4.2
ANKLE max plantarflexion at loading response	−26.9 ± 4.5*	−9.8 ± 6.2*	−18.4 ± 13.6	−17.3 ± 4.9	−24.5 ± 6.2	−2.6 ± 3.9
ANKLE max dorsiflexion in stance	4.7 ± 6.7	7.1 ± 8.3	−7.4 ± 11.7	3.1 ± 6.7	−9.8 ± 7.4*	15.9 ± 4.1
ANKLE plantarflexion at toe-off	−18.8 ± 9.3	−6.6 ± 8.1	−14.2 ± 11.0	−14.3 ± 10.7	−16.3 ± 6.9	−10.4 ± 5.4
ANKLE max dorsiflexion in swing	−34.3 ± 4.6*	−11.7 ± 8.0*	−19.5 ± 12.6	−23.4 ± 9.6	−26.2 ± 10.7	−13.4 ± 6.0
ANKLE max abduction in stance	1.3 ± 5.1*	2.5 ± 6.6	11.2 ± 8.6	0.8 ± 5.4	16.0 ± 9.1*	−0.1 ± 4.5
ANKLE max adduction in swing	36.4 ± 5.1*	16.2 ± 8.8*	21.1 ± 10.8	26.5 ± 6.8	26.2 ± 10.7	20.7 ± 6.2
ANKLE max eversion in stance	7.3 ± 6.4	5.3 ± 5.7	12.2 ± 10.5	3.0 ± 3.8*	18.5 ± 10.0	3.1 ± 5.2
ANKLE max inversion in swing	40.1 ± 5.3*	26.7 ± 9.5	23.7 ± 12.2	25.7 ± 7.6	25.7 ± 7.6	13.9 ± 6.4
ANKLE ROM—Coronal plane	32.7 ± 8.8*	21.9 ± 6.9	13.4 ± 6.4*	22.7 ± 6.4	13.6 ± 6.4*	13.8 ± 2.9
ANKLE ROM—Sagittal plane	39.1 ± 7.1*	19.8 ± 5.3	14.2 ± 7.5*	27.2 ± 4.7	19.3 ± 11.3	29.4 ± 5.1
ANKLE ROM—Horizontal plane	35.3 ± 7.3*	14.8 ± 5.8*	12.8 ± 6.4*	25.9 ± 7.5	16.5 ± 7.9	21.8 ± 4.2

*$P < 0.001$.

[#]Normative values are relative to 20 healthy subjects (11 men and 9 women. mean age of 27.9 years. unpublished).

Amongst the patients examined in the present study, cluster 4, the one with the highest walking speed, showed most gait parameters very close to normative data. Hip and knee joints were involved in this cluster, showing a wide range of motion, which allowed a suitable stride length and a regular stance to swing ratio. There was only a reduced eversion of the ankle and a hyperextension of the knee, but that does not seem to have overly influenced the pattern of walking.

Patients in cluster 2 showed the second highest speed amongst clusters. In this case, the knee, and particularly the ankle, was the joints characterizing the cluster. A reduced range of motion was present at the ankle in the transverse plane, together with a reduced sagittal range of motion. The equinus at initial contact was small and, with respect to other clusters, the ankle reached a wider dorsiflexion during swing and a smaller adduction in swing phase. The reduced motion at the ankle might suggest a rigidity of the foot during stance, which might have allowed a more stable base of support with respect to patients in the other clusters, thus explaining the better speed of progression.

Clusters 1, 3, and 5 were characterized by slow speed. Cluster 1 presented the greatest deviations at the ankle and the greatest range of motion in all the planes when compared to the other clusters. This amplitude of motion represents reasonably a source of instability for the ankle that requires particular attention from the patient during the initial contact and the loading response phase, slowing the gait cycle and significantly influencing the speed. This data is confirmed by the increased duration of the cycle time that pattern 1 shows with respect to the other clusters. The hip in this cluster persists in internal rotation throughout the gait cycle, and, together with the high amount of ankle inversion during swing, configures an internal rotation spastic gait, typical of hemiplegia.

Cluster 3 represents patients with the slowest walking speed and also in this case the ankle is the most representative joint of the cluster. The peculiarity of this cluster was the greatest reduction of ankle range of motion in all the sagittal, coronal, and transverse planes. A severe equinus foot (even if included in the cluster with significance at $P < 0.01$) was present throughout the stance phase. The hip joint was characterized by high flexion attitude in the sagittal plane associated with pelvic anteversion to compensate for ankle stiffness.

Cluster 5 was mainly characterized by a pattern with external rotation of the hip, hyperextension of the knee joint in the stance phase, and reduced knee flexion during the swing phase associated with equinus-abducted foot.

As stated previously, it is very difficult to try to make comparisons with data from Kinsella and Moran study [15], the only one which took into account foot equinus deformity as responsible for gait impairment. Both characteristics of patients and gait analysis protocol used were in fact different from those of the present study. Even more difficult is the comparison with other studies where a cluster analysis on gait pattern in stroke patients was carried out [11–13]. In these studies, in fact it is never specified whether patients presented an equinus foot. The only consideration we can attempt to make is that patients with lower velocity of the third group in Kinsella and Moran study [15] were also the patients with the most abnormal gait pattern of all the subgroup, with a severe equinus foot dysfunction. A muscle weakness of dorsiflexors and plantarflexors was hypothesized to be responsible for the slow gait in this group of patients, as previously suggested also by Mulroy et al. [11]. In these clusters, the use of an ankle foot orthosis was considered helpful. Clusters identified in the present study in terms of large amount of motion, stiffness, or quite normal kinematics would be of interest, supported by clinical examination, in delineating homogenous groups for decision making with respect to prescribing orthotics, chemodenervation, surgery, or only exercise.

This is the first study which takes into account objectively, besides the hip and knee joints, kinematic deviation of the ankle-foot complex in the three planes of space that reveals information of interest for appropriate therapeutic intervention. However, a limit of this study is the lack of clinical assessment of range of motion and level of spasticity in the patients, which might have contributed to better explaining dynamic dysfunction during gait. Being a retrospective study, it was not possible to retrieve such clinical information for all the patients. Furthermore, to simplify the interpretation of the many gait parameters included in the cluster analysis only variables with significance at $P < 0.001$ were included. The analysis of other variables, which have a role in the clusters, although with less weight, might reveal other useful information.

5. Conclusion

The definition of homogenous multiple clusters helped us to identify speed-related patterns of walking in hemiplegic patients, with particular attention to the ankle-foot complex.

All the patterns characterized by greater reduction in speed showed an equinus deformity of the foot that (1) might be responsible for slow speed when a joint instability in all planes is present (cluster 1), (2) may consist of significantly reduced ankle range of motion in all the planes associated with hip flexion for progression (cluster 3), and (3) might be associated with externally rotated pattern at the hip, extensor pattern at the knee, and foot abduction (cluster 5). Faster patterns were instead related to the absence of severe impairment at the foot-ankle complex or to a rigid foot, with lesser involvement of the upper joints.

Future research should aim at exploring the effects of intervention in modifying the ankle-foot complex dysfunction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Telerehabilitation in Poststroke Anomia

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Anomia, a word-finding difficulty, is a frequent consequence of poststroke linguistic disturbance, associated with fluent and nonfluent aphasia that needs long-term specific and intensive speech rehabilitation. The present study explored the feasibility of telerehabilitation as compared to a conventional face-to-face treatment of naming, in patients with poststroke anomia. Five aphasic chronic patients participated in this study characterized by: strictly controlled crossover design; well-balanced lists of words in picture-naming tasks where progressive phonological cues were provided; same kind of the treatment in the two ways of administration. ANOVA was used to compare naming accuracy in the two types of treatment, at three time points: baseline, after treatment, and followup. The results revealed no main effect of treatment type ($P = 0.844$) indicating that face-to-face and tele-treatment yielded comparable results. Moreover, there was a significant main effect of time ($P = 0.0004$) due to a better performance immediately after treatment and in the followup when comparing them to baseline. These preliminary results show the feasibility of teletreatment applied to lexical deficits in chronic stroke patients, extending previous work on telerehabilitation and opening new vistas for future studies on teletreatment of language functions.

1. Introduction

Patients suffering from neurological disorders due to stroke or other brain injuries require intensive and long lasting treatments. Several national rehabilitation guidelines suggest that a reduction of hospitalization time followed by the delivery of treatment at home improves patients' outcomes and reduces costs. Nevertheless, a high percentage of discharged patients do not receive adequate motor and speech rehabilitation care, because of high staff costs and geographical barriers.

Impairment of language functions represents the second most disabling *sequela* following motor impairment and the most common cognitive deficit caused by cerebral lesions. It has been estimated that one-third of poststroke patients suffer from aphasia [1].

Aphasia is an acquired communication disorder, caused by a lesion of the brain structures involved in the processes of comprehension and production of oral and written language [2]. Lexical impairments are frequently present in aphasia and anomia is one of its principal manifestations. Anomia is associated with a breakdown in retrieving words for spoken language production. It impacts the ability to formulate sentences and participate in functional communicative exchanges, therefore, negatively conditioning the patients' quality of life as well as the lives of family members and caregivers [3].

The conventional treatment for aphasia usually begins during hospitalization in the intensive rehabilitation unit. The therapeutic management of aphasia is a long-term process that frequently does not end with a complete recovery of language and communicative functions. For many patients the progress toward functional communication is steady but slow, while other patients need to be assisted to learn compensatory strategies for an effective social communication.

However, after discharge the complex *sequela* associated with stroke reduce patient's autonomy and the possibilities to reach the rehabilitation centre.

Moreover in rural areas, travel distances limit the access to specialized services affecting the quality and the quantity of rehabilitation interventions for speech disorders.

Because of the often chronic nature of the language and communicative deficits in aphasia and the difficulties that patients have in accessing specialized service providers, the ongoing management of chronic communication disorders represents a challenge for speech-language pathologists (SLPs) [7]. Recent advances in telecommunication technology have driven the development of telerehabilitation, the delivery of rehabilitation services via information and communication technologies [8] to provide rehabilitation care to patients discharged at home.

Telerehabilitation allows for continuity of service through the entire rehabilitation cycle including assessment, intervention, consultation, and education, and it has recently emerged as an effective support to provide rehabilitation care to patients discharged at home [9]. Furthermore, recent studies have shown that early discharge from hospital coupled with home treatment significantly increases clinical outcomes in poststroke patients, by affording early reintegration and positively enhancing quality of life [10, 11].

Telerehabilitation in the field of speech-language pathology has increasingly been endorsed as an appropriate model of service delivery by professional organizations in different countries. The position statement of the American speech-language and hearing association (ASHA) is that "telepractice is an appropriate model of service delivery for the professions of audiology and speech-language pathology," because it "may be used to overcome barriers of access to services caused by distance, unavailability of specialists and/or subspecialists, and impaired mobility" and offers "the potential to extend clinical services to remote, rural, and underserved populations" [12].

Although speech-language pathology services lend themselves to telerehab applications, these are relatively new to the field of speech-language pathology. Some studies showed good reliability between conventional face-to-face and remote assessment and treatment [13, 14] on voice and articulation disturbances [15, 16]. Less studies involved aphasic deficits [17, 18] and specifically on lexical retrieval [19].

The aim of the present study was to explore the feasibility of telerehabilitation as compared with conventional face-to-face treatment of naming. Anomia treatment could be a good topic to compare the same treatment in different modalities because it allows a rigorous and controlled methodology, as well as quantitative measures of outcome.

2. Materials and Methods

2.1. Participants. We selected 5 poststroke consecutive chronic patients among 32, examined by the speech and language pathologists at IRCCS San Camillo Hospital in Venice and at Grosseto Hospital, from January to August 2013. The patients were characterized by

(i) having a single left ischemic stroke and aphasic disturbances persistent from 2 years or more;

(ii) anomic deficits as evidenced by the Aachen Aphasia Test (AAT) [20] (naming less than 80% of correct items);

(iii) comprehension good enough to understand the tasks of the study (AAT score more than 55% of correct items);

(iv) absence of additional neuropsychological deficits (scores 30%) on attentional abilities and on nonverbal intelligence evaluated by visual search [5] and Raven's progressive matrices [6].

Patients' demographic and clinical characteristics are presented in Table 1.

The cognitive and linguistic profiles are presented in Table 2.

All subjects gave written informed consent and the study was approved by the human ethics committee.

2.2. Experimental Design. The overall design of the study is shown in Figure 1. Participants first performed a baseline naming task repeated twice (see Section 2.4). Moreover, they underwent neuropsychological and linguistic assessments before entering treatment (Table 1).

Subsequently, all participants carried out two versions of the naming treatment: face-to-face treatment and teletreatment. The presentation of the first and second treatment was counterbalanced across participants in such a way that some participants began with the face-to-face treatment and some with teletreatment. There were eight sessions of equal duration for each treatment program. In each session, participants performed a confrontation-naming task whereby they were asked to name pictures of concrete objects presented on a computer screen. In the face-to-face treatment, participants sat in the room with a speech-language pathologist whereas during teletreatment the therapist communicated with the participant over the Internet. There was a three-week washout period after the first treatment cycle, during which no therapy was administered.

At the end of each treatment condition, participants' naming was assessed to determine short-term treatment efficacy. Three weeks after the completion of the treatment, participants were assessed again to determine long-term treatment efficacy (followup).

The outcome measure was naming accuracy (percent correct) on the therapy set, taken at baseline, immediately after the therapy, and three weeks later (followup). To examine for possible generalization effects to untreated items, we compared accuracy on treated items with control nontreated items. For all posttherapy measures, both treated and control items were presented in a random order. Baseline refers to naming accuracy on an individually defined set of items, which was equal to zero before treatment.

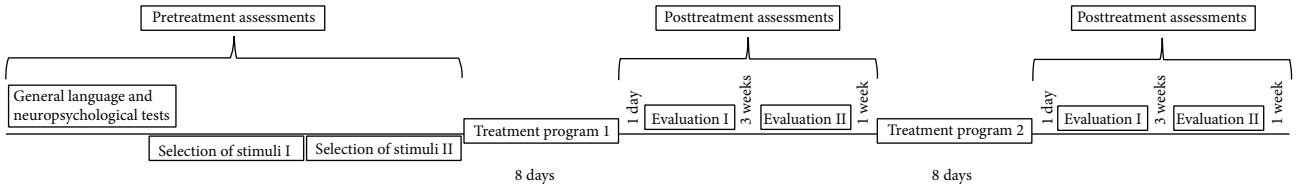


Figure 1: Experimental design.

Table 1: Demographic and clinical characteristics of patients.

Pts	M/F	Age (yrs)	Prevalence (R/L)	Language	Lesion	Site (TAC or RMN)	Aphasia	Time from onset (yrs)
1 G.D.	M	57	R	Monolingual Italian	Ischemic	P-O	Wernicke	2
2 F.L.	M	71	R	Monolingual Italian	Ischemic	T-P	Wernicke	3
3 L.V.	M	66	R	Monolingual Italian	Ischemic	F-T-P Caudatus, Posterior Putamen	Broca	4
4 E.M.	F	63	R	Monolingual Italian	Ischemic	Insular	Broca	4
5 A.C.	M	70	R	Monolingual Italian	Ischemic	Frontal and Insular	Broca	3

Table 2: Linguistic and basic cognitive profile of the recruited patients (% correct).

	G.D.	F.L.	L.V.	E.M.	A.C.
AAT subtests (% correct)					
Token test	40	30	14	44	76
Repetition	44.6	78.6	72	83.3	92
Written language	63.3	94.4	7.8	18.8	80
Naming	50	52.5	13.3	54.2	79.0
Comprehension	74.2	73.3	57.5	67.5	96.6
Phonemic fluency[a]	N.A.	21	8	7	8
Semantic fluency[a]	15	13	2	10	31
Neuropsychological tests					
Attention[b]	51.7	81.7	30.0	36.7	63.3
Nonverbal intelligence[c]	77.8	86.1	36.1	47.9	39.6

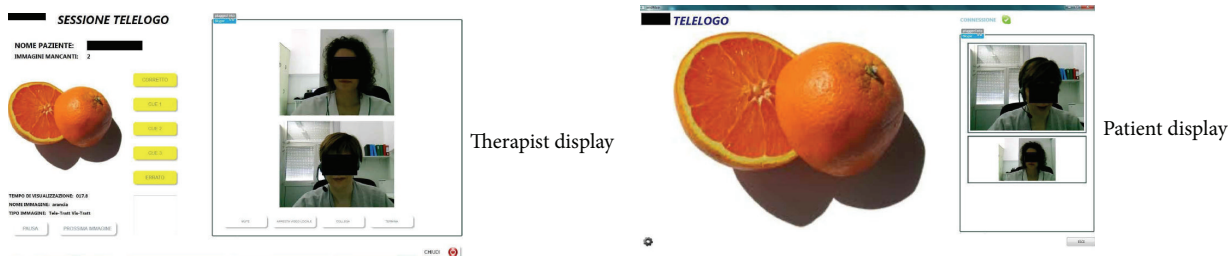
[a]Phonemic and semantic fluency: raw score (Novelli et al., 1986 [4]); [b]Visual Search (Spinnler, 1987 [5]); [c]Raven's progressive matrices (Carlesimo et al., 1996 [6]); NA: not applicable.

2.3. Neuropsychological Assessment. Standardized batteries were used to test general language and neuropsychological abilities in our patients (see Table 1). The standardized Italian version of the Aachen Aphasia Test (AAT) was used to describe patients' general language performance and the severity of anomia. Lexical ability was also assessed using the phonemic verbal fluency test (F.A.S.) and the semantic verbal fluency test [4]. To exclude additional neuropsychological deficits that could preclude the treatment, we also assessed attention by means of attentive matrices and nonverbal intelligence, by means of Raven's progressive matrices.

2.4. Stimuli. Two separate pretreatment baseline sessions were performed on different days. In each session, participants were asked to name a set of 255 pictures. Pictures were displayed on a computer screen for up to ten seconds, using customized presentation software (see below). If participants failed to name the picture within this time frame, the therapist advanced the trial to the next item and marked the item incorrect. Items that were scored incorrect on both pretreatment sessions were used to construct individual treatment and control lists for each participant. There were two treatment lists (face-to-face treatment and teletreatment) and two control lists (face-to-face control list and teletreatment control list) per participant. The four lists had different words and the same number of items and were balanced for word frequency, word length (in syllables), familiarity, concreteness, and age of acquisition. The words used were selected from a database for which naming norms and several psycholinguistic measures are available [21] and the pictures were colored photos.

2.5. Software and Materials. The pictures were presented on a computer screen using customized software. The software runs on Windows 7 or XP and allows for remote communication between the therapist and the patient using an embedded Skype platform. The application displays two different interfaces: (a) the therapist's display and (b) the participant's display. The therapist's display controls and registers all experimental information including participant information, training session, and image display. The participant's display in the teletreatment condition shows 2 windows: an interactive window with the therapist (who appears on video) and a window with the target pictures (see Figure 2). In the face-to-face version, the participant's display shows only the window with the target pictures. The customized software was installed on two Intel based 17″ laptops connected to the Internet and equipped with internal video cameras and external headphones. The Skype program was only enabled during teletreatment.

2.6. Treatment. During each treatment session, target pictures were presented once for naming on a computer screen in a random order. If no response was given within 10 seconds or the response was incorrect, progressive phonemic cues were provided by the therapist. A maximum of three



(a) (b)

Figure 2: Two interfaces (one for the therapist and one for the patient) used during teletreatment.

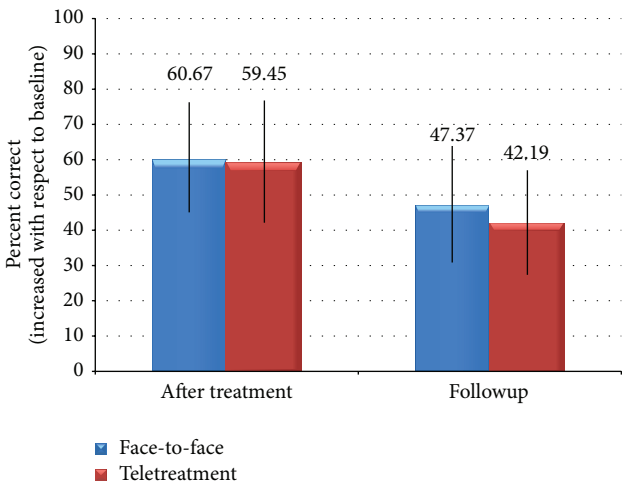


Figure 3: Patient's improvement on naming treated items compared to baseline naming performance.

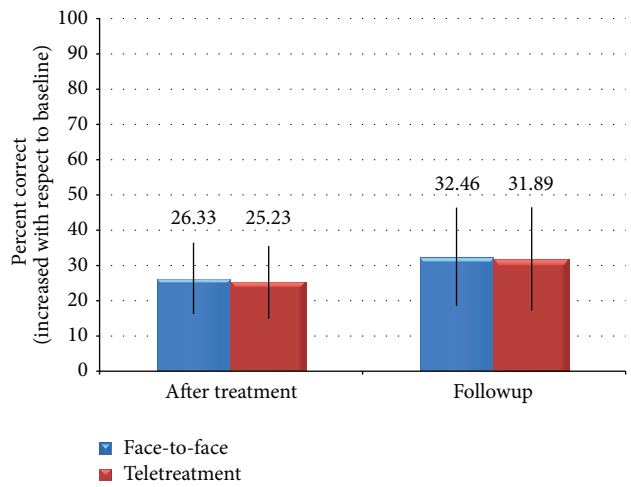


Figure 4: Patient's performance on nontreated items with respect to baseline performance.

consecutive cues were provided per picture (ranging from the initial phoneme to the full name). If the participant failed to produce the correct target word after cueing, the therapist named out loud the target asking the patient to repeat it. The same procedure was followed in the face-to-face and the teletreatment versions.

2.7. Statistical Analysis. Analyses of variance (ANOVAs) were used to compare naming accuracy in two treatment conditions (face-to-face and teletreatment) at three time points: baseline, after treatment, and followup (3 weeks after the end of the treatment). ANOVAs were also used to examine performance on nontreated items.

3. Results

All patients completed the study. Difficulties on the use of computer at home or on acceptance of teletreatment did not emerge.

3.1. Effects of Anomia Treatment on Treated Items. Picture-naming performance on the treated items was evaluated before and after training. The percentage of items named correctly before and after treatment is shown in Figure 3. A 2× 3 ANOVA with treatment type (face-to-face, teletreatment) and time (baseline, immediately after treatment, and 3 weeks after treatment) revealed a significant main effect of time ($F(2, 24) = 11.29$, $P = .0004$, and $\eta^2 = .48$), no main effect of treatment type ($F(1, 24) = .04$, $P = .844$, $\eta^2 = .0008$), and no interaction between factors ($F(2, 24) = .02$, $P = .98$, and $\eta^2 = .0008$). Post-hoc Tukey's HSD tests showed that patients performed significantly better immediately after the treatment ($P < .01$) than at baseline. There was no evidence that the treatment effect declined at followup. The patients' performance immediately after treatment did not differ from the performance 3 weeks after treatment.

3.2. Effects of Anomia Treatment on Control Items. Generalization of picture-naming performance on nontreated items was evaluated after training. The percentage of correct naming in posttraining measurements is shown in Figure 4. A 2 × 2 ANOVA with treatment type (face-to-face, teletreatment) and time (immediately after treatment, followup) revealed no main effect of time ($F(1, 16) = .27$, $P = .613$, and $\eta^2 = .016$), nor treatment type ($F(1, 16) = .004$, $P = .947$, and $\eta^2 = .0002$), and no interaction between factors ($F(1, 16) = .0004$, $P = .98$, and $\eta^2 = .00002$).

In the comparison between treated and control items, we observed a main effect of item type immediately after training ($F(1, 16) = 6.25$, $P = .02$, and $\eta^2 = .28$), due to a better performance on treated ($\sigma = 60.06$, $\delta = 34.77$) as compared to control items ($\sigma = 25.78$, $\delta = 21.52$). There was no main effect of treatment type ($F(1, 16) = .01$, $P = .934$, and $\eta^2 = .0003$) and no significant interaction between factors ($F(1, 16) = .00$, $P = .996$, and $\eta^2 = 9 \times 10^{-6}$).

In the followup, there was no main effect of item type ($F(1, 16) = .71$, $P = .41$, and $\eta^2 = .04$), no main effect of treatment type ($F(1, 16) = .04$, $P = .8504$, and $\eta^2 = .002$), and no significant interaction between factors ($F(1, 16) = .02$, $P = .880$, and $\eta^2 = .001$).

4. Discussion

In this study we compared the effects of anomia therapy provided face-to-face with anomia therapy provided remotely via cost effective internet connections.

Various studies already showed the feasibility of telerehabilitation for assessment and monitoring of aphasic disorders in poststroke patients; some of these demonstrated a good reliability between face-to-face and remote consultation [7, 17, 22]. But only three previous studies were focused on a remote home based treatment of poststroke aphasic patients: two authors [19, 23] in small studies with three and two patients, respectively, highlighted a good feasibility of teletreatment, but they did not deal with the question of comparing it with a face-to-face treatment.

The third study [24], a case study on one patient, presented a comparison between the two treatment types and a third treatment based on daily independent practice.

To our knowledge, our study is the first one comparing the effects of two different treatment delivery types (remote and face-to-face), both based on the same treatment procedure and applied to a single group of patients. The selection of patients who experienced a stroke two or more years before allows us to exclude any interference of spontaneous recovery.

In the evaluations administered immediately after the treatments, we found a significant improvement on treated items in both, telerehabilitation and face-to-face conditions; we did not find differences in the percentages of correct items between the two ways of treatment.

These data confirm the feasibility of teletreatment in poststroke patients, as suggested by previous authors [13]. In particular, our results indicate that a specific treatment of lexical deficits in aphasia using tailored and controlled activities can be achieved via an Internet-based videoconferencing system.

Notwithstanding the reduced sample size of the present pilot study, we observed statistically significant effects in either type of treatment with respect to the corresponding baseline assessment and no difference between treatments. These results highlight that the teletreatment of naming deficits of poststroke chronic patients seems to be as effective as the conventional face-to-face treatment. Still, increasing the sample size and evaluating the effects of the treatments in patients with different profiles constitute avenues for future development.

In the followup evaluations, three weeks after treatments, we observed a decline of correct items, similar for both kinds of treatment, not statistically significant with respect to the posttreatment evaluations. A similar decline has been reported in previous studies [19, 25], but the short time interval between posttreatment and followup evaluations prevents us from any assumption regarding the maintenance or the loss of the improvements.

Moreover, all patients successfully completed the study and none experienced major problems in handling the system. The videoconferencing platform allowed the therapist to provide all the assistance needed, including the cues and the feedback. Thus we can consider that neither the lack of physical interaction between patient and therapist nor the technical complexities of the system hampered the effectiveness of the teletreatment.

This consideration is consistent with the conclusions of various studies on teletreatment of motor deficits after stroke, which evidenced the clinical equivalence of a remote and a face-to-face motor treatment [14, 26, 27].

Taking together these remarks, it is possible to hypothesize a future development of telerehabilitation towards more complex applications able to supply poststroke patients, early discharged at home, with a complete telerehabilitation program (motor, speech, and cognitive), similar to that received during the hospitalization.

5. Conclusions

Our results are encouraging and indicate that the treatment of naming deficits from remote is not inferior with respect to the conventional face-to-face treatment. These results, consistent with a few other small studies, suggest the opportunity to implement the current software also for other language components (i.e., phonology, semantics, morphology, syntax, etc.) to provide a more appropriate intervention.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Reinforced Feedback in Virtual Environment for Rehabilitation of Upper Extremity Dysfunction after Stroke: Preliminary Data from a Randomized Controlled Trial

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Objectives. To study whether the reinforced feedback in virtual environment (RFVE) is more effective than traditional rehabilitation (TR) for the treatment of upper limb motor function after stroke, regardless of stroke etiology (i.e., ischemic, hemorrhagic). *Design*. Randomized controlled trial. *Participants*. Forty-four patients affected by stroke. *Intervention*. The patients were randomized into two groups: RFVE ($N = 23$) and TR ($N = 21$), and stratified according to stroke etiology. The RFVE treatment consisted of multidirectional exercises providing augmented feedback provided by virtual reality, while in the TR treatment the same exercises were provided without augmented feedbacks. *Outcome Measures*. Fugl-Meyer upper extremity scale (F-M UE), Functional Independence Measure scale (FIM), and kinematics parameters (speed, time, and peak). *Results*. The F-M UE ($P = 0.030$), FIM ($P = 0.021$), time ($P = 0.008$), and peak ($P = 0.018$), were significantly higher in the RFVE group after treatment, but not speed ($P = 0.140$). The patients affected by hemorrhagic stroke significantly improved FIM ($P = 0.031$), time ($P = 0.011$), and peak ($P = 0.020$) after treatment, whereas the patients affected by ischemic stroke improved significantly only speed ($P = 0.005$) when treated by RFVE. *Conclusion*. These results indicated that some poststroke patients may benefit from RFVE program for the recovery of upper limb motor function. This trial is registered with NCT01955291.

1. Introduction

Stroke is one of the most serious neurological disorders rated as the third cause of death worldwide [1]. Epidemiological data indicates a mortality of 30% in the first month after stroke independently from the type of cerebrovascular injury, while only 10% of patients was discharged from hospital without serious functional or cognitive impairments [2]. Among the survivors to a first stroke onset, 73% to 88% result in acute hemiparesis [3]. Indeed, the disruption of motor function is a major source of impairment affecting both upper and lower limbs, frequently impeding autonomy in the activities of daily living (ADL) [4, 5]. It was estimated that at least 60% of the patients affected by stroke present severe reduction in the ability to perform ADL [4, 6, 7], requiring an intensive rehabilitation care particularly focused on the recovery of the upper limb motor function.

Several studies using fMRI and transcranial magnetic stimulation (TMS) in humans provided evidence that functional adaptation of the motor cortex following stroke is still possible [4, 8–12]. Changes of cerebral activation in the sensory and motor systems occur early after stroke and may be a first step toward the restoration of motor function. Furthermore, many studies have demonstrated that neuroplasticity can occur even in case of chronic stroke [4, 13]. In fact, it was noted that task-oriented exercises induce regenerative capacities of the central nervous system (CNS), in poststroke patients [8, 14]. It was also noted that plasticity of the CNS, thus its adaptability to natural developmental changes [14, 15], is maintained lifelong regardless of age [16].

The traditional rehabilitation approaches based on one-to-one physiotherapist-patient interaction are the most widespread for the treatment of the upper extremity in clinical settings and its effectiveness was demonstrated by several studies [17–19]. However, recent evidence is enlightening the possibility that innovative approaches, based on the augmentation of specific kinematic feedbacks, could enrich the rehabilitation environment, possibly leading to a significant improvement of the motor function [20–24]. Innovative technologies have provided the opportunity to enrich the environments where motor rehabilitation program is carried out. This enrichment could potentially facilitate the physiological activation of the brain areas devoted to motor relearning. Following these principles, exercises should involve multiple sensory modalities exploiting the adaptive nature of the nervous system, in order to promote active patient participation [25]. Previous evidence has demonstrated that training in virtual environment promotes learning in normal subjects, as well as in poststroke patients, underpinned by the providing of augmented feedbacks related to motor performance and result [26–30]. Moreover, other effects dependent on the interaction with virtual environments were measured at cortical activation level using functional magnetic resonance imaging (fMRI). To date, neuroimaging evidence showed that reorganization of the motor cortex and related motor recovery were changed significantly after virtual reality based treatments [9, 13, 31]. As a consequence, reinforced feedback in virtual environment (RFVE) can promote the recovery of motor function in poststroke patients, by means of regular, intensive, and supervised training [5, 32, 33].

The first aim of the present study was to determine whether the RFVE was more effective than traditional rehabilitation (TR) treatments for the recovery of upper limb motor function after stroke. The second aim was to study whether any difference exists on the effect of RFVE, due to stroke etiology (i.e., hemorrhagic, ischemic).

2. Methods

2.1. Study Design and Participants. A single blind randomized trial was run considering as eligible the inpatients accepted at the Neurorehabilitation Department of IRCCS San Camillo Hospital Foundation (Venice, Italy). The patients enrolled were randomized in two groups (RFVE or TR) according to a simple randomization technique. In the RFVE group the patients were treated one hour a day by the experimental treatment and one hour a day by TR treatment. In the TR group the patients underwent two hours daily of TR training. Both treatments lasted 5 days weekly for 4 weeks.

The inclusion criterion for patients enrollment was the diagnosis of a first stroke (ischemic or hemorrhagic) occurring at last 1 year before the enrollment and never treated before with RFVE. The exclusion criteria were clinical evidence of severe cognitive impairment (i.e., a score lower than 24 points at the Mini-Mental State Examination), clinical history of neglect, the presence of complete hemiplegia (i.e., Fugl-Meyer upper extremity scale = 0 pts.), sensory disorders (i.e., a score lower than 16 points at sensibility subitem of the Fugl-Meyer scale), and history of traumatic injuries (e.g., fracture, joint dislocation with permanent dysmorphism after trauma) impairing the upper limb motor function.

The institutional review board of the IRCCS San Camillo Hospital Foundation approved the study protocol. All patients were informed about the aim and procedures of the study and written informed consent was obtained from all participants.

2.2. Interventions. The experimental and control rehabilitation programs lasted two hours a day, for five days a week, for four weeks. The patients allocated to RFVE group, were treated using the "Virtual Reality Rehabilitation System" (VRRS-Khymeia Group, Ltd., Noventa Padovana, Italy) composed by a PC workstation connected to a 3D motion-tracking system (Pohlemus LIBERTY Colchester, Vermont, US) and a high-resolution LCD projector displaying the virtual scenarios on a large wall screen. During the virtual reality treatment the subject was seated in front of the wall screen grasping a sensorized real object (i.e., ball, disc, or glass) with the paretic hand; in case of severe impairment of grasping the sensor was fixed to a glove worn by the patient (Figure 1). The real object, held by the subject, was matched to the virtual object displayed on the wall screen through an electromagnetic sensor placed onto the dorsal face of the hand (i.e., end-effector). The virtual scenarios could be created by the physiotherapist recording the movements carried out by himself while grasping the same sensorized object used for the patients. In the virtual scenario, the therapist determined the location of the starting position, the target to reach for each task, and the path to follow. Additionally, virtual obstacles in the arm workspace could be displayed with the aim of increasing the complexity of the motor task. A simple reaching movement could accomplish just a straight path, whereas others required more complex movements (Figure 2). Hence, the therapist created a sequence of motor tasks that the patient was asked to perform on his workstation along the therapy session. The physiotherapist determined the complexity of the task, tailored on patient's motor deficit.

The patients allocated in the TR group, were treated with the aim of reducing impairments and improving ADLs. Traditional stroke rehabilitation programs emphasize functional training to promote the individual recovery and to maintain the subjects as much independent as possible. The traditional rehabilitation for the upper extremity consisted of exercises of various movements in a horizontal or vertical plane. Also in the case of TR treatment the rehabilitation program was planned in accordance with the patients' current capacity. For each patient individual exercises were selected with progressive complexity and they were asked to perform exercises for postural control, exercises for hand preconfiguration, exercises for the stimulation of manipulation and functional skills, and exercises for proximal-distal coordination. All the exercises were performed with or without the assistance of a physiotherapist. To achieve the requested goal patients were asked to perform various movements, such as shoulder flexion and extension, shoulder abduction and adduction, shoulder internal and external rotation and shoulder circumduction, elbow flexion and extension, forearm pronation and supination, and hand grasping-release and clenching

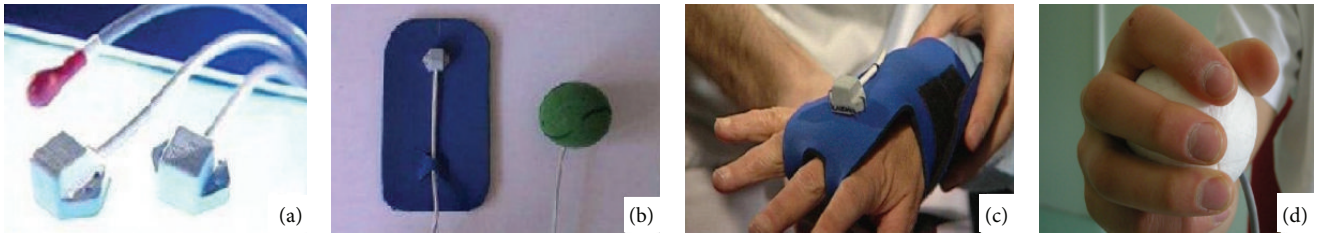

Figure 1: (a) Type of receivers, (b) application of receivers to different end-effectors, (c) sensorised glove for the application of receiver in case of severe motor deficit, and (d) modality of end-effector application in case of grasping being preserved.

Figure 2: The same motor task represented from lowest to highest complexity.

into a fist. We introduced exercises such as, for example, the following: to strengthen the shoulder abductors patient was asked to abduct their shoulder with their elbow extended, to strengthen the shoulder flexors the patient started with their arm down beside their body and finished the movement with their arm above the head, (movement was performed keeping the elbow straight), to improve the ability to reach the objects the patient was instructed to pick up the object and place it on the table in front of them and then put it back again, and to stretch or maintain range of the wrist joint the subject was asked to supinate and pronate their wrist through full range of motion according to the requested task.

2.3. Outcome Measures. The functional assessment included the Fugl-Meyer upper extremity (F-M UE) scale and the Functional Independence Measure (FIM) as measurements of motor function and independence, respectively. Furthermore, we conducted a kinematics analysis of the paretic arm considering as outcomes the mean linear velocity (speed), the mean duration of movements (time), and the mean number of submovements (peak). The kinematic assessment consisted of eight exercises (i.e., elbow extension, elbow flexion, shoulder adduction, reaching movement, forearm pronation/supination, shoulder abduction, shoulder flexion, and shoulder internal/external rotation), each one repeated 10 times. Patients were informed about the movement aim and sample movements were performed before the measurement to familiarize with the system. All the functional and kinematics assessments were conducted at the beginning and at the end of the treatment in both groups. The requested tasks during kinematic assessment were different from those used for RFVE treatment and TR training.

2.4. Data Analysis. The distribution skewness was studied with the Kolmogorov-Smirnov test and according to the results parametric or nonparametric tests were used to determine if the outcomes were statistically different in the comparison within and between groups. The enrolled patients were stratified a posteriori according to stroke etiology (i.e., ischemic, hemorrhagic) both in experimental and control groups. A subgroup analysis was run on the strata resulted for comparing any significant difference in the considered outcomes due to the kind of stroke. Statistical significance was set at $P < 0.05$ and IBM SPSS 20.0 package software was used for the analysis.

3. Results

A group of 120 eligible patients accomplishing the inclusion/exclusion criteria was screened; among them 46 were enrolled for randomization and allocated to RFVE ($n = 23$) and TR ($n = 23$) groups, respectively. During the study 2 patients dropped out from the TR group because they were discharged from the hospital earlier. Thus, data from 44 subjects that completed the intervention were included for the analysis. The complete flow of the trial is reported in Figure 3.

The overall group consisted of 29 (66%) men and 15 (34%) women, 24 (55%) patients affected by ischemic stroke and 20 (45%) by hemorrhagic stroke. The participants had a mean age of 64.3 ± 12.6 years and were enrolled in the study at a mean distance from stroke of 4.2 ± 3.1 months. All patients reported to be comfortable throughout the training and did not experience any side effect caused by interaction

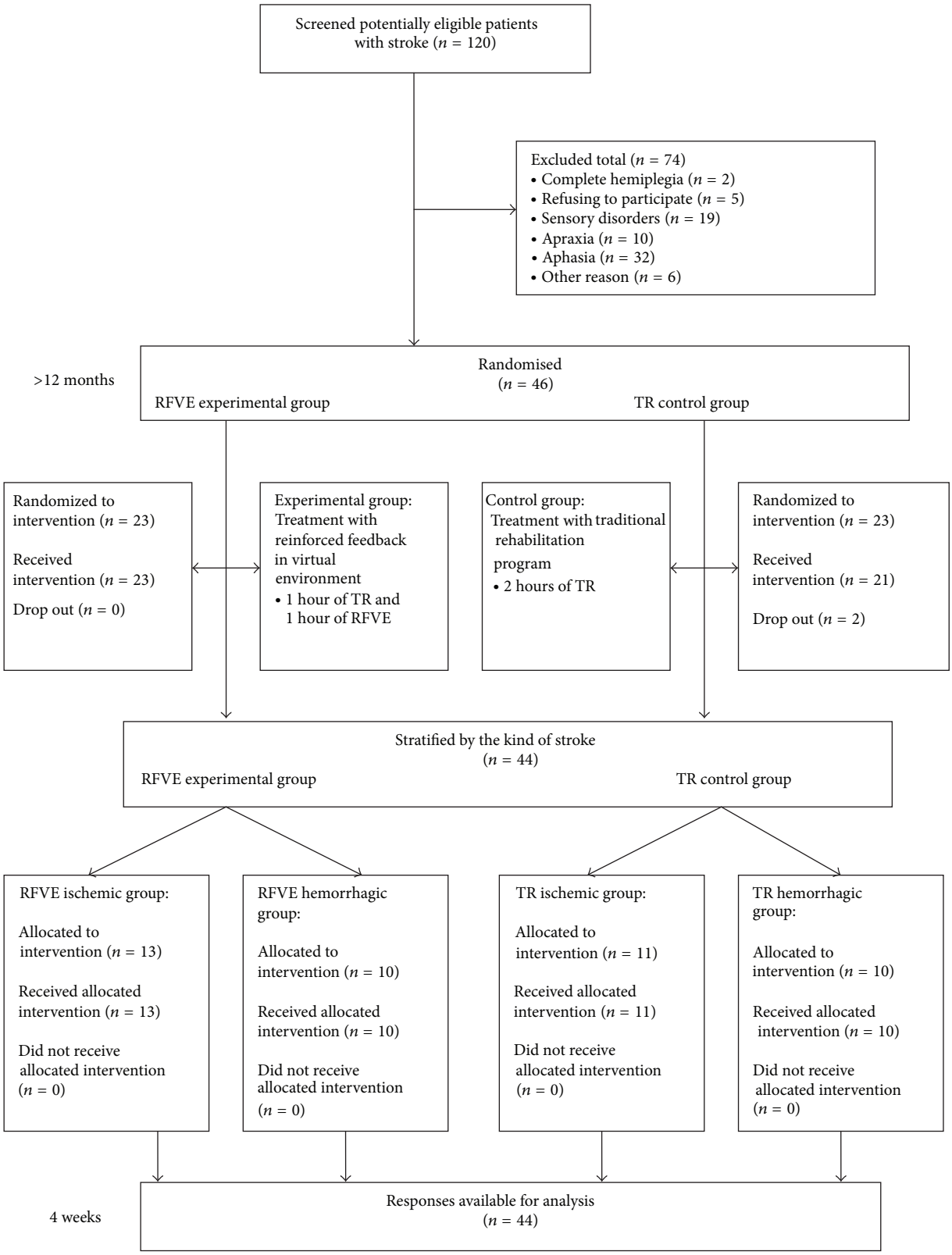

Figure 3: Flowchart of participants through the study.

with virtual environment (e.g., nausea, dizziness, headache, disorientation) [34].

The RFVE group consisted of 13 (57%) ischemic and 10 (43%) hemorrhagic stroke patients, 14 (61%) men and 9 (39%) women. The mean age was 63.1 ± 9.5 while the mean distance from stroke onset was 3.7 ± 2.3 months. The TR group consisted of 15 (71%) men and 6 (29%) women; moreover, 11 (52%) were affected by ischemic stroke and 10 (48%) by hemorrhagic stroke. The patients' mean age was 65.5 ± 14.2 years, and mean time since stroke onset was 4.8 ± 3.6 months.

All the outcomes were comparable between groups (i.e., F-M UE, $P = 0.306$; FIM, $P = 0.329$; time, $P = 0.768$; speed, $P = 0.590$; peak, $P = 0.841$), at baseline. Also the demographics characteristics were comparable (i.e., time from stroke, $P = 0.206$; age, $P = 0.289$; sex, $P = 0.602$).

Considering the overall groups, the results showed that FIM changed significantly after both treatments (RFVE group: $P = 0.001$; TR group: $P = 0.006$), while F-M UE scale improved significantly after RFVE training ($P = 0.001$) but not after TR treatment ($P = 0.053$). All the kinematics outcomes changed significantly after RFVE (time, $P = 0.001$; speed, $P = 0.001$; peak, $P = 0.001$) and TR (time, $P = 0.028$; speed, $P = 0.018$; peak, $P = 0.045$) treatments (Table 1).

The RFVE treatment showed to be significantly more effective than TR treatment, as measured by F-M UE (RFVE: 10.3%, TR: 4.8%; $P = 0.030$), FIM (RFVE: 12.5%, TR: 6.4%; $P = 0.021$), time (RFVE: 41.0%, TR: 15.6%; $P = 0.008$), and peak (RFVE: 26.1%, TR: 21.1%; $P = 0.018$), while speed did not change significantly between groups after therapy (RFVE: 35.7%, TR: 20.5%; $P = 0.140$).

With regard to subgroup analysis of patients following hemorrhagic stroke, all the outcomes improved significantly after the RFVE treatment (i.e., F-M UE, $P = 0.012$; FIM, $P = 0.005$; time, $P = 0.001$; speed, $P = 0.001$; peak, $P = 0.001$), while only FIM ($P = 0.035$), time ($P = 0.001$), and speed ($P = 0.001$) changed significantly after TR treatment (Table 1). Moreover, RFVE gained better results than TR treatment at FIM (RFVE: 17.5%, TR: 10.2%; $P = 0.031$) and time (RFVE: 41.5%, TR: 23.5%; $P = 0.034$).

With regard to subgroup of patients affected by ischemic stroke all the outcomes improved significantly after RFVE treatment (F-M UE, $P = 0.009$; FIM, $P = 0.004$; time, $P = 0.001$; speed, $P = 0.001$; peak, $P = 0.001$), while only speed ($P = 0.030$) and peak ($P = 0.004$) changed significantly after the TR treatment (Table 1). Moreover, only speed was significantly better after RFVE (40.5%) than TR (17.3%) treatments ($P = 0.005$). Finally, only FIM scale ($P = 0.035$) was significantly different between ischemic and hemorrhagic stroke patients undergoing RFVE treatment.

4. Discussion

In this study, we compared the effects of an innovative rehabilitation modality called reinforced feedback in virtual environment with the ones gained by traditional rehabilitation treatment for the recovery of upper limb motor function after stroke. The results demonstrated the therapeutic effect of the RFVE treatment, sustaining the beneficial integration with the TR treatment. When combined, the TR and the RFVE treatments seem to regain a better motor function compared to the recovery induced by the simple augmenting of the conventional rehabilitation program intensity. The RFVE showed significant better effects than conventional treatment, confirming the evidence coming from previous studies [27, 29, 32, 35]. Indeed, also kinematic outcomes showed a significant improvement, after the RFVE than the TR treatment. Moreover at the end of both treatments patients were asked to complete the satisfaction questionnaire. The result provided positive patients' feedback regarding the performance of 2 hours of treatment in both groups. The absence of statistically significant improvement within TR group in F-M UE scale may be explained as a result of patients dropped out from the control group. Moreover, the results from subgroup analysis showed contradictory results compared with findings from overall groups. The time from stroke was comparable between groups, but it should be acknowledged that a mean difference over 1 month may be clinically relevant, requiring a stratified analysis according to distance since stroke onset for future reporting of the complete trial. Considering these limitations, patients following hemorrhagic stroke seem to take greater advantage from RFVE treatment than ischemic and TR patients. In addition, data demonstrated that the effect of RFVE therapy is beneficial independently from stroke etiology (i.e., hemorrhagic, ischemic) for both motor and ADL functions.

Although the neural mechanisms associated with practice dependent motor recovery are not clearly understood, it has been suggested that intensive and repetitive use of the affected limb, as those stimulated by RFVE, may induce positive effect on neuroplasticity and improvement of motor function [5, 36]. Movement relearning implies a process of motor actions' selection in order to perform the requested task. We argued that in our proposal different paradigms (e.g., reinforcement learning, supervised learning) operate to promote motor learning, based on the feedbacks received from the artificial environment. In reinforcement learning the subject estimates directly meaningful information on the performed movement. This learning is based on knowledge of the results (KR), which in the RFVE training is represented by the score of each single movement, and on knowledge of the performance (KP), which in the RFVE training is represented by the trajectory of every trial displayed at the end of every session. In supervised learning paradigm the subject receives from a teacher a prompt to adjust the movement execution; in RFVE training such feedback is represented by a "virtual teacher" showing the correct movement execution in real time [37–39]. Based on these paradigms, we hypothesized that the treatment in virtual environment has an impact on the functioning of the upper limb. The motor and functional changes observed may have led to a reorganization of the cerebral cortex related to the affected limb.

The results from this study, even if preliminary, demonstrated the potential impact of the use of technology in clinical settings to tailor the rehabilitation sessions with the aim of increasing the intensity and specificity of practice. The findings demonstrated the feasibility of using RFVE to improve meaningfully the outcomes along the rehabilitation process after stroke. According to our sample size calculation

Table 1: Effects of experimental and control treatments on functional and kinematics outcomes.

	RFVE		TR	
	Pre-test	Post-test	Pre-test	Post-test
Overall				
Functional				
F-M UE	43.0 ± 14.7 (36.64–49.36)	49.8 ± 12.5*§ (44.42–55.32)	46.3 ± 17.5 (38.36–54.31)	49.5 ± 16.2 (42.13–56.92)
FIM	87.6 ± 29.6 (74.82–100.48)	103.3 ± 22.9*§ (93.44–113.26)	96.6 ± 24.6 (85.35–107.80)	104.6 ± 18.2* (96.32–112.91)
Kinematics				
Time (s)	11.7 ± 17.4 (9.75–13.61)	6.9 ± 8.4*§ (5.94–7.80)	9.6 ± 13.2 (8.03–11.27)	8.1 ± 11.1* (6.73–9.45)
Speed (cm/s)	15.7 ± 6.9 (14.93–16.46)	21.3 ± 11.2*§ (CI 20.04–22.52)	15.6 ± 7.1 (14.74–16.48)	18.8 ± 10.6* (17.54–20.14)
Peak (*n*)	13.4 ± 12.6 (12.03–14.81)	9.9 ± 12.6* (8.53–11.32)	12.8 ± 11.6 (11.39–14.22)	10.1 ± 12.8* (9.36–12.50)
Posthemorrhagic group outcomes				
Functional				
F-M UE	38.6 ± 19.3 (24.74–52.46)	47.6 ± 15.1* (36.79–58.41)	47.6 ± 17.5 (35.03–60.17)	51.5 ± 16.4 (39.75–63.25)
FIM	71.0 ± 32.2 (47.96–94.04)	93.1 ± 28.8*§ (72.49–113.71)	94.8 ± 26.0 (76.18–113.42)	107.7 ± 17.2* (95.37–120.03)
Kinematics				
Time (s)	13.5 ± 18.9 (10.40–16.69)	7.9 ± 9.0*§ (6.44–9.42)	8.5 ± 7.0 (7.21–9.82)	6.5 ± 7.2* (5.18–7.86)
Speed (cm/s)	15.1 ± 6.7 (14.40–16.63)	20.1 ± 10.1* (18.44–21.81)	16.3 ± 7.1 (15.02–17.65)	20.5 ± 9.3* (18.73–22.18)
Peak (*n*)	15.4 ± 13.7 (13.17–17.73)	11.6 ± 12.7* (9.54–13.77)	13.0 ± 12.6 (10.67–15.34)	11.2 ± 11.9 (8.99–13.40)
Postischemic group outcomes				
Functional				
F-M UE	46.3 ± 9.2 (40.77–52.0)	51.6 ± 10.5* (45.22–58.01)	45.1 ± 18.2 (32.92–57.44)	47.7 ± 16.6 (36.53–58.92)
FIM	100.4 ± 20.6 (87.98–112.95)	111.2 ± 13.6* (103.0–119.46)	98.1 ± 24.4 (81.73–114.64)	101.8 ± 19.4 (88.75–114.89)
Kinematics				
Time (s)	10.1 ± 16.0 (7.75–12.55)	6.0 ± 7.8* (4.83–7.17)	10.5 ± 16.5 (7.83–13.26)	9.3 ± 13.3 (7.13–11.50)
Speed (cm/s)	15.8 ± 7.1 (14.79–16.91)	22.2 ± 12.0*§ (20.43–24.02)	15.0 ± 7.0 (13.88–16.20)	17.6 ± 11.4* (15.70–19.43)
Peak (*n*)	11.7 ± 11.3 (10.06–13.45)	8.5 ± 12.3* (6.65–10.35)	12.6 ± 10.7 (10.88–14.40)	10.7 ± 13.5* (8.50–12.95)

Data are displayed as mean and standard deviation and 95% confidence interval in brackets.
RFVE: reinforced feedback in virtual environment training; TR: traditional rehabilitation treatment; F-M UE: Fugl-Meyer upper extremity; FIM: functional independence measure; time: mean duration of movement; speed: mean velocity of movement; peak: mean number of submovement; $^{*}P < 0.05$ within group analysis (Wilcoxon test); $^{\S}P < 0.05$ between group analysis (Mann–Whitney *U* test).

(with F-M UE scale as primary outcome) a minimum of 136 subjects should be enrolled to complete the study ($\alpha = 0.05$ and $\beta = 0.8$).Therefore, a bigger sample and more complex RFVE tasks are needed to confirm our preliminary data and to validate the findings.

5. Conclusion

Our results revealed that the application of augmented feedback by means of RFVE treatment combined with the TR program is more effective than the same amount of conventional rehabilitation treatment to reduce the upper limb dysfunction after stroke. The RFVE treatment augments the effects of the upper limb movement supporting the reacquisition of accurate motor control. The positive results indicate that the application of RFVE treatment is promising to reduce the impairment of the upper limb and may be clinically relevant for stroke rehabilitation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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