CONCURRENT NEUROPLASTIC AND BEHAVIORAL IMPROVEMENTS INDUCED BY UPPER-EXTREMITY REHABILITATION POST-STROKE

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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To my Mom and Dad, who have always been right next to me
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CONCURRENT NEUROPLASTIC AND BEHAVIORAL IMPROVEMENTS INDUCED BY UPPER-EXTREMITY REHABILITATION POST-STROKE

By

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Chair: Carolynn Patten
Major: Rehabilitation Science

Stroke is the leading cause of adult disability worldwide, with the most persistent motor impairments affecting the upper-extremity (UE). Among survivors, 73-88% present with sensorimotor impairments affecting UE function and 55-75% present with difficulties using the arm for daily living activities. The related physical disability compromises these individuals’ autonomy, may affect their psychosocial functioning and contributes to depression and reduced quality of life. While this problem is well recognized, identification of effective approaches for rehabilitation of UE hemiparesis has been elusive. This knowledge gap points to an urgent, unmet need to better understand the neural mechanisms of UE motor recovery post-stroke and develop mechanism-based interventions that promote restoration of UE motor function.

The long-term goal of this research is to restore UE motor function for persons post-stroke. The overall objective of this dissertation, which is the next step towards attainment of our long term goal, is to understand how therapeutic interventions for post-stroke hemiparesis affect key neural mechanisms that mediate motor recovery. The central hypothesis holds that an intervention that includes dynamic, high-intensity resistance training, induces positive changes at both behavioral and neurological levels...
by increasing central neural drive of the impaired hemisphere. This hypothesis is based on the notions that the most disabling impairments post-stroke are due to weakness in the affected limb, and also that dynamic resistance training post-stroke can help alleviate weakness through profound neural adaptations. Traditional clinical perspectives favor practice of functional tasks over resistance training because high-exertion activities were assumed to increase spasticity and impair motor performance.

This dissertation includes four studies in persons post-stroke which demonstrate that interventions including resistance training are harmless and induce more significant improvements in strength, upper-extremity function, restoration of more normal movement patterns and neurophysiologic adaptations (including reflex and transcranial magnetic stimulation responses) compared to functional task practice performed in isolation.
CHAPTER 1
INTRODUCTION

1.1 Upper Extremity Motor Dysfunction and Neural Mechanisms Post-stroke

1.1.1. Motor Dysfunctions Post-stroke

Stroke is the leading cause of adult disability worldwide. According to the World Health Organization, 15 million people suffer stroke each year, and fewer than 40 percent recover completely over the course of rehabilitation. The most persistent stroke-related motor impairments affect the upper-extremity, with approximately 80 percent of individuals presenting with sensorimotor impairments affecting arm function and about 65 percent presenting with persistent difficulties in using the affected arm for daily living activities, such as eating, writing, bathing and dressing. The resulting disability compromises stroke survivors’ autonomy, may have detrimental effects on their psychosocial functioning and reduce their quality of life. The prevalence and persistence of these motor deficits point to an urgent need to develop effective rehabilitation interventions that promote restoration of normal upper-extremity motor function.

Hemiparesis is the most common consequence of stroke and is characterized by loss of dexterity; spasticity, which involves components of both hyperreflexia and hypertonia; weakness, and potentially learned non-use. Here we address the most important manifestations of upper-extremity hemiparesis post-stroke and seek to identify the mechanisms that contribute to these manifestations of motor dysfunction.

1.1.1.1. What is spasticity?

Classically defined, spasticity is a velocity-dependent resistance to passive muscle stretch. The phenomenon of spasticity involves two components: hypertonia –
increased mechanical resistance to stretch, and hyperreflexia – exaggerated reflex activity in resting muscles.

Krakauer\textsuperscript{12} suggests, the primary neural mechanism that contributes to spasticity is related to loss of cortical inhibitory control on brain stem motor nuclei and spinal monosynaptic reflex circuits. Spasticity is comprised of increased resting muscle tone, hyperreflexia, and, in some cases, clasp knife phenomenon from the loss of inhibition on flexor reflex afferents. Spastic signs are elicited at rest, but the degree to which spasticity plays a role during actual movement remains uncertain\textsuperscript{12}.

Traditional perspectives in neurorehabilitation\textsuperscript{13} held that spasticity imposed the greatest impairment to motor function and represented the most significant limitation to motor recovery. Moreover, because spasticity appeared to be exacerbated with exertion, any form of high-effort activity was strictly proscribed in neurorehabilitation\textsuperscript{13}. Contrary to these beliefs, contemporary investigations have demonstrated first that spasticity is not a primary impairment to functional movement, moreover, acute bouts of effortful activity do not exacerbate spasticity\textsuperscript{14-16}. Further, one contemporary review suggested evidence for the harmlessness of high-exertion training, such as resistance training, in exacerbating muscle spasticity\textsuperscript{16}. Several studies have demonstrated the lack of a significant functional relationship between spasticity and functional motor performance\textsuperscript{12}. Thilmann et al.\textsuperscript{17} studied the stretch-induced EMG responses and found that, compared with controls, persons post- stroke had increased resistance to limb displacement at rest but not when the arm was actively moving, suggesting that spasticity does not contribute to motor control abnormalities in hemiparesis. In another study, Thilmann et al. studied both the stretch-induced EMG (hyperreflexia) and torque
(hypertonia) responses. They found that hypertonia was associated with muscle contracture rather than with reflex hyperexcitability, and detected no relationship between hypertonia and either weakness or loss of dexterity. Another study on 95 persons post-stroke showed that severe functional disability occurred almost equally either in the presence or absence of spasticity.

As mentioned, Patten et al.\textsuperscript{18} compared hyperreflexic and hypertonic responses using passive stretches imposed under controlled velocity conditions after high-intensity resistance training and functional task practice. These authors showed that high-intensity resistance training actually improved stretch-reflex response modulation.

In support of the importance of resistance training post-stroke, a recent review\textsuperscript{19} suggested that the presence of weakness post-stroke could aggravate spasticity in many ways, including: reduced traffic in descending pathways responsible for voluntary movement; muscle fiber atrophy and contracture; changes in the spatial and temporal patterns of muscle activation, causing an inefficient EMG-torque relationship; loss of functional motor units and changes in the properties of remaining units, producing a decrease in maximal force due to activation on a suboptimal portion of the force-length relationship\textsuperscript{20-25}.

Taken together, such observations shift the focus of neurorehabilitation away from spasticity, toward weakness as a prominent problem and introduces the potential attention of neurorehabilitation to high-intensity training.

\textbf{1.1.1.2. Dexterity}

Dexterity is the ability to coordinate muscle activity to meet environmental demands and is not limited to tasks involving the hand\textsuperscript{26}. Bernstein defined dexterity as the ability to adequately solve any motor task...precisely, quickly, rationally and deftly,
where flexibility with respect to the changing environment is an important feature\textsuperscript{27}. Canning et al.\textsuperscript{26} conducted a study to determine the relative contribution of strength and dexterity to function during recovery after stroke and to determine the predictive value of initial strength, dexterity and function on long-term function post-stroke. Interestingly, these authors found that strength and dexterity account for 71 percent of the variation in function in the six months post-stroke. The largest contribution of function was made by the shared component of strength and dexterity, implying that strength and dexterity interact during the production of motor behavior. However, strength also made an additional, separate, contribution to function. The authors suggested that this additional contribution of strength was related to the fact that strength is a prerequisite of movement; without enough strength, it is not possible to function. This study suggested therefore that loss of strength, and not dexterity, is the major contributor to physical disability post-stroke. Further, the study suggested that either strength and/or dexterity measured in the early stage can satisfactorily predict later function post-stroke. The overall findings of this study suggested that, when significant weakness is present, exercise designed to increase strength will likely decrease disability\textsuperscript{26}.

Several authors have attempted to study dexterity post-stroke; however, most of these used clinical assessments such as the Wolf Motor Function Test, the Fugl-Meyer Assessment, the NIH Stroke Scale or the Purdue Pegboard, which are usually insufficient to explain the subtle deficits of dexterity\textsuperscript{28}. Three-dimensional motion analysis, including kinematic, electromyographic and kinetic variables, is a sensitive tool to characterize abnormal dexterity post-stroke\textsuperscript{7, 29, 30}. For example, reach-to-grasp movements require accurate planning and execution of hand transport towards the
objects and adjustment of grip aperture in anticipation of the object’s proprieties.
Kinematic evaluations showed reach-to-grasp movements with the hemiparetic arm in stroke patients are slower and less accurate than in healthy controls. The additional prerequisite for executing dexterous tasks is the ability to produce, maintain and modulate grip forces. Compared to healthy controls, grip forces post-stroke are usually less coordinated and more variable in both the hemiparetic and non-paretic arm.

Nowak et al. quantified dexterity comprehensively at both hands using kinematic recording of finger and hand tapping, a reach-to-grasp movement, quantitative analysis of grip forces in a grasp-lift task and clinical rating scales. The authors found that, although most pronounced at the contralesional hand, the timing, accuracy and efficiency of reach-to-grasp and grasp-lift movements were significantly impaired in both hands. Also, the severity of impaired dexterity was not related to which hemisphere was affected and was similar for distal (grasping) and proximal (reaching) muscle groups of the arm, regardless of the performing hand. Finally, several performance deficits in the timing, accuracy and efficiency of reach-to-grasp and grasp-lift movements revealed strong correlations with clinical measures of hand function and sensory loss.

Buma et al. conducted a recent review of serial imaging studies investigating recovery of dexterity within 6 months post-stroke and identified trends in the association between task-related brain activation patterns and functional upper-limb recovery. Twenty-two of the 869 studies identified met the inclusion criteria. One important point to the authors in selecting the studies was their internal validity. The authors excluded studies that did not specifically measure dexterity of the paretic limb. Importantly, they did not consider clinical scales (or activities of daily living) as appropriate measures of
dexterity. After stroke, motor task performance showed unilateral overactivation of motor and non-motor areas, a posterior shift in activity in the primary motor cortex, and bilateral recruitment of associated motor and non-motor areas. Overactivation appeared to diminish longitudinally in parallel with neural recovery, but not in all individuals\textsuperscript{32}.

In addition, the authors suggested the future research should: use outcomes that specifically measure dexterity of the paretic limb and control for the extent of white-matter damage by using diffusion tensor imaging (DTI) and transcranial magnetic stimulation (TMS) to investigate changes in corticospinal tract integrity\textsuperscript{32}. Further, they suggested that measures of coordination dynamics should accompany serial imaging studies relating to recovery and cortical activation patterns to separate behavioral compensation from behavioral recovery\textsuperscript{32}.

Another study investigated the neural substrates of impaired finger tapping post-stroke. Using a light accelerometer they evaluated the regularity of index finger movements and generated a regularity index. The authors found significant correlations between the affected-hand regularity index and the functional magnetic resonance imaging response within the contralesional dorsal premotor and prefrontal cortices. Decreased tapping regularity was associated with increased activation of both premotor areas and prefrontal areas, contralesionally. These findings suggest involvement of the contralesional dorsal premotor and prefrontal areas in affected-hand functions post-stroke, and consequently a possible involvement in recovery of dexterity.

1.1.1.3. Learned non-use phenomenon

The phenomenon referred as learned non-use was described by Taub et al. (1966), and it probably corresponds to what Henry Meige (1904) described using the expression functional amnesia\textsuperscript{33}. 

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Taub’s learned non-use theory arose from experiments on deafferentation of a single forelimb in monkeys. Deafferented animals did not use of the forelimb spontaneously. However, restricting movement of the intact limb for several days could lead to spontaneous use of the deafferented limb. Furthermore, if the movement of the deafferented limb was prevented immediately after surgery and for the next 3 months, then use of the deafferented limb did not reveal any overt residual consequences. Wolf\textsuperscript{34, 35} proposed the use of this theory for the recovery of the upper-limb post-stroke in humans. Extension of this theory from deafferented monkeys to stroke in humans does not have experimental verification, but it is supported by clinical studies of constraint-induced movement therapy (CIMT) in improving upper-limb function post-stroke\textsuperscript{36}. CIMT is a treatment intervention in which the patient is strongly encouraged to use the affected arm while the unaffected arm is immobilized or constrained. This treatment is meant to help patients overcome learned non-use. Van der Lee\textsuperscript{37} argued that CIMT is no more effective than an equal dose of bilateral therapy and that CIMT is most effective in individuals with sensory disorders/hemineglect. The authors argued also that our knowledge of the learned non-use phenomenon in humans post-stroke and the possible pathological mechanisms behind it is still poorly developed\textsuperscript{37}.

Van der Lee conducted a review on the effect of CIMT post-stroke including four randomized clinical trials. Although the authors of all four studies reported positive results, the effect size calculated without covariates yielded no statistically significant differences from the control intervention group. In one of the studies a differential effect was found for patients with sensory disorders and hemineglect, leading to the hypothesis that learned non-use may be related to sensory impairments. In addition,
from a clinical relevance point of view, in studies that estimated the minimal clinically importance difference (MCID), the differences from the control intervention group were smaller than an MCID. These results are generally consistent with Taub’s deafferentation observations. The author concluded that the learned non-use theory requires further exploration. The evidence regarding the effectiveness of CIMT is not yet convincing\textsuperscript{37}.

Sunderland et al. studied whether hat CIMT is able to induce improvement in basic motor control. They suggested most of the studies implementing CIMT suffered from some lack of clarity in what is meant by improvement in motor performance. Some might suggest that improvement could be the increased spontaneous use of the paretic arm during daily activities. However, increased use of the arm does not necessarily mean that motor control of the arm is improved. Most of the studies with CIMT measured either gains in spontaneous use, such as tested by the Motor Activity Log, or improvements in function, such as tested by the Wolf Motor Function Test. Therefore, in CIMT studies, it is difficult to discriminate between true behavioral recovery and the use of alternative compensatory strategies. One explanation for the improved arm function and arm use after CIMT may be that impaired motor control does not always directly translate into functional losses because functional success (e.g., task completion) can be achieved using an abnormal movement pattern. The effect of CIMT may be the acquisition of compensatory skills in the use of the paretic arm\textsuperscript{36}. In addition, Sunderland et al. argued that the change in responsiveness of a single muscle to TMS or fMRI activation during motor performance can be explained by both restoration of lost cortical representations and acquisition of new representations for adaptive learning. A
clearer distinction between restitution and behavioral compensation will only be achieved by combining TMS or functional imaging with more detailed behavioral studies.

1.1.1.4. Muscle weakness

Weakness is defined as the inability to generate levels of muscle force under a specific set of testing conditions.

Recent literature suggests that weakness is the major contributor to physical disability post-stroke and that strength at early stages post-stroke can be used successfully to predict function. Several authors reported maximal grip force as a predictor of UE motor recovery and functional independence in acute stroke subjects. In addition, other authors described a relationship between impaired reaching performance, physical disability and learned non-use. A recent review of upper-extremity strength training in stroke found that the technique caused no adverse effects. Further, Harris et al. conducted a meta-analysis of randomized controlled trials from 1950 through 2009 and found evidence that strength training can improve upper-limb strength and function without increasing spasticity or pain in individuals with stroke. Nevertheless, controversy persists because traditionally, clinicians believe that strengthening the paretic upper limb may increase spasticity and impair motor performance.

Weakness involves both neural factors, which consist of the capacity of the nervous system to activate and modulate muscular activity, and muscular factors, which include the capacity of the muscle to generate force according to its physiological cross-sectional area. To generate force voluntarily, the motor areas of our brains must be able
to communicate effectively with the motor neurons in the spinal cord that are responsible for the muscle’s force generation.

Damage of the brain tissue following stroke reduces the communication of the corticospinal and other supraspinal pathways with the lower spinal levels. As a consequence of reduced neural information coming from higher levels, it has been proposed that the spinal cord undergoes a loss of motorneurons and impairment of the primary force-control mechanisms\textsuperscript{21, 24}. However, disuse/non-use and impaired muscle activation could also lead to atrophy and changes in the muscle fibers\textsuperscript{44}, which contribute to secondary weakness post-stroke.

The ability to accurately generate force depends on two strategies: recruitment of motor units and rate coding\textsuperscript{45-48}. Motor unit recruitment is the progressive activation of a muscle by successively recruiting motor units to accomplish increasing gradations of contractile strength. Rate coding consists of increasing the motor unit firing-rate frequency to increase force production (i.e., Henneman’s size principle)\textsuperscript{45, 49}.

\subsection*{1.1.2. Neural Mechanisms Post-stroke}

Force control depends on the integrity of the sensorimotor system, and when injury to sensorimotor areas of the brain occurs, such as in stroke, control of force is impaired. People post-stroke experience a range of force or motor control deficits, including exaggeration of force, which is considered a compensatory strategy to maintain force when sensorimotor processes are affected. In addition, force control post-stroke may exhibit timing deficits, such as impairment in the time required to release force as well as an abnormal time to achieve stable force. Last, even when the required force is achieved, force control post-stroke may create difficulty in maintaining a constant force while executing a task\textsuperscript{20, 50}.
Because functional muscle force is the product of both muscular and neural factors, damage to either of these factors may produce weakness. It is hypothesized that neural factors are the predominate cause of weakness in neurologic pathologies, including post-stroke hemiparesis, because of the significant brain lesion. However, secondary inactivity and impaired muscle activation could also lead to atrophy and changes in the muscle fibers\(^4\).

1.1.2.1. Activation impairment

Damage to the brain tissue following stroke reduces the communication of the corticospinal and other supraspinal pathways with the lower spinal levels. With reduced neural information coming from higher levels, the spinal cord undergoes a loss of connectivity to motorneurons and an impairment of the primary force control mechanisms\(^1\)

The literature\(^2\) reveals several changes to the force-control mechanisms post-stroke that occur at the spinal level and include a change in motorneurons (i.e., a loss of motorneurons, or a change in the recruitment order and firing rates of motor units)\(^2\), nerve changes (i.e., a change in peripheral nerve conduction)\(^2\) and muscle change (i.e., a change in the morphological and contractile properties of motor units and the mechanical properties of muscles)\(^2\). It has been suggested that most of such motor unit remodeling could occur between two and six months post-stroke\(^2\).

**Effect of strengthening in the presence of a healthy nervous system.**

Resistance or strength training can increase muscular strength. Literature in the field has demonstrated that the physiological adaptations supporting increments in strength occur within the muscle itself\(^5\). These adaptations consist of an increase in muscle cross-sectional area, called hypertrophy, which occurs 4-6 weeks after training begins.
and is called the hypertrophic phase of strengthening. However, resistance training also induces change within the nervous system\textsuperscript{52}. Enoka\textsuperscript{53} described phenomena that show evidence of the presence of neural adaptation in response to strengthening, such as an increase in a muscle's strength in the absence of muscular adaptations, strength changes in the untrained contralateral limb contralateral, and specificity of strength adaptations to the training movements. The neural phase of strengthening occurs over the first 1-6 weeks of training and is characterized by rapid gains in strength, negligible changes in muscle cross-sectional area, a cross-transfer effect to an untrained homologous limb and increased agonist muscle activation\textsuperscript{54}.

Carroll et al.\textsuperscript{51} suggested that in an undamaged brain, resistance training is associated with an increase in short-term motor-unit synchrony, which is argued to result from changes in synaptic efficacy within the motoneuron pool. This implies that, after resistance training, the number or the strength of the connections to the motoneurons of trained muscles may increase. This suggests that resistance training may improve the synaptic efficacy between the cortico-spinal cells and spinal motoneurons. Further, in an experimental study with healthy volunteers, Carroll et al.\textsuperscript{55} investigated whether resistance training had the capacity to cause adaptations in the motor cortex. Specifically, they determined the effects of resistance training on the magnitude of responses to transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES). Their results demonstrated that a program of resistance training that increases strength alters the input-output properties of the corticospinal pathway. The magnitude of the EMG responses to both forms of transcranial stimulation was smaller following resistance training. Since the same effect of training occurred in

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response to both TMS and TES stimulations, and knowing that TES is less influenced by cortical excitability, the authors concluded that the training effect was due to a change in the functional proprieties of the circuitry within the spinal cord. Specifically, they suggested that a corticospinal input of a given magnitude activated fewer motoneurons with greater synaptic efficacy during muscle contraction than prior to training. Therefore, they excluded the effect of training in the reorganization of the motor cortex.$^{55}$

Other authors used TMS evaluations to demonstrate neural adaptive effects of resistance training with equivocal results. Griffin et al.$^{56}$ demonstrated that four weeks of isometric tibialis anterior training increased MEP amplitude by 32 percent, while Jensen et al.$^{57}$ demonstrated a depression in cortical excitability measured by decreased recruitment curve slopes.

However, recently Falvo et al.$^{58}$ demonstrated that three weeks of resistance training elicited significant strength gains which were accompanied by neural adaptation at the level of the cortex. The authors were able to demonstrate supraspinal adaptations using movement-related cortical potentials (MRCP). MRCPs consist of surface negative potentials, detected at the scalp via electroencephalography (EEG) during voluntary movement. Following training, the authors found MRCP amplitude was attenuated at several scalp sites overlying motor-related cortical areas and the onset of MRCP was anticipated (2% earlier). In conclusion, the 3-week training protocol in Falvo's study elicited significant strength gains which were accompanied by neural adaptations at the level of the cortex. The authors interpreted their findings of
attenuated cortical demand for submaximal voluntary movement as evidence for enhanced neural efficiency as a result of resistance training\textsuperscript{58}.

**Effect of strengthening post-stroke.** As previously mentioned, although weakness is one of the most disabling factors post-stroke and strengthening has been shown to be both harmless and effective, strengthening is not yet part of routine neurerehabilitation programs.

A recent review suggested that first, strength training increases grip strength with a large effect size, 0.95. Since grip strength is a predictor of disability and mortality in older adults\textsuperscript{59}, remediation of low grip strength by strength training should be an important aspect of treatment post-stroke. Second, the review supported the effectiveness of strength training for all levels of upper-limb motor impairment. Specifically, it reports an effect size of 0.45 for stroke with moderate impairment and an effect size of 0.2 for stroke with mild impairment. These findings suggest that strength training may be important for people with moderate impairment post-stroke, while people with mild impairment may benefit more from functional training\textsuperscript{16}.

Kokotilo et al.\textsuperscript{50} conducted a systematic review of neuroimaging studies that examined reorganization of brain function during force production and force modulation after stroke. Their review includes a number of imaging modalities, including functional magnetic resonance (fMRI), TMS, electroencephalography (EEG) and magnetoencephalography (MEG). They conclude that motor reorganization occurs with respect to force generation and modulation after stroke. Key findings across studies were that during force production, increased activation in motor areas, including the undamaged contralesional hemisphere, occurred in people with more severe stroke,
and recruitment of these motor areas often diminished as recovery improved. With respect to force modulation, increased activation in motor areas occurred with greater force generation in people with stroke, and those with more severe stroke showed greater activation with increasing force-production levels. This review, as the author suggested, provided evidence of reduced recruitment of secondary motor areas during force production as a function of time since stroke. Last, brain activation can be shifted by certain rehabilitative interventions in people post-stroke.

Our research team has conducted a set of studies that contribute evidence that resistance training as an intervention post-stroke that can induce restoration of both the neural circuitry and movement patterns.

First, Patten et al.\textsuperscript{60} conducted a randomized clinical trial of upper-extremity rehabilitation to compare the effects of functional task practice, and a hybrid intervention of functional task practice combined with dynamic high-intensity resistance training post-stroke. Further, Patten et al. compared the effects of high-intensity resistance training and hybrid training on stretch-reflex modulation. The findings of this study suggested that first, upper-extremity rehabilitation involving high-exertion activity did not exacerbate either the hyperreflexic or hypertonic components of spasticity in adults post-stroke. Second, they illustrated that high-intensity resistance training promoted a more appropriate modulation of stretch-induced EMG responses. These neurophysiologic adaptations were associated with upper-extremity motor function improvement evaluated with the Wolf Motor Function Test – Functional Ability Scores (FAS). Subsequently, Corti et al.\textsuperscript{61} compared power training (i.e., dynamic high-intensity resistance training) with functional-task-practice training on a battery of clinical scales.
and kinematics of reaching. As previous mentioned, kinematic analysis is more objective than clinical scales and offers a better understanding of the mechanics of arm movement\textsuperscript{62}. Kinematics describe movements of the body through space and time, including linear and angular displacements, velocities and accelerations. Three-dimensional motion capture is therefore a powerful measure for studying upper-extremity kinematics during motor performance in hemiparetic persons\textsuperscript{5}. This measurement approach affords a sensitive, quantitative and reproducible assessment that allows differentiation between compensatory and recovery strategies, which standard clinical scales do not.

1.1.2.2. Inter-hemispheric inhibition (IHI)

Following stroke, activity in the affected hemisphere (AH) is disrupted; not only by the infarct itself, but also by inhibition from the unaffected hemisphere (UH) which further reduces the excitability of the AH. As first described by Ward and Cohen\textsuperscript{63} and more recently stated by Nowak’s\textsuperscript{64} hypothesis of inter-hemispheric competition post-stroke, the primary motor cortex (M1) of the UH becomes disinhibited and exerts exaggerated inhibition onto the M1 of the AH.

Decreased excitability of the ipsilesional cortex has been observed after stroke by using electrophysiological recordings\textsuperscript{65}, cortical stimulation\textsuperscript{66} and functional neural imaging studies\textsuperscript{67}. This decreased cortical excitability has been attributed to damage from glutamate receptor expression from neurons in the infarct zone. As a consequence, it is argued that there is reduced inter-hemispheric inhibition (IHI) via transcallosal pathways from the AH to the UH\textsuperscript{68, 69}. Consequently, the UH becomes disinhibited, creating additional inhibition on the affected hemisphere. Indeed, the magnitude of transcallosal inhibition exerted from the UH is positively correlated with the
severity of the functional impairment of the affected hand. It is possible that inter-hemispheric competition contributes to weakness after stroke.

**Mechanisms for rebalancing inter-hemisphere competition after stroke.** Accordingly, the inter-hemispheric competition hypothesis suggests that balancing excitability between the AH and UH may improve functional behavior in people post-stroke.

Among several innovative, non-invasive techniques for improving motor recovery post-stroke, repetitive transcranial magnetic stimulation (rTMS) shows considerable promise. rTMS involves focused magnetic stimulation applied to the skull to target a particular brain area. In healthy adults, rTMS at frequencies less than 1Hz can suppress motor cortex excitability, causing an inhibitory effect, while at higher frequencies (e.g., >1Hz) rTMS can increase cortical excitability, causing facilitation. The capacity for rTMS to influence cortical excitability contributes to the rationale for its use as a therapeutic adjuvant that may enhance the efficacy of rehabilitation for persons post-stroke. Asymmetric cortical excitability resulting from stroke may promote maladaptive neuromotor strategies. Repeated use of maladaptive, compensatory motor strategies will disrupt normal physiological activity in transcallosal pathways producing an imbalance in the mutual inhibitory projections between hemispheres. Further, modulation of cortical excitability with rTMS may induce synaptic plasticity and promote physiologic activity in transcallosal pathways which, taken together, will potentially limit development of maladaptive neural strategies. In this context, rTMS has been also been proposed as a theoretical approach to restore the balance of inter-hemispheric inhibition post-stroke (e.g., reduce inter-hemispheric competition).
The current literature reveals positive effects of rTMS post-stroke including: modulation of cortical excitability (e.g., MEP amplitude, recruitment curves, motor threshold) towards decreased excitability of the unaffected hemisphere (UH) and increased excitability of the affected hemisphere (AH). However, it is important to note that no studies to date have directly investigated the effects of rTMS on IHI. Thus, support for the theoretical explanation that rTMS rebalances inter-hemispheric inhibition remains to be demonstrated. This current working hypothesis holds that inhibitory rTMS over the UH reduces transcallosal inhibition from the unaffected to the affected/ipsilesional hemisphere and facilitatory rTMS over the AH increases excitability of the AH and increases transcallosal inhibition from the affected to the unaffected/contralesional hemisphere. Consistent with effects noted in healthy individuals, rTMS (trains of stimuli separated by inter-train intervals) has been used in two ways in persons post-stroke: low-frequency (e.g., \( \leq 1 \) Hz) stimulation of the UH to reduce hyper-excitability of the contralesional hemisphere, or high frequency (e.g., \( >1 \) Hz) stimulation of the AH to increase excitability of the ipsilesional hemisphere. A more recent form of stimulation is Theta Burst Stimulation (TBS), which employs repeating bursts of very low intensity, combined-frequency rTMS. Each burst consists of three stimuli (delivered at 50 Hz) repeating at 5 Hz. TBS is also used in two ways: a continuous train of 100 bursts (300 stimuli) (cTBS) is used to suppress corticospinal excitability; while an intermittent pattern (20 trains of 10 bursts, varied ISI, total 600 pulses) (iTBS) is used to enhance corticospinal excitability.

1.2. Strategies for Functional Improvement: Recovery versus Compensation

The terms motor compensation and motor recovery have been used somewhat inconsistently among clinicians and researchers across several disciplines. This
imprecise use of important terms has caused misunderstanding in the definition of goals and motor outcomes of rehabilitation interventions. There is a need for definitions that allow neuroscientists and clinicians to use a common language and that encompass the underlying aspects of a mechanism in order for the terms to be meaningful for neurorehabilitation. Clear definition of these terms will allow for the development of more effective rehabilitation strategies that focus on enhancing compensation and/or recovery.\textsuperscript{78, 79}

In the past, there has been a lack of consistency among researchers and clinicians in the use of terminology that describes changes in motor ability following neurological injury.\textsuperscript{78} Specifically, the terms motor compensation and motor recovery have been used in different ways. The lack of clear definitions for these terms is a potential barrier to interdisciplinary communication. Commonly, the term recovery has been used to refer simultaneously to the restitution of damaged structures or functions and to describe clinical improvements regardless of how these may have occurred. Recently, Levin et al. (2008)\textsuperscript{78} provided unambiguous definitions of recovery and compensation at the neural and behavioral levels. These definitions are provided in Table 1-1.

1.2.1. Behavioral Recovery versus Compensation

Behavioral recovery involves the reappearance of motor patterns present prior to stroke,\textsuperscript{78} while behavioral compensation is the appearance of new motor patterns, including substitution with different, impaired motor components.\textsuperscript{78} Determining whether upper-extremity motor improvements result from recovery is a fundamental issue for developing appropriate rehabilitative interventions that induce restoration strategies. Reinforcing a pattern of compensatory movements, also termed ‘learned baduse’, may, over time, reinforce either substitution or learned nonuse of the affected arm.\textsuperscript{80}
Compensatory patterns may induce processes of recruitment and retraining even in those situations when the nervous system could be capable of higher levels of plasticity including restoration\textsuperscript{81-84}.

At the behavioral level, Levin et al. distinguish between body function (impairment) and activity (function) levels. For body function, the emphasis is on the motor control of movement regardless of task accomplishment. Recovery corresponds to the reappearance of movement patterns present prior to the injury, including normalization of muscle tone, electromyographic activation, movement kinematics and temporal and spatial coordination. Compensation would be associated with the appearance of alternative movement patterns during the accomplishment of the task\textsuperscript{5, 85}. For example, a individual post-stroke may improve the excursion of his arm by using exaggerated trunk displacement instead of using elbow extension and shoulder flexion\textsuperscript{86}.

At the activity level, recovery corresponds to execution of the task using the same end effectors and joints in the same movement patterns typically used by nondisabled people. Compensation is associated with substitution, which means the person accomplishes the task using different end-effectors. For example, stroke patients may be able to open a jar only by stabilizing it against the chest and using only the unaffected hand instead of both hands.

1.2.2. Neural Recovery versus Compensation

Neural recovery is characterized by reactivation in brain areas previously non-activated by the ischemic event and corresponds to restitution or repair of structures to their original state. When one population of neurons dies at the site of injury, it cannot be reactivated and remains in that dead state for remainder of the patient’s life. Also, the areas surrounding the injury may be inactivated, but these areas may be reactivated
by spontaneous recovery or by appropriate intervention. Reactivation of these residual areas is the metaphor of neural restoration. On the other hand, neural compensation is defined as the processes by which residual brain areas take on new or adapted functions to make up for functions of the lost tissue. Neural restoration is characterized by activation in alternative brain areas not normally observed in nondisabled individuals. 

If we recall the definition of plasticity - an observable change in neuronal structure or function - then both neural recovery and neural compensation are examples of neuroplasticity. The functional integrity of residual neural circuits are either restored (recovery) or adapted (compensation) through changes in the synaptic connections within these circuits.

1.2.3. Neural Strategies Supporting Functional Improvement

Different neural strategies can be identified that involve neural recovery and/or compensation and take advantage of the inherent functional redundancy within the brain. These strategies include Restoration, Recruitment and Retraining (Table 1-2). Since these strategies may occur concurrently during rehabilitation, it is not trivial to dissociate them, especially in human studies. Kleim uses another analogy to explain how differently these neural strategies may work:

If a subset of the violin players had been removed, the remaining violin players may simply stop playing because without their comrades the music doesn’t sound the same or the conductor decides not to use them (learned nonuse). There are several ways that the orchestra can adapt to improve the sound of their music. First, the remaining violin players could be asked to continue to play (restoration). The other string instrument players could also be asked to take on a larger role and play their instruments louder or differently (recruitment) to make the music sound more like the original

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1 Kleim JA. Neural plasticity: Foundation for neurorehabilitation. Unpublished manuscript.
score. In neither case are the musicians being asked to play a new instrument; they simply use their existing talents to compensate for the reduced number of violin players. The final strategy might be to ask the other musicians to learn to play the violin and even switch instruments at certain points in the score (retraining). This is a very different kind of strategy and certainly has limits. Cello players might be more readily capable of making that switch than flute players.

The interpretation of this analogy suggests that a person following stroke may have a lesion due to the infarct, which causes neural tissue affected by the injury to be lost. In addition, perilesional tissue areas are also compromised since they were originally connected to the lost tissue area. These areas may re-activate spontaneously or by specific pharmacological treatment to solve secondary effects such as inflammation and edema (restoration). It is possible that they will stay deactivated for the patient’s entire life and that other brain areas will compensate for the function lost (recruitment or retraining). The brain may engage new residual areas that are capable of contributing to the same behavior as the lost tissue (recruitment), or it may engage remote areas to perform the lost function (retraining). These neural strategies may be facilitated by the use of adequate electrical stimuli or particular rehabilitation interventions based on principles of neuroplasticity. While restoration of the neural circuits and brain areas to their pre-stroke condition constitutes neural recovery, recruitment and retraining strategies both correspond to neural compensation. Determining the relation between neural and behavioral recovery and compensation and dissociating the neural strategies from one another is not trivial since they may occur simultaneously. However, identifying these strategies and relating them to functional improvement are the challenges of neurorehabilitation. Meeting these challenges will help to tailor treatment and to enhance the effectiveness of neurorehabilitation interventions$^{81-84}$. 
1.2.4. Appropriate Outcome Measures to Distinguish Recovery and Compensation

Misinterpretation of the concepts of restoration and compensation among clinicians and researchers may be due, in part, to the selection of outcome measures\(^87-\)\(^91\). The selection of appropriate outcome measures is problematic. Selection depends on several factors, such as the various etiologies of stroke, heterogeneity of symptoms, variability of severity, and the possibility of spontaneous recovery after stroke\(^87-\)\(^91\). In addition, another essential factor in selecting outcome measures is establishing which domain of motor function needs to be evaluated\(^87-\)\(^91\).

In the past, clinical outcomes scales meant to measure improvement mainly focused on task accomplishment and were not qualitatively sensitive enough to discriminate improvement in task performance\(^78\). Therefore, with the emphasis placed on task accomplishment, there was little attention paid to the motor control aspects of movement. Without attention to motor control, it was not possible to distinguish between recovery and compensation\(^78\). Recently, some authors tried to classify outcome measures in stroke rehabilitation, summarizing aspects of measurement theory that are pertinent for evaluation measures\(^87-\)\(^91\).

**Neural measures.** Neural measurements correspond to imaging and neurophysiologic techniques\(^78\). These techniques allow us to distinguish the neural strategies underlying functional improvements and therefore to distinguish between neural recovery and compensation. There are a variety of imaging approaches, each offering advantages and disadvantages with respect to spatial and temporal resolution, interpretability, practicability and cost\(^92\). Neural imaging approaches include: computed axial tomography (CAT), diffuse optical imaging (DOI), electroencephalography (EEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET),
magnetoencephalography (MEG), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and tractography. Neurophysiologic approaches include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), electroencephalography, electromyography (EMG) and reflex probes (i.e., stretch reflex and H-reflex techniques). Used concurrently with behavioral probes, these measures allow us to better understand the relationship between behavior and the central nervous system, including the brain and spinal cord.

**Behavioral measures.** In order to distinguish between behavioral recovery and compensation, we need to distinguish between impairments and activity measures. Upper-limb impairment measures include clinical scales such as the Modified Ashworth Scale (MAS)\textsuperscript{25}, Fugl-Meyer Upper-Extremity Motor Score (UEFMS)\textsuperscript{93} and the shoulder-elbow portion of the UEFMMS (30 points)\textsuperscript{94}, the European Stroke Scale (ESS)\textsuperscript{95}, the Chedoke-McMaster Hand and Arm Inventory (CMHAI)\textsuperscript{96} and the Reaching Performance Scale\textsuperscript{78}. Other motor deficits may be quantified in terms of active joint range of motion, muscle strength, and ability to perform movements of individual joints\textsuperscript{1}. More detailed kinematic analysis of motor patterns during the performance of functional tasks would provide even more relevant information about movement patterns and motor compensations\textsuperscript{78}.

Measures of impairment appear to be closely related to the volume of brain loss and are probably the best markers of prognosis\textsuperscript{91}. However, the extent to which measures of impairment relate to the volume of brain loss is not totally apparent. Impairment scales may be most sensitive to change and may have the greatest capacity to differentiate between treatments\textsuperscript{91}. However, for clinical significance, it is
important to relate changes in impairment to changes in activity. Activity measures are the most frequently used primary outcome measure in rehabilitation research. However, most evaluation specifies neither how the task is accomplished nor which compensatory movements were used. Difficulties arise in interpretation of studies that use such clinical and functional tests to indicate recovery because improved scores on these tests may be due to either improvement of the appropriate motor pattern or enhancement of compensatory strategies. On the other hand, activity measurements generally focus on basic activities of daily life (ADLs). A portion of the stroke population sustains complete recovery in ADLs. Thus, measures of ADL exhibit a ceiling effect and may not show a difference in outcome between groups. Other significant limitations, which may reveal differential effects of treatments, may not be captured. A challenge is activity measures are not directly correlated with pathology or impairment, and other factors may influence the outcome (e.g. depression, psychological and social conditions, etc.). More detailed kinematic analysis of motor patterns during the performance of functional tasks would provide more relevant information about movement pattern and motor compensations. Kinematic analysis is a more objective method than clinical scales and offers a better understanding of the mechanics of arm movement. Kinematics describe movements of the body through space and time, including linear and angular displacement, velocities and accelerations. Three-dimensional motion capture is therefore a powerful measure for studying upper-extremity kinematics during motor performance in hemiparetic persons. This measurement approach affords a sensitive, quantitative and reproducible assessment
that allows us to discern between compensatory and recovery strategies, which
standard clinical scales do not.

1.3. Neuroplasticity

1.3.1. Brief History and Key Concepts

The word plasticity entered the English language in the 18th century in the
classical language of materials science, possibly from French or German. By the middle of
the 19th century, it was starting to appear in the language of biology to refer to the
adaptability of an organism to changes in its environment. The use of the term in this
context continued into the 20th century and remains to this day. The roots of the
term ‘plasticity’, in reference to the structure of the nervous system, currently remain
unclear. However, some argue that the psychologist William James was the first to
use the term to describe the nervous system in his classic textbook Principles of
Psychology (1890). He stated:

Plasticity, then, in the wide sense of the word, means the possession of a
structure weak enough to yield to an influence, but strong enough not to
yield all at once. Each relatively stable phase of equilibrium in such a
structure is marked by what we may call a new set of habits. Organic
matter, especially nervous tissue, seems endowed with a very extraordinary
degree of plasticity of this sort; so that we may without hesitation lay down
as our first proposition the following, that the phenomena of habit in living
beings are due to plasticity of the organic materials of which their bodies
are composed.

In contrast to the scholarly view that the adult brain is immutable, James argued
that as neural pathways are repeatedly engaged, they become deeper, wider, stronger,
like ruts in a well-travelled country road.

In 1896, the Belgian, Jean Demoor, published La Plasticité morphologique des
neurones cérébraux (Arch. Biol., Paris, 14: 723-752). Since Demoor did not claim the
novel use of this word, some say Santiago Ramón y Cajal was the first to use it in
Europe. Cajal had indeed used the term plasticity in the transactions of the International Medical Congress held in Rome in 1894. Cajal applied the words dynamism, force of internal differentiation, adaptations [of the neurons] to the condition of the environment and plasticity among others, to describe the potential of the brain to adapt to the environment.

Marinesco in Bucarest and Jean Nageotte in Paris, along with Aldo Perroncito in Golgi’s laboratory in Pavia, and Cajal himself, were the most important early contributors in the field of neuroplasticity. However, it was not for another 50 years that the Oxford English Dictionary recognized the use of plasticity in relation to the nervous system. The current edition of the dictionary attributes the first use to a 1978 article published in Nature on the developing visual system. However, there were numerous references to plasticity of the nervous system in English prior to 1978.

Indeed, in 1949, Donald Hebb, whose theory is often summarized by the phrase, cells that fire together, wire together, proposed a form of synaptic plasticity driven by temporal contiguity of pre- and post-synaptic activity; that is, an increase in synaptic efficacy arises from the pre-synaptic cell’s repeated and persistent stimulation of the post-synaptic cell. This prediction was verified decades later with the discovery of long-term potentiation (LTP), which is the theoretical basis of some of the current rehabilitation therapies. This theory is also called Hebb’s rule or cell assembly theory and states:

Let us assume that the persistence or repetition of a reverberatory activity (or trace) tends to induce lasting cellular changes that add to its stability...When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency,
as one of the cells firing B, is increased. (Hebb, DO. 1949. The organization of behavior, New York: Wiley)

Similarly, in 1953, John Eccles devoted a chapter to Plasticity in the Nervous System in *The Neurophysiological Bases of Mind*. Eccles described alteration in the synaptic efficacy of group Ia afferent synapses on spinal motoneurons subjected to various manipulations such as tetanic stimulation and deafferentation. Eccles postulated the likelihood of similar plastic changes at higher levels of the nervous system, suggesting the phenomena of memory and learning. In *The Physiology of Synapses* (1964), Eccles suggested that plastic alterations in synaptic efficacy underlying learning should be accompanied by morphological changes.

Through the 1960s, the term plasticity appeared frequently and in different contexts, such as Eccles' sense of synaptic plasticity, behavioral plasticity following cerebral lesions, anatomical plasticity as a growth of dendrites in response to environmental enrichment and chemical plasticity as alteration of level of neurotransmitters and metabolites.

During the 1970s, following Eccles' ideas, subsequent studies showed that the cognitive abilities observed in rats raised in enriched environments were accompanied by increased number and strength of synapses in the cerebral cortex. In addition, these studies demonstrated that more specific behavioral training paradigms induced the same kind of changes in neuron structure in a variety of organisms, including: insects, birds and primates. These findings suggested that plasticity is a fundamental property of all nervous tissues and that it has an important property for the sake of rehabilitation: it is experience-dependent. Today, the terms plasticity and neuroplasticity have
entered the everyday scientific vocabulary. But the lack of clear and precise definitions has led to inappropriate use of the terms \(^79, 97\).

1.3.2. Definition of Neuroplasticity

The term neuroplasticity has been so overused without a specific definition that some argue that it has become uninformative\(^81\). It has been used to mean anything from behavioral adaptations to new situations to alterations in the efficacy of individual synapses\(^97\). Jones writes, and Kleim argues that, it is a term that neuroscientists like to invoke when discussing phenomena they vaguely understand\(^81\). While there is no universally agreed-upon definition of neuroplasticity, Kleim\(^2\) recently offered this one:

Any change in neuron structure or function that is observed either directly from measures of individual neurons or inferred from measures taken across populations of neurons\(^81\).

By specifying a measurable change in neuron structure or function, changes in behavior are not, on their own, a measure of neuroplasticity. Behavioral changes may certainly be mediated by neural plasticity, but measures of behavior are not per se direct measures of neural plasticity. Behavioral measures alone do not give information regarding mechanisms that control adaptation of the nervous system to a new environment or to treatment. Similarly, measures of neuroplasticity by themselves do not directly tell us about behavioral adaptations occurring in a new environment or under a new treatment\(^81\).

The essential issue for new rehabilitation scientists is to understand how behavior and neuroplastic processes are interconnected. Our research team think that the connection between neuroplasticity and behavior is bidirectional. Specifically, we are

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\(^2\) Kleim JA. Neural plasticity: Foundation for neurorehabilitation. Unpublished manuscript.
interested in how neuroplasticity supports behavioral changes to induce recovery of normal function, and, vice versa, in how behaviors support neuroplastic processes that induce recovery of neural structure.

1.3.3. Use-Dependent Neural Plasticity in an Intact Nervous System: Motor Learning and Motor Experience

In this section, we will show how learning in the intact nervous system is supported by neuroplasticity. For the sake of simplification, we will refer to research literature that focuses on motor learning; however, similar neuroplastic changes are observed across all forms of learning (such as sensory or cognitive learning) but occur within different neural circuits, depending on the behavior being learned.

Most research showing neuroplastic changes after motor learning uses rat models. Rats can be trained to reach through a slot to retrieve a food pellet located on a ledge outside the training cage. To successfully retrieve the pellet, the rat has to learn to control the reaching movement. Animals trained on the reaching task show changes at the synaptic level, such as dendritic growth\textsuperscript{103}, synaptogenesis\textsuperscript{104} and enhanced synaptic responses\textsuperscript{105} at the forelimb motor cortex. Further, after training, rats show an expansion of wrist and digit movement representations in the motor cortex map derived by brain microelectrode stimulation\textsuperscript{106}. Similar studies using monkeys performing a pellet-retrieving task showed similar effects. After weeks of training, monkeys demonstrate an increase in the finger movement’s representation\textsuperscript{107}.

Studies using transcranial magnetic stimulation (TMS) have demonstrated that short-term activity may induce changes in the human motor cortex. Acquisition of a fine-motor skill through sustained practice over a period of several weeks of complex movements (a five-finger sequence of keystrokes on piano) induced expansion of the
motor cortical map and a decrease in motor threshold of practicing muscles\textsuperscript{108}. In addition, the training led to a functional-behavioral gain as evidenced by improved motor precision (e.g., fewer mistakes while performing the task)\textsuperscript{108}. Similar results were reported for the leg motor area. A 32-minute period of skilled ankle training in healthy humans induced an increased recruitment curve of the tibialis anterior muscle, suggesting that the training increased motor cortical excitability\textsuperscript{109}. In addition short-interval intracortical inhibition, as measured by a paired-pulse TMS technique, was reduced, while no changes were observed in intracortical facilitation\textsuperscript{109}.

A few TMS studies have demonstrated that motor skills highly developed over several years are also associated with long-term changes in cortical reorganization. Motor cortical maps of the first dorsal interosseous muscle in the reading hand of proficient Braille readers are significantly larger than those of the non-reading hand\textsuperscript{110}, while the motor cortical representation of the abductor digiti minimi muscle was reduced. Interestingly, the cortical map in proficient Braille readers correlates with the amount of daily practice\textsuperscript{111}. Indeed, several days of non-reading induced a dramatic reduction in the size of the reading finger cortical map. A group of people who play racquet sports\textsuperscript{112} with many years of high-level experience showed an increase in MEP amplitude, a decrease in resting motor threshold and inter-hemispheric asymmetry in cortical map location\textsuperscript{112}. Thus, the results may indicate that practiced, skilled motor performance could be associated with long-term plasticity of the motor cortex. Similarly, another study investigated interhemispheric inhibition, measured by paired-pulse TMS, in professional musicians who began musical training at an early age\textsuperscript{113}. Conditioned TMS was applied to the hand area of the motor cortex of one hemisphere, followed 4-16
ms later by a test stimulus applied to the contralateral hemisphere. Tests were performed in two conditions: 1) at rest, and 2) with the first dorsal interosseous muscle contralateral to the conditioned hemisphere voluntarily active. Compared to control subjects, conditioned TMS in musicians was 29 percent less effective at reducing the size of the test MEP at rest, and 63 percent less effective in the active condition\textsuperscript{113}. These results may imply that these differences in IHI have functional relevance; however, mechanisms of functional relevance that correlate with reduced interhemispheric inhibition in musicians are still unclear\textsuperscript{113}.

Magnetic resonance imaging studies show augmented activity within premotor cortex\textsuperscript{114} and cerebellar cortex during the early stages of learning\textsuperscript{115}, while a study of the later stages of learning\textsuperscript{116} showed augmented activation of the primary motor cortex. Studies of musicians demonstrated structural plastic changes within motor-brain areas with highly developed motor skills. One study\textsuperscript{117} showed the cortical representation of the digits of the left hand of string players was larger than controls. The effect was smallest for the left thumb, while the right hand did not show differences in the digit representation. The amount of cortical reorganization of the finger digits was correlated with the age at which the subject began to play an instrument. Another study showed that amateur and professional keyboard players have greater gray matter volume within motor and premotor cortices and cerebellum than non-musicians. In addition, the differences in gray matter volume correlated with musical status. Indeed, professional musicians had greater volume than amateurs, who had greater volume than non-musicians. The development of motor skills through years of keyboard playing is
sufficient to induce cortical growth. Most likely, translating the knowledge derived from animal studies, gray matter in musicians reflects dendritic and synaptic growth\textsuperscript{81-84}.

A study\textsuperscript{118} using an innovative imaging technique, diffusion tensor imaging (DTI), supports and advances evidence of activity-dependent plasticity in the human brain. DTI showed differences in white matter architecture between musicians and non-musicians\textsuperscript{118}. Musicians displayed greater functional anisotropy (FA) (the most used indicator of white matter organization at the microstructure level) in the genu of corpus callosum, which the authors hypothesized is the result of the cognitive processes of musical study\textsuperscript{118}. Musicians displayed lower FA in the corona radiata and the internal capsule, which the authors hypothesized as being due to the effects of intensive motor training\textsuperscript{118}. The results of the paper supported the notion that intensive activity (the musical training) leads to distinct plastic changes in white matter architecture.

Findings of all these studies demonstrate that a healthy central nervous system (in animals and humans) is able to adapt to the environment and to activity through plastic changes. Every time we acquire a new motor skill, the nervous system encodes the skill as enduring neurobiological changes. This is called learning-dependent or activity-dependent neural plasticity\textsuperscript{81-84}.

1.3.4. Use-Dependent Neural Plasticity in an Injured Nervous System: a Relearning Process

The functional improvement in an injured nervous system can be associated with a relearning process. Within this perspective, through rehabilitation, patients are guided to re-acquire the ability to produce behavior lost as a result of injury. As such, the nervous system should rely on the same fundamental neurobiological mechanisms it used to acquire the behaviors initially when the nervous system was intact\textsuperscript{81-84}. 
However, the neural environment after injury may be different and may negatively affect the mechanisms underlying learning. First, secondary changes associated with the injury, such as edema and inflammation, may affect the normal functioning of the residual tissue. Further, the neural structure remote to the lesion and without a specific function may substitute for damaged structure through compensatory strategies\textsuperscript{81-84}. In addition to complications within the neural environment, the behavioral signal coming from the hemiplegic body to the injured nervous system also may be abnormal as a consequence of the motor impairments. For example, to maintain function, movement may be performed using compensatory strategies. Appropriate afferent information is one of the fundamental drivers of positive plasticity\textsuperscript{81-84}. Therefore, the neural circuits receiving aberrant afferent information may negatively influence plastic changes. Following injury of the nervous system, therefore, both the changes in the neural and behavioral environments must be considered in the new learning process.

Despite the added complexities associated with injury, Kleim\textsuperscript{81-84} suggested that the same fundamental neural and behavioral signals that drive neural plasticity and support functional change should still be functioning (Figure 1-1). Kleim (unpublished manuscript) elegantly summarized the relearning process in an injured CNS using an orchestra analogy:

Teaching cello players to play music written for the violin is very different from teaching violin players to simply play new violin music. If all brain areas could adapt and perform all functions then rehabilitation would be much easier. In fact we would not need formal therapy as patients could simply relearn the lost behaviors in the same way they learned them in the first way; by interacting normally during daily lives. This is not how the CNS functions. Specific structures are evolutionally designed to perform certain functions and become more and more specialized through life. So there are limits to the capacity for the CNS to acquire new function after injury. Relearning is much harder than learning because we are forced to use a
compromised set of circuits or circuits that may not have been designed to perform the relearned function. Not surprisingly then, the relearning curve will not be as steep as the initial learning curve. Small gains in performance require large amounts of training.

1.3.5. Not All Plasticity is Good

Although neuroplasticity usually has a positive connotation corresponding to changes in the central nervous system that promote functional improvement in development or after injury, neuroplasticity may sometimes support maladaptive changes. These changes can result from abnormalities in the neural and behavioral signals that drive plasticity. One example is dystonia. Dystonia may develop in persons who perform repetitive movements, such as musicians, artists and athletes. Electromyographic analysis of dystonic movements reveals loss of inhibition between agonist and antagonist muscles, excessive finger activation and inability to release muscle contraction. Neuroimaging studies of the somatosensory cortex show alterations in the representations of the hand and fingers. These changes represent a maladaptive cortical plasticity in which the brain is not able to represent the overused fingers distinctly. Specifically, the somatotopic representation of the hand shrinks and enlarges its receptive fields, which extend across multiple digits. Neuroimaging studies in monkeys after excessive repetitive movements show similar findings. In the context of neurorehabilitation post-stroke, it is important to keep in mind that rehabilitation itself can induce plastic changes that are counterproductive. Many patients develop compensatory strategies (bad habits) that are easier to perform than more difficult, but ultimately more effective strategies. These compensatory strategies may induce maladaptive plasticity. The compensatory strategies and the associated neuroplastic changes may reduce the level of functional improvement that can be
achieved. Since true behavioral and neural recovery is not always possible, neurorehabilitation needs to focus on maximizing a balance between compensation and recovery to elicit the maximal functional improvement possible\textsuperscript{81-84}.

1.3.6. Plasticity is not only in the Brain

Traditionally, plasticity was thought to take place only at the brain, but recently clinical and experimental observations indicate that plasticity is ubiquitous in the central nervous system\textsuperscript{125}, including the spinal cord. Inputs from the periphery or from the brain can cause lasting changes in the spinal cord that affect its output\textsuperscript{126,125}. Besides the obvious damage at the brain site following stroke, the spinal cord also may undergo secondary damage\textsuperscript{81-84}. This damage may depend on the lost/impaired inhibition coming from the supraspinal structures and on the lost/impaired afferent information secondary to disuse/non-use and/or anesthesia conditions. Commonly used measures of the spinal-cord circuitry are the stretch reflex (produced mainly by the monosynaptic pathways composed of the primary afferent from the muscle spindle, its synapse on the motor neuron, and the motor neuron\textsuperscript{125}), and its electrical analogue, the H-reflex techniques, evoked by direct electrical stimulation of the primary afferents\textsuperscript{125}. However, while the pathway is spinal, it is subjected to descending influences from the brain that act directly on the motor neuron and on the primary afferent connection, which can affect the stretch and H-reflexes\textsuperscript{125}. Using these techniques, several authors have suggested that post-stroke, the spinal circuitry undergoes plastic changes in both the paretic\textsuperscript{127-130} and non-paretic sides\textsuperscript{68}. A few articles have reported that neurointervention post-stroke might induce changes of both stretch\textsuperscript{18} and H-reflex responses\textsuperscript{131,132}. One important finding in relation to neurointervention-induced plasticity comes from a recent study on healthy subjects\textsuperscript{133}. In contrast to the traditional view that the paired
associative stimulation (PAS)-induced plasticity is cortical in origin, Meunier et al. demonstrated that PAS induces parallel changes in cortical and spinal excitability\textsuperscript{133}. These findings may be utilized to induce and measure spinal cord plasticity after stroke or spinal cord injury.

1.4. Neurorehabilitation-induced Plasticity Post-stroke

1.4.1. Evolution of Neurorehabilitation

Historically, the management of patients post-stroke involved bed-rest and convalescence\textsuperscript{134}. Using Voltaire’s (1694-1778) words, 	extit{the role of the physician is to entertain his patient while nature takes it course}\textsuperscript{134}. The concept of physical therapies developed through the early to mid-1900s to help world-war and polio survivors\textsuperscript{134}. The branch of medicine focusing on active rehabilitation was created and was associated with a shift from do nothing to do something\textsuperscript{134}. Advances in understanding neurological dysfunction, and the observation that patients tolerated and benefitted from physical exercise, influenced the rehabilitative interventions. The observation that patients had better motor outcomes when exposed to an enriched environment rather than bed-rest became even more reported and accepted\textsuperscript{134}. However, the critical aspect that characterized the enriched experience remained unresolved. Distinct approaches to rehabilitation practice emerged in parallel to increasing understanding of the human nervous system and the response to physical intervention. The debate evolved from do something to do something specific\textsuperscript{134}. The questions became, what is the most effective type of therapy? What dosage? Which intensity?\textsuperscript{134}.

Presently, these questions remain unanswered. However, we do know that neural plasticity is a key neurobiological factor in determining functional improvement after injury of the nervous system\textsuperscript{81-84}. The challenge now for neurehabilitation is to figure out
how to identify the critical behavioral and neural signals that drive plasticity within specific neural circuits in order to select or develop novel, more effective therapeutic interventions. Important issues in meeting this challenge are: 1) to appropriately quantify plasticity, and 2) to appropriately quantify behavioral recovery.

A number of innovative methods have been studied during the past 10 years that show promise in restoring upper-extremity function post-stroke. Some of these methods are: robotic therapy\textsuperscript{135}, electrical stimulation (FES)\textsuperscript{136}, task-oriented and repetitive training\textsuperscript{137}, constraint-induced movement therapy (CIMT)\textsuperscript{138}, power training (or dynamic resistance training)\textsuperscript{9, 50} and non-invasive brain stimulation, such as repetitive transcranial stimulation (rTMS)\textsuperscript{139}, theta-burst stimulation\textsuperscript{140}, transcranial direct current stimulation (TDCS)\textsuperscript{64} and paired-associative stimulation (PAS)\textsuperscript{141}. Despite greater evidence of neurorehabilitation-induced plasticity post-stroke in animal models, few studies have demonstrated the effects of the above-listed therapies in inducing neuroplastic changes in humans. The majority of human studies were not able to show whether the therapy was actually inducing plastic changes since the measurement used was not intended to detect neuroplasticity, but rather changes in motor behavior\textsuperscript{81-84}. As mentioned, while it is true that behavioral changes are most likely mediated by neural plasticity, measures of behavior are not themselves direct measures of neural plasticity\textsuperscript{81-84}.

Technological evolution within the past decade led to the introduction of new functional neuroimaging and electrophysiological techniques that have provided substantial insight into the adaptive changes of cerebral networks associated with plasticity and recovery post-stroke. Some recent studies take advantage of these non-
invasive tools to measure neuroplasticity in humans post-stroke. Therefore, here we present studies from both animal and human literature that support neurorehabilitation-induced plasticity by using appropriate techniques to measure and quantify neuroplasticity.

1.4.1.1. Evidence for neurorehabilitation-induced plasticity post-stroke

**Examples in animal research.** A series of studies on monkeys demonstrated processes of motor cortex reorganization following stroke injury. In monkeys not receiving post-injury behavioral training, the remaining, undamaged hand representation decreased in size\(^{107}\). In contrast, monkeys that received post-injury behavioral training showed retention of the hand representation\(^{142}\). In some cases, the hand territory expanded into the elbow and shoulder representation\(^{142}\). Similar examples of restoration occurred after small lesions in monkey somatosensory cortex with rehabilitative training. After training, monkeys showed a reemergence of the representation of the fingertips in areas outside of the infarct where representations were initially lost\(^{143}\). Other studies, in the rat motor cortex, showed that injury post-stroke results in a loss of motor limb representation\(^{144}\). The loss of movement representation was accompanied by a loss of synapses and forelimb motor impairments as the rats had difficulties reaching for food. However, with several days of training on a forelimb reaching task, both synapses and the movement representations could be restored\(^{144}\). The studies demonstrated that rehabilitation training that encourages use of the affected arm or forelimb can re-engage the impaired neural circuits\(^{143,144}\).

**Examples in human research.** As mentioned, few studies have shown evidence for neurorehabilitation-induced plasticity in humans. However, traditional (i.e. functional MRI), innovative neuroimaging (DTI), and electrophysiological techniques (TMS) have
opened a window on the human nervous system that may allow us to understand and measure plastic changes post-stroke. The following rehabilitation techniques have shown some evidence for neuroplasticity in humans.

1.4.1.2. Behavioral interventions

Although many factors affect the phenomenon of neuroplasticity, one of the most important modulators is behavioral experience. Importantly, Xerri et al. suggested that motor maps undergo plastic changes through motor skill acquisition more than through repetitive use alone. Further, compensatory approaches at critical time periods may have a cost in terms of recovery of function.

Relatively few studies have investigated whether the training implemented induced neuroplasticity in addition to behavioral functional improvements. The following will present findings of intervention approaches that included both behavioral and neurobiological outcomes.

Constraint-induced movement therapy (CIMT). Constraint-induced movement therapy (CIMT) forces use of the affected side by restraining the unaffected side. With CIMT, the therapist constrains the patient’s unaffected arm in a sling and/or a mitt. The patient then uses his or her affected arm repetitively and intensively for two weeks, generally.

A functional MRI study demonstrated that two-weeks of CIMT in people post-stroke could induce a reduction of contralesional primary cortex activation. Also, the laterality index \( (LI)^3 \) correlated with the Wolf Motor Function Test. Liepert et al.

\[ LI = \frac{\text{contralateral}-\text{ipsilateral}}{\text{contralateral}+\text{ipsilateral}}; \text{contralateral and ipsilateral activation to the hand movement - LI ranges from -1 (all ipsilateral activation) to 1 (all contralateral activation).} \]
studied intracortical inhibition with TMS and brain activation with functional MRI after two weeks of CIMT post-stroke. After treatment, the authors did not find any change in intracortical inhibition in either hemisphere, although, interestingly, ipsilesional activation was reduced\textsuperscript{147}. Another study demonstrated that CIMT was able to improve scores in the Motor Activity Log and that these improvements were associated with a reduction of overactivation in the ipsilesional hemisphere and an increase in motor map size\textsuperscript{148}. Kim et al. showed that two weeks of CIMT improved motor function as evaluated with Fugl-Meyer, and the 9-hole peg test, induced an increase in ipsilesional brain activation in three subjects and of contralesional brain activation in four subjects\textsuperscript{149}.

**Repetitive task training.** One study used positron emission tomography (PET) during passive elbow movement to study training-induced brain plasticity in severe stroke and demonstrated that task-oriented arm training induced greater activation of the ipsilesional somatosensory cortex than no treatment\textsuperscript{150}.

**Bilateral training.** Luft et al.\textsuperscript{151} demonstrated that bilateral arm training with rhythmic auditory cueing (BATRAC) increased activation of the ipsilesional cerebellum and contralesional primary motor and somatosensory cortices. Brain activation was studied with functional MRI during elbow movements. The authors did not find differences in motor functional outcomes between BATRAC and standard intervention group.

**Motor learning.** Carey et al.\textsuperscript{152} studied hand movement recovery (Box and Block score and tracking accuracy) and cortical reorganization (functional MRI) in people with chronic stroke after an intensive finger movement-tracking program. After treatment,
stroke patients showed an improved laterality index (LI) and increased activation of the ipsilesional motor and somatosensory areas and premotor cortex.\(^{152}\)

**Functional training combined with high-intensity resistance training.** Patten et al.\(^{18}\) demonstrated that an intervention of combined upper-extremity functional task practice and high-intensity resistance training promoted more appropriate modulation of stretch-reflex responses than functional task-practice alone. This neurophysiologic improvement was associated with upper-extremity motor recovery.

Despite the fact that these studies suggest intervention-facilitated recovery, most of them offer no evidence for intervention-induced neuroplasticity. Most have a small number of subjects and often do not provide an appropriate control condition.\(^{153}\) Further, these studies cannot definitely answer the question, does specific motor training induce neuroplastic changes in persons post-stroke?

Importantly, a common feature of the training programs that showed behavioral and neurobiological improvement is high intensity training.\(^{154-156}\) Intensity and repetition are important principles driving plasticity, an idea that supported by several studies in animals but also in humans (studies on musicians).\(^{153}\)

**1.4.1.3. Non-invasive cortical stimulation**

**Repetitive TMS (rTMS).** rTMS consists of regularly repeated stimulation of the cerebral cortex by trains of magnetic pulses.\(^{157}\) rTMS can modulate the excitability of the motor cortex beyond the period of stimulation.\(^{157}\) By convention, stimulating frequencies greater than 1 Hz are referred to as high- frequency rTMS and have been shown to increase corticospinal synaptic excitability, while stimulating frequencies lower than 1 Hz are referred to as low-frequency rTMS and have been shown to decrease
corticospinal synaptic excitability\textsuperscript{158}. Mechanisms similar to LTP and long-term depression (LTD) are thought to be involved in the generation of these effects\textsuperscript{158}.

rTMS after stroke is mainly used as an attempt to restore balance to the interhemispheric inhibition after it has been disrupted by an infarct. In the stroke population, the affected hemisphere (AH) is disordered not only by the infarct itself, but also by the resulting asymmetric inhibition of the unaffected hemisphere (UH), which further reduces the excitability of the AH. In stroke rehabilitation, low-frequency rTMS is applied to the UH to reduce excitability of the contralesional hemisphere, and high-frequency stimulation of the AH is applied to increase excitability of the ipsilesional hemisphere\textsuperscript{157} (Appendix A).

Application of a single-session of constant high-frequency rTMS to the AH\textsuperscript{159-162} demonstrated the possibility of inducing plastic changes in the excitability of the motor cortex post-stroke. Kim et al.\textsuperscript{160} applied 10Hz stimulation with an intensity of 80% resting motor threshold (RMT) and evaluated behavioral changes in finger motor tasks and corticomotor excitability before and after the intervention. They found that real rTMS resulted in larger improvements in MEP amplitude, movement accuracy and speed. Their results suggested that motor learning was dramatically amplified after high-frequency rTMS in the AH. Similarly, Ameli et al.\textsuperscript{159} applied 10Hz with an intensity of 80% RMT. Interestingly, they found different effects of high-frequency rTMS in people with only subcortical stroke and in people with additional cortical stroke. In subcortical stroke, rTMS was associated with improved kinematics of the index finger and hand tapping; these improvements were associated with reduced activity of the contralesional primary motor cortex (M1), measured with functional MRI. In people with additional
cortical stroke, rTMS was associated with deteriorated kinematics of the affected hand; these effects were associated with a widespread bilateral recruitment of primary and secondary motor areas\textsuperscript{159}. These changes were revealed after stimulation of M1 and not after stimulation over the vertex (sham condition). This study suggested that the effectiveness of facilitatory rTMS applied over ipsilesional M1 depends on the functional integrity of the stimulation site and/or the dimensions of the brain area affected by the stroke. Yozbatiran et al.\textsuperscript{162} also studied the effects of higher-frequency rTMS, but their study concentrated only on behavioral effects, which do not tell us about plastic changes that may occur in the nervous system.

Further, five multiple-session studies\textsuperscript{163-167} assessed whether the effects from a single session of high-frequency rTMS accumulate, inducing longer lasting functional improvement and neuroplastic changes. In a single-blinded longitudinal, randomized, sham-controlled study, Khedr et al.\textsuperscript{164} applied rTMS at 3Hz frequency and 120\% RMT over the AH for 10 consecutive days. They found that real rTMS resulted in larger improvements on the Scandinavian Stroke Scale, the NIH Stroke Scale (NIHSS) and the Barthel Index (BI) compared to sham rTMS up to 10 days after stimulation\textsuperscript{164}. However, single-pulse TMS did not show any changes in cortical excitability. More recently, Khedr et al. performed two single-blinded, longitudinal, randomized, sham-controlled studies. One study\textsuperscript{163} compared 1Hz rTMS applied with continuous stimulation for 15 minutes at 100\% RMT and 3Hz rTMS at 130\% RMT. Both treatment groups underwent one session every day for five days. Each real rTMS group experienced greater improvements in keyboard tapping, pegboard, NIHSS and BI than the sham group. These improvements were greater in the 1Hz than the 3Hz group at
three months after stimulation. In terms of cortical excitability, 1Hz rTMS induced an increase in MEP amplitude and a decrease of active motor threshold (AMT) in the AH, and a decrease in amplitude of MEP and an increase of AMT in the UH. 3Hz rTMS induced only an increase in amplitude of MEP and a decrease of AMT in the AH. In the other study, Khedr et al. compared 3 Hz rTMS at 130% RMT with 10Hz rTMS at 100% RMT. Real rTMS produced greater improvements in muscle strength and greater alleviation of disability than sham stimulation, and these improvements were evident even at one-year follow-up. In addition, in the real rTMS groups, the AH experienced a decrease in both RMT and AMT, which was associated with an increase in MEP amplitude. The authors did not find significant differences between 3Hz and 10Hz stimulation, although 3Hz seemed to produce greater changes. Mally et al. examined whether active movement could be induced by rTMS even several years after stroke and investigated which hemisphere would be the best location for stimulation in order to attenuate spasticity and develop movement in the paretic arm. However, the study did not evaluate whether rTMS induced neuroplasticity. Malcolm et al. tested the potential adjuvant effect of rTMS in people undergoing constraint-induced movement therapy (CIMT) for upper-limb hemiparesis. Stroke participants underwent one session per day for 10 consecutive days of 20Hz rTMS at 90% RMT followed immediately by CIMT. The study failed to show significant differential effects on the Wolf Motor Function Test (WMFT), the Motor Activity Log (MAL) and Box and Block test (BBT). However, in most of the measures, the rTMS group showed greater improvement, even six months after intervention with rTMS. Moreover, the rTMS group showed a significantly greater
reduction of RMT after treatment, which indicates that some neural changes occurred at the cortical level.

Other studies investigated the application of low-frequency rTMS on the contralesional hemisphere to reduce transcallosal inhibition and to assess whether low-frequency rTMS may induce changes in cortical excitability. Mansur et al.\textsuperscript{168} and Liepert et al.\textsuperscript{169} showed that inhibition of UH by low-frequency rTMS resulted in a substantial gain of function, but neither of these studies measured any neuroplastic change. Two double-blind studies involving single-sessions of real versus sham low-frequency rTMS on the UH\textsuperscript{69, 170} demonstrated that rTMS reduced both the amplitude of RMT in the UH and the duration of interhemipsheric inhibition (IHI). IHI was evaluated with ipsilateral silent period\textsuperscript{170}. These improvements were associated with an improvement in pinch acceleration of the affected hand. In addition, this improvement in motor function was significantly correlated with a reduced IHI duration. Similarly, Nowak et al.\textsuperscript{171} applied low-frequency rTMS on the UH for 10 minutes in subcortical stroke patients. rTMS improved the kinematics of finger and grasp movements in the affected hand. At the neural level, functional MRI demonstrated that rTMS reduced over-activity in the contralesional primary and non-primary motor areas.

Fregni et al. conducted a five-session study applying low-frequency rTMS on the UH in chronic stroke\textsuperscript{172}. rTMS resulted in a significant improvement in motor function performance measured with the Jebsen-Taylor hand function test and Purdue Pegboard test in the affected hand. Corticospinal excitability decreased in the rTMS stimulated UH and increased in the AH. In addition, the author showed a significant correlation between motor function improvement and corticospinal excitability change in the AH.
These findings suggest that both low-frequency and high-frequency rTMS may induce functional improvement and these improvements are associated with neuroplastic processes in the brain.

**Theta-burst stimulation (TBS).** Theta-burst stimulation (TBS) is a novel form of rTMS that consists of repeating bursts of stimuli. Each burst consists of three stimuli repeating at 50 Hz; bursts are repeated at 5 Hz. The intensity of stimulation is set at 80% of active motor threshold (AMT). In normal individuals, a continuous train of 100 bursts, named cTBS, can suppress corticospinal excitability. With an intermittent pattern (iTBS), corticospinal excitability is enhanced. cTBS is therefore used to suppress the UH and iTBS to facilitate the AH in people post-stroke.

Talelli et al. tested a group of stroke patients under three conditions: excitatory TBS over the stroke hemisphere (iTBS), inhibitory TBS (cTBS) over the intact hemisphere and sham stimulation. iTBS consisted of 20 trains of 10 bursts at 5Hz with an intensity of 80% of AMT, while the cTBS consisted of continuous trains of 100 bursts with an intensity of 80% of AMT. After iTBS there were improvements in simple reaction time in the paretic hand, which remained shorter throughout the testing period compared to the sham stimulation. No effect in peak grip force was revealed. The amplitude of the MEPs at rest and during active muscle activation, and the area under the input-output curves, also increased on the lesioned side. cTBS did not affect speed and peak grip force of the contralateral hand, although it suppressed MEPs evoked in the healthy, but not in the paretic, hand. This study suggested that TBS is safe and that iTBS transiently improves motor behavior and cortical spinal output in the paretic hands. Similarly, Di Lazzaro et al. compared the application of iTBS and cTBS. In contrast to
the previous study, they found that both the facilitatory TBS on the affected motor cortex and the inhibitory TBS on the unaffected motor cortex produced a significant increase in the amplitude of MEPs evoked by the stimulation of the AH. RMT decreased in the AH and increased in the UH, while MEP amplitude increased in the AH and decreased in the UH, respectively. The authors concluded that TBS could enhance excitability of the lesioned motor cortex and could be useful in re-establishing the balance of excitability between the two hemispheres. In a more recent study, Di Lazzaro et al. 174 correlated changes produced by iTBS (using the same parameters as in their previous study) to outcomes at a six month follow-up. They found that iTBS produced increased MEP amplitude in the AH, which correlated with recovery measured at follow-up by the Modified Rankin Score (a scale for measuring the degree of disability or dependence) 174. This study showed, for the first time in humans, that the level of long-term potentiation (LTP) in the AH was correlated with the long-term recovery of functional activity 174. These findings demonstrate that both iTBS and cTBS may induce motor recovery and plastic changes in cortical excitability.

**Paired associative stimulation (PAS).** Paired associative stimulation (PAS) consists of a paradigm for repetitive, low-frequency, single-pulse electrical nerve (usually median) stimulation or a train of electrical stimuli applied to the motor points of muscles, followed by TMS over the contralateral motor cortex 175. It is based on the principles of associative LTP in experimental animals and the Hebbian concept of spike-timing-dependent plasticity, with two inputs paired to arrive at a single neuron at approximately the same time 176. PAS-induced changes in cortical excitability share a number of physiological properties with LTP and LTD. In humans, it takes about 20
milliseconds for the fastest sensory impulses from the median nerve to reach the sensory cortex. The integration of the information from sensory cortex to motor cortex takes about 2-5 milliseconds\textsuperscript{177}. If the TMS is applied 25 milliseconds (PAS25) after median nerve stimulation, motor cortex neurons are synchronously activated by the afferent input (presynaptic) and TMS (postsynaptic activation). Repeated pairings then result in an increase in the net efficiency with which subsequent TMS pulses can activate corticospinal neurons\textsuperscript{177}. Repeated pairs of PAS25 lead to enhanced motor cortex excitability (LTP). In contrast, repeated pairs of PAS10 (TMS pulse given 10 milliseconds after median nerve stimulation) reduce the motor cortex excitability (LTD) since the postsynaptic activation (TMS) precedes the presynaptic activation (afferent input) at the motor cortex\textsuperscript{178}.

In a recent study involving a single session, PAS protocol was applied at 5 and 12 months post-stroke. PAS induced facilitation of the extensor carpi radialis MEP on the paretic side 5 months after stroke, a fraction of which was still present 12 months after stroke\textsuperscript{141}. These effects were associated with clinical improvement measured with the Fugl-Meyer motor scale and dynamometry of wrist extension\textsuperscript{141}. Another recent study applied inhibitory PAS (120 pairs at 0.5Hz) in stroke patients\textsuperscript{179} with stimulation of the common peroneal nerve innervating the nonparetic tibialis anterior muscle followed by TMS of the contralesional motor cortex. As expected, this slightly decrease in excitability of the contralesional motor cortex was accompanied by increased motor cortical excitability of the lesioned side assessed during walking. This effect may be achieved through decreasing the interhemispheric inhibitory drive from the contralesional to the ipsilesional primary motor cortex\textsuperscript{179}. While these findings suggest
that the PAS technique has promise, further studies are needed to gather evidence that PAS induces functional improvements that are associated with neuroplastic processes\textsuperscript{179}.

\subsection*{1.5. Objective of this Dissertation}

Studies cited above have demonstrated that the most disabling impairments post-stroke are due to weakness in the affected limb, and also that resistance training post-stroke can help alleviate weakness. Resistance training is harmless and induces improvements in strength, upper-extremity function, restoration of more normal movement patterns during reaching tasks and neurophysiologic adaptations in stretch-reflex modulation.

In contrast, studies suggest that both functional task practice and CIMT induce improvement of arm function, not by alleviating weakness or restoring normal movement patterns, but by encouraging compensatory strategies. Therefore, we propose that future research needs to focus further on the relationship between motor behavioral recovery and nervous system reorganization to determine whether strengthening effectively induces behavioral and neurophysiological recovery. In addition, brain stimulation may be used as adjuvant to training protocols in persons post-stroke to enhance its effects\textsuperscript{139}. Recent studies suggest that rTMS has the potential to modulate cortical excitability. rTMS may therefore be used in an attempt to restore balance of interhemispheric competition post-stroke\textsuperscript{70} in association with resistance training.

The overall objective of this dissertation is to improve recovery of upper-extremity function post-stroke and to improve our understanding of mechanisms underlying recovery by using a multimodal method of investigation that provides insight into the
dynamic relationship between neurophysiology and motor behavior and pays particular attention to the selection of measures that distinguish between recovery and compensation.

The following are the main questions this dissertation attempts to answer:

1) **Treatment efficacy at the behavioral level:**
   - What are the behavioral effects of functional training and high-intensity resistance training for the upper-extremity post-stroke?
   - Do the therapeutic interventions induce compensation or recovery of normal movement patterns?
   - Does training intensity affect the efficacy of the treatment?

2) **Treatment efficacy at the neural level:**
   - Do the therapeutic interventions induce neuroplastic changes?

3) **Locus of therapeutic-induced neuroplasticity**
   - Are the neuroplastic changes at the supraspinal, spinal or both levels?
   - Are the neuroplastic changes ipsi- or contralateral to the lesion?

Chapter 3, 4, 5 and 6 of this dissertation describe the individual studies we performed as an attempt to answer these research questions.
Table 1-1. Definitions of recovery and compensation at the neural and behavioral levels.

<table>
<thead>
<tr>
<th></th>
<th>Recovery</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neural</strong></td>
<td>Restoring function in neural tissue that was initially lost due to injury or disease.</td>
<td>Residual neural tissue takes over a function lost due to injury or disease.</td>
</tr>
<tr>
<td><strong>Behavioral: Body Function</strong> <em>(Impairment)</em></td>
<td>Restoring the ability to perform movements in the same manner as it was performed prior to injury or disease.</td>
<td>Performing movement in a manner different from how it was performed prior to injury or disease.</td>
</tr>
<tr>
<td><strong>Behavioral: Activity</strong> <em>(Function)</em></td>
<td>Restoring the ability to perform a task in exactly the same manner as it was performed prior to injury.</td>
<td>Performing a task in a manner different from how it was performed prior to injury or disease.</td>
</tr>
</tbody>
</table>


Table 1-2. Neural strategies supporting functional improvements.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Restoration</th>
<th>Recruitment</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td>Re-engaging residual brain areas initially dysfunctional after injury or disease.</td>
<td>Engaging new residual brain areas.</td>
<td>Training residual brain areas to perform new functions.</td>
</tr>
<tr>
<td><strong>Functional platform</strong></td>
<td>Internal and external redundancy.</td>
<td>External redundancy.</td>
<td>Internal and external redundancy.</td>
</tr>
</tbody>
</table>

Figure 1-1. Schematic diagram illustrating how experience-dependent neural plasticity supports learning\(^4\). There are key behavioral signals that are inherent to any learning experience that serve to drive specific neural signaling systems that in turn induce enduring neuroplastic changes within those brain areas (sensory, motor, cognitive) engaged during training. This neural plasticity serves to encode the training experience and improves future performance of the trained behavior.

\(^4\) Kleim JA. Neural plasticity: Foundation for neurorehabilitation. Unpublished manuscript.
CHAPTER 2
COMMON METHODS

2.1. Measures

In this dissertation, we suggest a multimodal method of investigation that explores the complex and dynamic relationship between neurophysiology and motor behavior and pays particular attention to the selection of measures that distinguish between recovery and compensation. The multimodal assessment includes:

2.1.1. Clinical Evaluation

We used Wolf Motor Function Test (WMFT) to investigate the behavioral motor function. In this test participants are timed as they complete 15 activities that involve progressively more difficult arm movements and interactions with objects.

The WMFT is classified as an activity measure in the International Classification of Functioning, Disability and Health (ICF) and is one of the most used clinical tests to evaluate UE function post-stroke. The clinometric properties of the WMFT have been established, shown to have high interrater reliability (intraclass correlation coefficients, ≥ 0.88), internal consistency (Cronbach α ≥ 0.86), and test-retest reliability (r ≥ 0.90)\(^{180}\).

2.1.2. Three-dimensional Motion Analysis

2.1.2.1. General information about technique

We used three-dimensional motion analysis to study motor behavior. This measurement approach allows us to distinguish between behavioral compensation and recovery. It affords a sensitive, quantitative and reproducible assessment of abnormal movements\(^ {62, 181}\). Three-dimensional motion analysis included kinematic and electromyographic evaluation. Kinematics enabled us to study movement patterns used during the accomplishment of the task\(^ {5, 85}\), for example, the exaggerated use of trunk
movements to compensate for reduced elbow and shoulder flexion\textsuperscript{86}. Electromographic evaluation enabled us to study the abnormal patterns of muscle activation during movement performance; for example, potential coactivation of biceps and triceps brachii muscles during active extension of the elbow, which is argued to be a frequent manifestation of hemiplegia.

\textbf{2.1.2.2. Data collection}

Motion analysis was performed using a functional reach-to-grasp task with the affected arm. Kinematic data were recorded with a 8-camera motion analysis system\textsuperscript{5} and using 26 reflective markers positioned at: C7, sternal notch, right and left acromion, lateral epicondyle, radial and ulnar styloid processes, third dorsal metacarpal phalangeal joint, dorsal interphalangeal joint of the index finger, and triads were placed on the superior thirds of the upper arm and forearm. Static trials included an additional marker on the medial epicondyle to create the kinematic model. Surface electromyography (EMG) was recorded using pre-amplified electrodes\textsuperscript{6} placed over the muscle bellies of the anterior deltoid, posterior deltoid, infraspinatus, major pectoris, biceps brachii, the long head of the triceps, extensor carpi radialis, and flexor carpi radialis muscles of the affected arm. Kinematic and EMG data were recorded simultaneously. Subjects were seated on a backless stool with the affected arm placed immediately lateral to the affected thigh and were asked to reach and grasp a soda can and a pencil placed at 80 percent of their arm length at self-selected speed. 10 trials of the reaching movement were recorded. Additional EMG data were recorded during

\textsuperscript{5} Copyright © Vicon 612, Oxford Metrics, Oxford, UK

\textsuperscript{6} Copyright © 2012, Motion Lab Systems, Inc, Baton Rouge, LA, USA
maximal voluntary isometric contractions (MVIC) of each muscle group using standard manual muscle techniques\textsuperscript{182}.

### 2.1.2.3. Data analysis

We used custom-designed MATLAB\textsuperscript{7} programs to analyze and extract kinematic and EMG data. From the kinematic trajectories, we calculated parameters commonly used in the literature:

- **Mean Velocity.** A measure of movement speed corresponding to the average of the hand’s speed during the entire movement.

- **Reach-path-ratio and sub-movements.** Ratio of the actual wrist path and an ideal straight line between the start and end positions. Sub-movements were defined as the number of times the hand velocity exceeds 5 percent of peak velocity.

- **Range of motion at shoulder and elbow.** Difference in degrees between the maximum and minimum joint angles achieved.

- **Trunk displacement.** Displacement of the sternum markers in the sagittal plane.

From the EMG data, we calculated parameters of magnitude and timing. Intensity was expressed as the relative (percentage MVIC) amount of muscle activation. It was defined as the peak envelope value during the reaching trial divided by the peak envelope value during the MVIC trial. Timing for each muscle’s activation was expressed as a percentage of movement duration.

#### 2.1.3. Transcranial Magnetic Stimulation (TMS)

#### 2.1.3.1. General information about technique

We used TMS to study cortical excitability. This measurement approach allowed us to test whether the intervention induced neuroplastic changes at the brain. TMS

\textsuperscript{7} MathWorks\textsuperscript{®}, Inc., Massachusetts, USA
influences ongoing brain activity by generating weak electrical currents in brain tissue through electromagnetic induction\textsuperscript{183}. These electrical potentials are strong enough to depolarize neurons and affect normal electrical processes in nearby brain tissue. TMS causes action potentials directly or indirectly in descending corticospinal motor neurons\textsuperscript{183}. The effects of TMS can be measured by recording EMG in the arm, hand, or finger muscles. Two TMS techniques commonly are used to study the neural mechanisms: single- and paired-pulse stimulation. We used both, single- and paired-pulse stimulation to study the hemispheric cortical excitability, inter-hemispheric inhibition (IHI) and intracortical inhibitory circuits. Motor threshold, MEP amplitude and recruitment curve (RC) slope were used to study hemispheric cortical excitability\textsuperscript{244}. Ipsilateral silent period (iSP)\textsuperscript{253} was used to study IHI. Cortical silent period (cSP)\textsuperscript{236}, EMG suppression (a.k.a ‘Davey technique’ or ‘Davey suppression’)\textsuperscript{184} and short-latency intracortical inhibition (SICI)\textsuperscript{185} were used to study the intracortical inhibitory circuits.

2.1.3.2. Data collection

During TMS testing, participants were seated comfortably in a semi-reclined chair. Stimulation was delivered using one or two Magstim\textsuperscript{®} 200\textsuperscript{28} stimulators connected through a Bi-stim module to a figure-eight coil while recording MEPs from the contralateral first dorsal interosseous (FDI) muscle by means of pre-amplified EMG electrodes\textsuperscript{9}. The coil was placed tangentially over the scalp, with the handle pointing backwards and laterally at a 45° angle away from the midline, inducing a posterior-anterior current in the target hemisphere. For each subject, we first identified the optimal

\textsuperscript{8} The Magstim\textsuperscript{®} Company LTD, Copyright © 2011, Whitland, Wales, UK

\textsuperscript{9} Copyright© 2012, Motion Lab Systems, Inc, Baton Rouge, LA, USA
scalp location for induction of the largest MEPs in the contralateral FDI. The target site was marked as the hot-spot on a tightly fitting cap worn by the subjects and on the neuronavigation system. All the following measures were recorded for both hemispheres:

- The resting motor threshold (rMth) is the lowest stimulation intensity able to elicit ≥5/10 MEPs of at least 50µV amplitude at rest;

- Recruitment curve (RC) is generated by stimulation over the motor threshold hotspot at progressively increasing intensities. Testing proceeds by placing the coil at the hotspot and recording 10 stimuli in 5% increments beginning at an intensity of 10% below motor threshold. Data collection for the RC is terminated when a plateau of the sigmoidal curve is observed₂²⁴;

- Cortical SP (cSP) and ipsilateral (iSP) are obtained using single pulse TMS delivered at 150% of motor threshold while the participant produces a sustained, submaximal contraction (~50% maximal effort) of the FDI muscle contralateral (cSP) or ipsilateral (iSP) to the stimulation²⁵³,²³⁶;

- EMG suppression (a.k.a. Davey’s technique or Davey’s suppression) reveals suppression of EMG in the limb contralateral to stimulation by subthreshold (about 20% below motor threshold) TMS, without any prior excitatory response¹⁸⁴;

- SICI is studied using paired-pulse stimulation, in which an MEP evoked by a suprathreshold test stimulus (~120% of motor threshold) is preceded at variable interstimulus intervals (ISIs) by a subthreshold conditioning stimulus (~80% of motor threshold). At ISIs ranging from 1 to 6 ms, the paired stimulations induce a short intracortical inhibition (SICI - reduced MEP).

2.1.3.3. Data analysis

We used custom-designed MATLAB® programs to analyze TMS data and construct RC’s slopes and calculate iSP. EMG data were band-pass filtered (5-1000 Hz) and notch filtered (60 Hz).

- Recruitment curve (RC): Peak amplitude and area of the averaged MEP signal are calculated at each stimulus intensity. We considered the presence of MEP if the peak-to-peak amplitude of the averaged signal was ≥ 50 µV. MEP onset was defined as the last crossing of the mean baseline EMG level before the MEP peak and the MEP offset as the first crossing of the mean baseline EMG level after the MEP peak. The peak-to-peak amplitude and the area under the MEP
are calculated at each stimulation intensity. For construction of the RC, MEP amplitude and area are normalized to both Mth and maximum MEP amplitude. A non-linear fit of the data to Boltzmann Equation is performed, followed by a linear regression fit of the modeled data in the steepest portion of the range. The slope of this range is determined. Motor threshold is established as the stimulation intensity at which the regression line fitting the steepest portion of the RC intersects the abscissa.

- Cortical (cSP), ipsilateral silent period (iSP) and EMG suppression (a.k.a. Davey’s technique): EMG data are rectified and averaged over multiple stimuli at a given stimulus intensity. The mean and the standard (SD) deviation of the baseline EMG level for 100 ms before TMS stimulus is determined from the averaged signal. We considered the presence of an MEP (either ipsilateral or contralateral) if the post-stimulus EMG exceeded the pre-stimulus mean baseline EMG by > 1 SD for ≥ 5 ms. MEP onset was defined as last crossing of the pre-stimulus mean baseline EMG before the MEP peak and the MEP offset as the first crossing of the pre-stimulus mean baseline EMG after the MEP peak. MEP area is calculated between the MEP onset and offset (MEP duration). Similarly, we considered the presence of an iS if the post-stimulus EMG fell below the pre-stimulus mean baseline EMG by ≥1 SD for > 5 ms. The iSP onset is defined as the first crossing of the pre-stimulus mean baseline EMG after the MEP peak and the MEP offset as the first crossing of the pre-stimulus mean baseline EMG after the iSP onset for at least 5 ms. The iSP duration is the time between the onset and the offset values. We defined the silent period area as the area between the pre-stimulus mean baseline EMG and the EMG signal during the silent period duration. The percent of inhibition is calculated as the percent of the total area under the pre-stimulus mean baseline EMG during the silent period duration.

- SICI: For each ISI, signal averaging of multiple stimuli is performed. The peak amplitude is calculated and normalized as percent of the single-pulse MEP amplitude.

2.1.4. Stretch Reflex

2.1.4.1. General information about technique

The stretch-reflex is commonly used in assessment of spasticity, a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerk\(^{11, 130}\).

The stretch-reflex (myotatic) is the muscle contraction in response to stretching within the muscle. It is a monosynaptic reflex, which provides regulation of skeletal muscle length and rate-dependent changes in muscle length. When muscle lengthens,
the muscle spindle is stretched and the activity increases leading to increased alpha motoneuron activity, muscle contraction and reduction of muscle length, which reduces muscle spindle activity\textsuperscript{130}.

2.1.4.2. Data collection

Stretch reflex modulation at the elbow was studied by imposing ramp-and-hold stretches. Participants were positioned on the Biodex\textsuperscript{10} dynamometer chair while the device is used to passively impose elbow extensions. Following each stretch the elbow was held in extension for 5 s before being passively returned to the starting position, and held in flexion for 10 s. EMG was recorded from the biceps brachii, brachiradialis and triceps brachii using pre-amplified electrodes.

Torque, position and EMG data were collected before and during passive elbow extension stretches. Two conditions were performed: the first, passive, in which subjects were instructed to relax as the limb was moved through the full range of elbow motion by the dynamometer; the second, preloaded, in which the subjects performed an isometric contraction of elbow flexor muscle at 20\% of MVIC before and during passive elbow extension stretches. Data were collected at four criterion speeds (i.e., 90°/s, 150°/s, 210°/s and 270°/s). To quantify passive joint torques, two additional trials will be performed at 10°/s. The reliability of both EMG and torque responses has been established for ramp-and-hold stretches obtained using this paradigm\textsuperscript{218}.

2.1.4.3. Data analysis

Torque, position and EMG data were analyzed using MATLAB\textsuperscript{©}. The slow (10 deg/s) passive torque response at each position was subtracted from the torque

\textsuperscript{10} Copyright© 2012, Biodex Biomedical System 3.2, Shirley, NY, USA
measured during stretches imposed at all speeds. EMG activity was evaluated as the mean amplitude calculated over a 100 ms sliding window. For each trial, EMG was defined as active when the mean amplitude exceeded threshold (i.e., mean baseline, resting EMG plus 2.5 standard deviations). Data were used to obtain the following parameters indicative of stretch reflex modulation:

- **EMG Burst Duration.** The percentage of the movement time during which EMG activity was present.
- **Position Threshold.** The joint angle, expressed in degrees of elbow flexion, at which muscle activity was first identified.
- **Burst Intensity.** The mean amplitude of EMG activity when the muscle was active minus the baseline resting activity.
- **Torque.** The average torque calculated over a 100 ms window centered at 40 degrees of elbow flexion.

### 2.1.5. H-reflex

#### 2.1.5.1. General information about technique

The H-reflex (or Hofmann reflex) is an involuntary reaction of muscles after electrical stimulation of sensory fibers (Ia afferents stemming from muscle spindles) and is the electrical analogue of the monosynaptic stretch-reflex. The H-reflex is evoked by low-intensity electrical stimulation of the afferent nerve, rather than a mechanical stretch of the muscle spindle, that results in monosynaptic excitation of the alpha-motoneurons. The H-reflex bypasses the muscle spindle and the fusimotor activity that may influence the sensitivity of the Ia afferents to engage a reflex circuit. The response is usually a wave, called H-wave, occurring 28-35 ms after the stimulus. The electrical stimulation of the mixed peripheral nerve produces two responses in the muscle, an M-wave (short-latency direct motor response due to stimulation of motor axons) and an H-reflex. At supra-maximal stimulation, the H-reflex is absent due to
collision of the antidromic motor volley with the orthodromic afferent volley and the M-wave is maximum\textsuperscript{187,188}.

2.1.5.2. Data collection

Participants were positioned in sitting with the wrist positioned in neutral flexion/extension; forearm in mid-prone; elbow at 45° flexion; shoulder abduction and flexion at 15°; and neutral shoulder rotation. H-reflexes was evoked bilaterally. A custom-fabricated forearm splint was used to provide stabilization and maintain the forearm in mid-prone.

H- and M-waves were electrically evoked using a constant current stimulator\textsuperscript{11} triggered by a second stimulator (S8800 Stimulator, Grass technologies, West Warwick, RI, USA) at a frequency of 0.2 Hz (to minimize homonymous or paired-reflex depression\textsuperscript{189}). EMG was recorded on the Flexor Carpi Radialis (FCR) muscle at a sampling frequency of 10kHz.

The stimulating electrode was placed in the medial bicipital groove to stimulate the median nerve and the position was adjusted to evoke FCR H-reflexes (in absence of M-wave). A stimulus location was chosen where at least 10 H-reflexes were evoked at increasing stimulus intensities without an M-wave. This procedure was used to assure capture of H-reflex responses on the ascending limb of the recruitment curve\textsuperscript{188}.

Once the stimulation site was located, stimulation intensity was sequentially increased (typically by 0.05 mA increments) from a sub-H-reflex threshold intensity to the point when H-reflex amplitude reached the maximum and begins to decline.

\textsuperscript{11} Copyright© 1998, Digitimer DS7A, Digitimer Ltd., Hertfordshire, England
Thereafter, current intensity was increased at a faster rate (0.2 – 1 mA) until a maximum M-wave (Mmax) was elicited.

2.1.5.3. Data analysis

The peak-to-peak amplitude of both, H- and M-waves in each recruitment curve was normalized to the Mmax of the same recruitment curve. The H-slope (Hslp) was calculated on the ascending limb of the H-reflex recruitment curve defined as a range from 10-85% of maximum H-wave amplitude. Similarly, the M-slope (Mslp) was calculated for the M-wave recruitment curve. On the ascending limb of the H-reflex recruitment curve, both H- and M-waves rise in a relatively linear fashion, thus allowing calculation of the slope of a linear regression line through the data points representing H- and M-waves in this range of stimulation intensities. Finally, Hslp was normalized to Mslp, expressed as the ratio - Hslp/Mslp. This ratio has been reported to be the most effective way to detect changes in spinal excitability187.

The peak-to-peak H-reflex and M-wave amplitude was calculated from five maximal responses and averaged. H-reflex and M-wave thresholds (HTH and MTH, respectively) were determined using the minimal stimulation intensity at which a visually discernible reflex response is elicited 3 out 5 times.

2.2. Interventions

2.2.1. Functional Task Practice (FTP)

One-on-one treatments were delivered by a licensed physical therapist.

From a list of upper-extremity activities, the treatment therapist chose 7 activities that were relevant to the individual participant’s therapeutic goals61. Treatment was delivered in three sessions per week each lasting 90 minutes. Each session was comprised of 5-15 minutes of stretching (depending on the patient’s individual needs).
followed by 60-70 minutes of task-based activity therapy. Five activities were performed per session (10-15 minutes per activity) and each activity was incorporated into therapy twice per week (Figure 2-1).

2.2.2. Constraint-Induced Movement Therapy (CIMT)

CIMT intervention consisted of the classical CIMT protocol described by Wolf\textsuperscript{138}: 6 hours per day of massed practice of the affected arm combined with shaping, behavioral contracts and constraint of the unaffected arm for 90% of waking hours for two weeks.

2.2.3. Power Training

We delivered dynamic, high-intensity resistance exercise for the shoulder, elbow and wrist using an isokinetic dynamometer (Biodex System 3.0 Pro). The treatment protocol involved 7 exercises (shoulder flexion, shoulder abduction, shoulder external rotation, elbow flexion/extension, wrist flexion/extension), 3 sets of 10 repetitions of each exercise. The speed of movement was progressively adjusted upward over the duration of training for each study\textsuperscript{61}.

2.2.4. Repetitive TMS (rTMS)

Inhibitory rTMS was administered over the contralesional M1 – corresponding to the hot spot for the ipsilesional/non-paretic muscle representation. In addition, participants wore a tight-fitting lycra swim cap. Skin-mounted surface electromyogram preamplifier was placed over the FDI muscle contralateral to the stimulated hemisphere. Subjects were seated in a Biodex chair adjusted such that hips, knees and ankles were maintained at 90 degrees and were asked to relax. MEP threshold was measured before and after each rTMS session using a figure-8 coil centered at the scalp vertex and connected to a Magstim\textsuperscript{®} Rapid\textsuperscript{2} high-power magnetic stimulator (Magstim\textsuperscript{®} Ltd,
Stimulations were delivered at an intensity of 100% motor threshold, 1 Hz frequency, biphasic waveform and 1200 stimulations in a single, continuous train lasting 20:00\textsuperscript{172}. 
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<tr>
<th></th>
<th>Monday</th>
<th>Wednesday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>Activities</td>
<td>1,2,3,4,5</td>
<td>Activities 3,4,5,6,7</td>
<td>Activities 5,6,7,1,2</td>
</tr>
</tbody>
</table>

3.1. Background

Current debate centers on whether therapeutically-induced improvements in upper-extremity function in persons post-stroke reflect acquisition of compensatory movement strategies or restoration of more normal movement patterns. Restoration involves reappearance of motor patterns present prior to stroke, while compensation involves appearance of new motor strategies, including substitution with different, atypical components. Although compensatory movements may enable task performance in the short term, these may be detrimental to overall outcome in the long term by contributing to problems including pain and reduced range of joint motion. Moreover, the use and reinforcement of atypical movement components may interfere with attainment of normal upper-extremity motor patterns and thus limit genuine recovery. Compensatory strategies may also have a detrimental psychosocial impact. Both the self-perception and appearance of aberrant movement to others contribute to depression and, ultimately, avoidance of using the impaired arm. These problems underscore the compelling need to discriminate between compensation and restoration in neurorehabilitation. This distinction is critical to development of effective rehabilitation interventions that promote restoration of motor function present prior to stroke.
Kinematic analysis of upper-extremity (UE) motor performance enables sensitive, quantitative and reliable\(^6\) assessment of abnormal movements\(^{190}\) and thus may facilitate discrimination between compensation\(^7\) and restoration of arm function post-stroke\(^{62, 191}\). To date, the majority of UE kinematic studies in persons post-stroke have been cross-sectional investigations of reaching\(^2, 5, 43, 62, 191-196\) or grasping tasks\(^{86, 193, 197}\) which reveal: slowness, spatial coordination deficits, temporal joint dyscoordination and compensatory movements that interfere with normal performance\(^2, 5, 43, 62, 86, 191-197\).

Investigations of intervention-related changes in UE motor performance using kinematics have focused on evaluating the effects of: constraint-induced movement therapy\(^{192, 198}\) and functional unilateral\(^{86, 197, 199, 200}\) or bilateral\(^{201}\) repetitive task training. These therapeutic approaches are believed to facilitate neural plasticity through repetitive execution of functional movements. Although weakness is recognized as a major factor contributing to disability post-stroke\(^{15, 43, 44}\), strengthening is not typically included as a neurorehabilitation technique. Historical clinical perspectives cautioned against high-exertion activities for neurologic populations because they were assumed to increase spasticity and impair motor performance\(^{44}\). More recently it has been argued that remediation of impairments (i.e., weakness) does not generalize to functional task performance. To date, only two studies have directly compared UE strengthening and functional task practice with kinematics\(^{199}\). Both studies utilized resistive therapeutic bands and concluded that strengthening does not improve paretic UE motor function. On careful review, however, the methods lack any rationale assuring either sufficient intensity or means for progression of the strengthening activities, thus it is likely these studies failed to offer sufficient overload\(^{202}\). Additionally, the importance of positioning,
specifically trunk stabilization, has been confirmed by demonstration of greater improvements in UE movements following treatment activities performed with external trunk stabilization\textsuperscript{86,203}. These studies positioned participants in a standard chair, which may not provide optimal trunk stabilization and may even enable acquisition of compensatory movements. Taken together, these factors may explain the failure of this paradigm to produce meaningful effects on either strength or paretic UE function.

While there is now considerable evidence that systematic high-intensity progressive resistance training increases strength, improves activity and produces behavioral improvements in the hemiparetic UE without increasing spasticity\textsuperscript{14,16}, the majority of the literature reports effects of combined strengthening and functional task practice. Therefore, the behavioral effects of resistance training alone remain unclear.

Here we compared two forms of UE rehabilitation for persons post-stroke: 1) functional task practice (FTP) and 2) dynamic high-intensity resistance training, or power training (POWER). Our primary aim was to compare these two interventions using a battery of standardized clinical evaluations and kinematics of goal-directed UE movements. This approach enabled concurrent investigation of changes in function, as understood by commonly used clinical tools, and movement strategies used by persons post-stroke during reaching tasks. We hypothesized that following POWER behavioral motor improvements would reveal restoration of motor patterns more similar to healthy individuals while following FTP behavioral changes would reveal compensatory movement strategies. Our secondary aim was to determine the effects of treatment order. We hypothesized that FTP preceded by POWER would reveal greater
behavioral motor improvements because FTP would be more effective following restoration of neuromechanical function.

3.2. Methods

3.2.1. Participants

This study was a single-center, randomized controlled trial\(^1\). Participants included fourteen persons with UE hemiparesis post-stroke meeting the following inclusion criteria: single, unilateral stroke within 6-26 months of enrollment (confirmed by diagnostic imaging); voluntary movement in the major shoulder and elbow agonists in the horizontal plane (e.g., gravity eliminated)\(^{204}\), active wrist extension, thumb abduction and extension of any two digits. Exclusion criteria were: presence of significant UE joint pain, limitations in passive range of motion (ROM) or proprioception deficits at the elbow or shoulder joint; lesions involving the brain stem or cerebellum, cognitive deficits affecting the ability to follow 3-step commands and conditions involving any unstable cardiovascular, orthopedic or neurological impairment precluding exercise. All procedures were approved by the Stanford University panels on human subjects research.

3.2.2. Procedures

After providing written informed consent, all participants were enrolled in a two stage cross-over design (Figure 3-1). Participants were randomized to either: 1) POWER or FTP, followed by 2) the alternate therapy. Each treatment block lasted ten weeks and involved 30 sessions (i.e., 3 90-minute sessions per week), thus each participant received a total of 90 hours of one-on-one treatment with a licensed physical

\(^1\) This work was conducted at the Rehabilitation R&D Center at the VA Palo Alto Health Care System.
therapist. The treatment blocks were separated by a two-week evaluation period. Clinical and kinematic assessments were conducted by blinded assessors: 1) at baseline, 2) following the first and 3) second treatment blocks. To assure baseline equivalence between treatment orders, the shoulder-elbow components of the upper-extremity Fugl-Meyer Motor evaluation to identify higher (≥20/30 points) and lower functioning (<20/30 points) individuals. Separate randomization orders were prepared, allocated to sealed envelopes and stored by the study coordinator in a locked drawer. Following baseline clinical assessment, the blinded evaluator drew a sequentially numbered sealed envelope from the appropriate grouping (i.e., higher vs. lower) and provided it to the treating physical therapist who broke the seal to reveal assignment to either treatment Order A (FTP followed by POWER) or B (POWER followed by FTP). Participants were blinded to their randomization.

3.2.3. Measures

3.2.3.1. Clinical assessments

Clinical outcomes were assessed using tools for which: 1) validity and reliability have previously been established in individuals post-stroke, and 2) represent assessment across all levels of the ICF. Specifically, this clinical battery included: the Modified Ashworth Scale (MAS), Fugl-Meyer Upper-Extremity Motor Score (UEFMMS) and the shoulder-elbow portion of the UEFMMS (30 points), and European Stroke Scale (ESS) to characterize impairment; the Chedoke-McMaster Hand and Arm Inventory (CMHAI) to characterize activities; and the Reintegration to Normal Living index (RNL) to characterize participation.
3.2.3.2. Kinematics of functional reach-to-grasp:

Kinematics were obtained during performance of self-paced functional reach-to-grasp. Participants were seated in a straight-back chair with the paretic UE resting on the ipsilateral thigh, the shoulder in neutral flexion/extension and internal rotation, the elbow in 75-90 degrees of flexion with the wrist resting in pronation, and instructed to reach, grasp and retrieve a full soda can positioned on a table top at 80% of arm’s length (i.e., ‘Coke can’ task\(^{180}\)). Two trials were obtained.

A 7-camera Motion Capture System\(^{13}\) recorded (120 Hz) displacements of 16 reflective markers, which were used to reconstruct three-dimensional movements of the arm, forearm and trunk. During dynamic trials, markers were positioned at: C7, sternal notch, right and left acromion, lateral epicondyle, radial and ulnar styloid processes, third dorsal metacarpal phalangeal joint, dorsal interphalangeal joint of the index finger, and triads were placed on the superior thirds of the upper arm and forearm. Static trials included an additional marker on the medial epicondyle to create the kinematic model. A 2.2 cm-wide piece of reflective tape on the superior border of the soda can identified the reaching target.

3.2.4. Therapeutic Intervention

The treatment algorithms have been previously described in detail\(^{54}\) (in which the two interventions were combined in a HYBRID therapy). Here, all participants received both forms of intervention in separate bouts to allow comparison of individual treatment effects. FTP involved practice of functional tasks using a progression of six therapeutic goals and nine activity categories. Specific therapeutic tasks were chosen from these

\(^{13}\) Copyright© 2011, Qualisys, North America Inc, Charlotte, NC
activity categories based on participant-specific goals and baseline functional level and practiced on a structured rotation within the framework of the overriding therapeutic goals. POWER involved five reciprocal upper-extremity movements: shoulder abduction/adduction, shoulder flexion/extension, shoulder external/internal rotation, transverse plane elbow flexion/extension and wrist flexion/extension, which were trained using a commercially available dynamometer. Custom-designed attachments to enable participants with impaired grasp to engage the dynamometer, were used by all participants. POWER involved a standardized progression in which movement speed and the number of training sets (i.e., 10 repetitions each) were adjusted to maintain a constant period of active muscle work within each session. Both the FTP and Power programs are elaborated in Figure 3-2.

3.2.5. Kinematic Analysis

Marker data were identified using Qualisys Track Manager, modeled using Visual3D and kinematic trajectories analyzed using custom-written MATLAB scripts. Kinematic data were low-pass filtered (12 Hz cutoff) using a bi-directional 4th order Butterworth filter. The start-of-movement (SOM) was defined as the first point at which the velocity of the marker on the third metacarpalphalangeal joint exceeded 5% peak velocity and the end-of-movement (EOM) as the last point at which velocity of this marker fell below 5% peak velocity.

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14 Copyright© 2012, Biodex Biomedical System 3.2, Shirley, NY, USA
15 Copyright© 2011, Qualisys Qualisys, North America Inc, Charlotte, NC
16 Copyright© 2010 C-Motion, Version 4.00.19, Inc C-Motion, Germantown, Maryland
17 MathWorks®, Version 7.0, Inc., Massachusetts, USA Natick, Massachusetts
The following parameters were calculated from the kinematic trajectories: i) mean velocity - to quantify movement speed; ii) reach-path-ratio (RPR) and sub-movements-to quantify movement accuracy; iii) time-to-peak hand velocity, time-to-max shoulder flexion and time-to-max elbow extension - to quantify motor coordination; iv) shoulder and elbow range of motion and trunk displacement - to quantify movement execution.

Movement time was defined as the time between SOM and EOM. Maximum hand velocity was defined as the maximum tangential linear velocity of the marker on the third metacarpal-phalangeal joint and mean velocity as the average of the hand’s speed during the entire movement. Sub-movements were defined as the number of peaks in the hand velocity profile as defined by SOM and EOM, described above\textsuperscript{5, 43, 191, 207, 208}.

Time-to-peak hand velocity, time-to-max shoulder flexion and time-to-max elbow extension were defined as the time between SOM and maximum hand velocity, maximum shoulder flexion and maximum elbow extension, respectively. Range of motion (ROM) was calculated for shoulder flexion and elbow extension as the difference between the maximum and minimum joint angle achieved. Trunk displacement was defined as the sagittal plane displacement of the sternum marker.

**3.2.6. Statistical Analysis**

Statistical analysis was performed with MATLAB\textsuperscript{®}. Data were tested for normality using the Kolmogorov-Smirnov test. Kinematic data revealed normally distributed data (p > .05), while clinical scores were significantly non-normal (p < .05). Hence, Wilcoxon Rank Sum and Signed Rank tests were used to test clinical variables, while two-sample and paired t-tests were used for kinematic variables. Paired t-tests were used to test for differences between the two trials in kinematic parameters. Significant differences were
not revealed between trials, thus the mean value for each parameter was carried forward for group analysis.

Three sets of comparisons were performed for both clinical and kinematic data: the first two evaluated treatment-specific changes between FTP and POWER, while the third tested the treatment order (A=FTP>POWER vs. B=POWER>FTP). The full set of comparisons included:

- The primary treatment effect, characterized by comparing Block1 change scores between FTP and POWER.

- To probe for a potential period effect, the difference in magnitude of Block1 and Block2 change scores was compared within each treatment order (i.e., (POWER minus FTP) for Order A vs. (FTP minus POWER) for Order B). If FTP and POWER produced equivalent effects, this comparison would be non-significant since both between-blocks differences would reveal a potential period effect. However, a non-zero difference between Orders A and B would reveal additional information regarding differential treatment effects for FTP vs. POWER.

- The effect of treatment order was determined by comparing the overall change between baseline and end of Block2 (i.e., sum of Block1 and Block2 change scores for each group (Order A vs. Order B).

P-values were corrected for multiple comparisons using Holm’s step down procedure. Unless otherwise noted, statistical significance was set at p <.05. Only effects that retained significance after correction are reported in text. All effects and corresponding p-values are reported in Table 3-2 and Table 3-3. Effect sizes, calculated using the mean difference divided by the pooled standard deviation, are reported for each clinical or kinematic measure.

**3.3. Results**

Individual subject characteristics are summarized in Table 3-1. At baseline, participants revealed a mean age of 59.8(±15.0) years (2 female), 15.22(±6.7) months post-stroke and UEFMM score of 33.71(±9.6) points. Concealed allocation resulted in
eight and six participants randomized to treatment orders A and B, respectively. Clinical characteristics revealed no significant differences between groups at baseline.

3.3.1. Clinical Results

Results and effect sizes for all clinical measures are summarized in Table 3-2.

**Treatment effect (FTP vs. Power).** The primary treatment effect revealed a significant difference from 0 in the CMHAI for both treatments, and in Fugl-Meyer Shoulder/Elbow score for Group A only. Between-group differences, approaching statistical significance, were revealed only in the Fugl-Meyer Shoulder/Elbow score. Following correction for multiple comparisons, no significant within or between-group differences remained. Thus, based on clinical assessments, our results indicate that both groups improved without differential treatment effects.

**Period effect (FTP vs. POWER).** Marginal between-group differences were revealed only in the Fugl-Meyer Shoulder/Elbow score and MAS for wrist flexion. However, following correction for multiple comparisons, no significant differences remained either within or between-groups for any of the clinical scales.

**Treatment order effect.** The overall treatment effect for both Order A and B was significantly different from 0 in the CMHAI and UEFMMS. Marginal differences between-groups were revealed only in the CMHAI. However, following correction for multiple comparisons, no significant differences were revealed either within or between-groups for any of the clinical scales.

3.3.2. Kinematic Data

Results and effect sizes for kinematic variables are summarized in Table 3-3.

**Treatment effect. (FTP vs. POWER).** The primary treatment effect revealed significant differences from 0 in: time-to-max elbow extension, time-to-max shoulder
flexion, shoulder flexion ROM, sub-movements and trunk displacement. Between-group differences were revealed in elbow extension ROM and trunk displacement (Figure 3) indicating that following Block1, POWER revealed greater improvements in elbow extension ROM and reduced trunk displacement. These comparisons retained statistical significance following correction for multiple comparisons.

**Period effect. (FTP vs. POWER).** Differential treatment effects were revealed in several parameters. Mean velocity and peak hand velocity time improved more after FTP, while maximum elbow extension time maximum shoulder flexion time, elbow extension ROM, shoulder flexion ROM and trunk displacement improved more after POWER. Following correction for multiple comparisons, between-group differences in mean velocity and trunk displacement retained statistical significance to reveal greater improvements in mean velocity following FTP, while trunk displacement improved more after POWER.

**Treatment order effect.** The overall treatment effect differed significantly from 0 in: time-to-max shoulder flexion, time-to-peak hand velocity and trunk displacement. Between-group differences were revealed in trunk displacement indicating that participants randomized to treatment Order B (POWER>FTP) revealed greater improvements in trunk displacement (i.e., reduced trunk displacement). These effects retained statistical significance following correction for multiple comparisons.

**3.4. Discussion**

**3.4.1. Compensation versus Restoration**

Here we investigated concurrent clinical and kinematic changes following two UE rehabilitation treatments, functional task practice (FTP) and power (POWER) training, with the primary aim of understanding whether improved UE function post-stroke results
from utilization of compensatory movements or restoration of more normal movement patterns. As hypothesized, behavioral motor improvements (e.g., kinematics) post-POWER reveal restoration of more normal movement function. In contrast, behavioral changes post-FTP reveal compensatory movement strategies. While mean reaching velocity increased post-FTP, this apparent improvement involved concurrent reductions in shoulder flexion and elbow extension ROM, and increased trunk displacement – changes indicating reinforcement of compensatory movement strategies⁵. Following POWER, participants increased shoulder flexion and elbow extension ROM, reduced associated trunk displacement and also demonstrated greater improvements in time-to-max shoulder flexion and elbow extension, parameters contributing to normal inter-joint coordination. As revealed by a shift toward normal across numerous kinematic parameters⁶, motor patterns more similar to healthy individuals were revealed following POWER. These behavioral manifestations can be attributed to restoration or true motor recovery.

3.4.2. Effect of Treatment Order

We addressed our secondary aim, understanding the effect of treatment order, using a crossover design. As hypothesized, our data reveal that POWER followed by FTP produced greater improvements, primarily significantly reduced trunk displacement, indicating a marked reduction of compensatory movements. Notably, this reduced compensation was accompanied by reappearance of normal patterns of shoulder and elbow movement present prior to stroke.

3.4.3. Use of Kinematics to Investigate Motor Control

It is important to note that clinical assessments of motor function revealed similar improvements after both POWER and FTP. Clinical scales focus on gross indicators of
task accomplishment (i.e., success or failure of task completion, assistance required, time-to-task-completion) but are unable to discern differences in actual movement performance. This focus on task completion ignores that individual subjects may adopt unique approaches. Indeed, comparable change scores may result from utilization of wholly different movement strategies involving either adoption of compensatory movements or acquisition of normal movement patterns. In this light, results of the present study emphasize the important contribution of kinematics\textsuperscript{191} to understanding the effects and efficacy of neurorehabilitation. The goal of rehabilitation is not only to facilitate behavioral improvement at the level of task completion, but to promote neural recovery and, ultimately, improve the individual’s quality of life\textsuperscript{211}. Accurate evaluation of motor dysfunction is therefore fundamental to developing rehabilitation interventions with the capacity to produce neural recovery that manifests in improved behavioral function. In contrast to the clinical assessments, our results illustrate that UE kinematics\textsuperscript{43, 62, 191, 199} discriminate between normal and compensatory movement strategies and therefore reveal the actual effects of rehabilitation interventions. While the therapeutic goal in this study was not specifically to train to normal\textsuperscript{212}, our kinematic data reveal differential intervention responses with reacquisition of many features of normal movement following POWER.

3.4.4. Neuroplasticity and Specificity of Training

The capacity for neural plasticity after stroke is now well recognized and may include different degrees of physiologic recovery. Current evidence suggests that in both animal and human models with and without stroke, neural recovery and reorganization of neuronal function are not only spontaneous processes but are strongly influenced and modulated by activity (e.g., activity-dependent plasticity)\textsuperscript{213}. Because
recent studies demonstrate that neural plasticity is task specific, task-related practice is considered essential for driving neuroplasticity. However, as Daly suggests, a central assumption of motor learning is that the neural structures controlling movement are required to adapt to constraints that are imposed by: the structure of the musculoskeletal system, the physical laws governing movement, and the impairments that are present. Building on these assumptions, the constraints imposed on the individual in a given motor task must be incorporated into a successful treatment plan. For example, an individual impaired by weakness may be unable to reach and grasp a soda can, thus performance (e.g., completion) of this task would necessarily involve compensation with other body segments or utilization of motor strategies not typically involved in the movement. Rehabilitation using repetitive task-practice would reinforce these abnormal movements and the motor skill acquired would not be the one desired. Latash has proposed that the choice of a particular movement pattern is based on priorities and that under atypical conditions (i.e., structural or biomechanical changes within the neuro-musculo-skeletal system post-stroke), the CNS may reweight its priorities for movement execution leading to altered movement patterns. This perspective suggests that therapeutic approaches directed toward remediation of underlying impairments may reduce the need for reweighting movement priorities. Weakness is one of the most significant impairments post-stroke. Results of the present study indicate that therapeutic intervention directly addressing weakness effectively restores motor control in the hemiparetic UE.

Our results also suggest that an effective therapeutic approach most likely involves multiple stages, each with a specific goal. The present study design reflects
two such stages: i) remediation of hemiparetic weakness by training the individual to recruit and control the requisite force for task execution, followed by ii) utilization of this enhanced neuromechanical capacity in repetitive practice of close-to-normal movements. Therefore, our results are consistent with contemporary principles of neuroplasticity. First, force production is a neurologic phenomenon and there is considerable evidence that strengthening elicits profound adaptations at both supraspinal and spinal levels in non-disabled and neurologically impaired populations. Moreover, the neural phase of strengthening is argued to involve motor learning. Second, weakness contributes to impaired movement patterns and functional motor performance, while changes in critical movement parameters are demonstrated post-strengthening. Finally, repetitive practice of close-to-normal movements is an important aspect of training specificity. Our results suggest that functional outcomes are enhanced when therapeutic interventions train the capacity of the motor system prior to engaging in repetitive task-practice.

3.4.5. Limitations

We acknowledge limitations of the present study. First, FTP did not provide trunk stabilization, while POWER provided some stabilization from the dynamometer chair and chest strap. Other authors have suggested that implicit feedback provided by trunk stabilization may be influential in re-learning of normal motor strategies. Important in this regard is our use of a crossover design and its capacity to monitor differential treatment responses in the same individuals. While all participants received both FTP and POWER, our results reveal a significant order effect when POWER preceded FTP. If the primary affordance of POWER training was the trunk restraint, it is unlikely to have been retained throughout the FTP treatment, which reintroduced the opportunity to
utilize and practice with compensatory trunk movements. Second, while not an explicit limitation, both treatments were based on systematic approaches for intensity and progression; however the physical and physiological demands of POWER were indeed more intense than FTP. Consistent with the literature which indicates that better functional outcomes are associated with higher treatment intensity \( ^{202, 222} \), our data suggest that FTP in isolation may lack the requisite intensity to stimulate the appropriate neuroplastic processes underlying recovery of normal movement patterns. Third, heterogeneity in lesion location among our participants precludes our ability to make direct associations between lesion location and functional outcome. There is a need for further research to analyze the relationship between CST involvement and individual responses to interventions. Finally, our kinematic analysis is based on two trials of each movement. There is no consensus regarding the appropriate or optimal number of behavioral trials to sample. Some investigators capture multiple trials to understand the variability/consistency over repeated trials of a movement\(^{191}\), however in studying individuals with severely compromised motor function our primary concern was to avoid inducing a confounding effect of fatigue.

By current standards of clinical rehabilitation in the United States, 60 sessions of one-on-one treatment delivered over twenty weeks may not readily translate to clinical practice. However, our findings offer an opportunity for reconsideration of appropriate rehabilitation practice models. Importantly, participants in this study presented with lower functional status than in many currently reported studies\(^{54, 223}\), yet substantial UE improvements were revealed across levels of measurement. Our results suggest that our approach of 90 minute treatments thrice weekly for an extended period enables
incorporation of progressive, incremental physiological and behavioral changes into movements encountered in the course of daily life. An additional consideration for rehabilitation practice models is that the systematic power training component of this intervention could be incorporated in the outpatient or community settings where multiple individuals can participate simultaneously.

3.4.6. Clinical Relevance

Here we directly compared two intervention approaches with the aim of demonstrating differential mechanisms of motor recovery. Our findings demonstrate that POWER promotes restoration of normal movement patterns, which may result from increased neural drive from the impaired hemisphere. Importantly, our results demonstrate that it is possible to correct compensatory movement strategies in persons post-stroke and confirm the lack of deleterious effects of high-intensity activities in persons with neurological disorders. Taken together, our results offer novel insight for identifying effective UE rehabilitation interventions that promote restoration of normal motor function. Further experimental studies are necessary to identify the physiological mechanisms that underlie restoration of normal movement.
Table 3-1. Participant characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Affected Side</th>
<th>Premorbid Laterality</th>
<th>Age, years</th>
<th>Time since onset, months</th>
<th>Mechanism of stroke</th>
<th>Lesion Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>24</td>
<td>F</td>
<td>R</td>
<td>61.1</td>
<td>25.2</td>
<td>occlusion</td>
<td>cortical</td>
</tr>
<tr>
<td>Group A</td>
<td>36</td>
<td>M</td>
<td>R</td>
<td>64.5</td>
<td>11.8</td>
<td>infarct</td>
<td>subcortical</td>
</tr>
<tr>
<td>Group A</td>
<td>14</td>
<td>M</td>
<td>L</td>
<td>47.7</td>
<td>13.2</td>
<td>ischemic</td>
<td>cortical</td>
</tr>
<tr>
<td>Group A</td>
<td>26</td>
<td>M</td>
<td>R</td>
<td>66.1</td>
<td>19.8</td>
<td>embolic</td>
<td>subcortical</td>
</tr>
<tr>
<td>Group A</td>
<td>29</td>
<td>M</td>
<td>R</td>
<td>62.3</td>
<td>13.6</td>
<td>infarct</td>
<td>cortical</td>
</tr>
<tr>
<td>Group A</td>
<td>33</td>
<td>F</td>
<td>L</td>
<td>82.3</td>
<td>10.6</td>
<td>hemorrhagic</td>
<td>subcortical</td>
</tr>
<tr>
<td>Group A</td>
<td>48</td>
<td>M</td>
<td>R</td>
<td>22.0</td>
<td>6.8</td>
<td>infarct</td>
<td>cortical</td>
</tr>
<tr>
<td>Group A</td>
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<td>L</td>
<td>46.3</td>
<td>23.9</td>
<td>embolic</td>
<td>cortical</td>
</tr>
<tr>
<td>Mean</td>
<td>31</td>
<td></td>
<td></td>
<td>56.53</td>
<td>15.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Group B   | 39     | M             | R                    | 61.1       | 24.4                     | infarct             | cortical        |
| Group B   | 29     | M             | L                    | 64.5       | 18.5                     | infarct             | subcortical     |
| Group B   | 34     | M             | L                    | 47.7       | 20.2                     | infarct             | cortical        |
| Group B   | 44     | M             | L                    | 66.1       | 11.1                     | dissection          | cortical        |
| Group B   | 49     | M             | R                    | 62.3       | 6.8                      | hemorrhagic         | subcortical     |
| Group B   | 29     | M             | R                    | 82.3       | 7.2                      | ischemic            | cortical        |
| Mean      | 37.33  |               |                      | 64.16      | 14.7                     |                     |                 |

**Note:** Participants were randomly assigned to Groups A or B, reflecting treatment order, where A = FTP followed by POWER and B = POWER followed by FTP. Baseline equivalence between groups was confirmed for Upper-Extremity Fugl-Meyer motor score, age and time since stroke onset (all ps>0.05). Mechanism of stroke was determined from review of medical records and lesion location by confirmatory neuroimaging.
<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Mean (SD)</th>
<th>Wilcoxon Rank Sum</th>
<th>Wilcoxon Signed Rank</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Order A)</td>
<td>(Order B)</td>
<td>P-Value</td>
<td>(Order A)</td>
</tr>
<tr>
<td><strong>Primary Treatment Effect (Difference Following Treatment 1 (Eval1))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chedoke McMaster</td>
<td>14.83 (7.93)</td>
<td>9.43 (7.18)</td>
<td>0.284</td>
<td>0.031</td>
</tr>
<tr>
<td>European Stroke scale</td>
<td>2.86 (2.41)</td>
<td>3.167 (4.1)</td>
<td>0.772</td>
<td>0.031</td>
</tr>
<tr>
<td>Fugl-Meyer Shol/Elbow Score (30 pts)</td>
<td>3.57 (1.99)</td>
<td>1.43 (4.12)</td>
<td>0.062</td>
<td>0.016</td>
</tr>
<tr>
<td>Fugl-Meyer Motor Score (66 pts)</td>
<td>7.00 (9.09)</td>
<td>6.71 (4.40)</td>
<td>0.564</td>
<td>0.156</td>
</tr>
<tr>
<td>MA Elb Ext</td>
<td>-0.29 (1.25)</td>
<td>0.29 (0.76)</td>
<td>0.389</td>
<td>1.000</td>
</tr>
<tr>
<td>MA Elb Flex</td>
<td>-0.71 (1.11)</td>
<td>-0.29 (0.95)</td>
<td>0.477</td>
<td>0.250</td>
</tr>
<tr>
<td>MA Sh Abd</td>
<td>-0.29 (0.76)</td>
<td>-0.14 (0.70)</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>MA Sh Ext</td>
<td>-0.86 (1.21)</td>
<td>-0.14 (0.38)</td>
<td>0.229</td>
<td>0.250</td>
</tr>
<tr>
<td>MA Sh Flex</td>
<td>0.00 (0.63)</td>
<td>0.00 (0.58)</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>MA Wrist Ext</td>
<td>-0.29 (0.76)</td>
<td>-0.71 (1.11)</td>
<td>0.393</td>
<td>1.000</td>
</tr>
<tr>
<td>MA Wrist Flex</td>
<td>-0.29 (0.76)</td>
<td>0.57 (1.13)</td>
<td>0.110</td>
<td>1.000</td>
</tr>
<tr>
<td>RNL</td>
<td>-1.57 (7.14)</td>
<td>0.86 (6.54)</td>
<td>0.481</td>
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<td>Fugl-Meyer Shol/Elbow Score (30 pts)</td>
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<td>Fugl-Meyer Motor Score (66 pts)</td>
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<td>MA Wrist Ext</td>
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<td>Order Effect (Overall Difference (Eval3))</td>
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Note: Table describes mean change (SD) in clinical scores, p-values and effect sizes for comparisons as described in methods. Abbreviations: MA – Modified Ashworth Scale; RNL – Reintegration to normal living index.
Table 3-3. Kinematic data.

<table>
<thead>
<tr>
<th>Kinematic Variable</th>
<th>Mean (SD)</th>
<th>Between-group comparisons</th>
<th>Within-group comparisons</th>
<th>Effect size</th>
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<td>(Order B)</td>
<td>P-Value</td>
<td>Order A</td>
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Table 3-3. Continued

<table>
<thead>
<tr>
<th>Kinematic Variable</th>
<th>Mean (SD)</th>
<th>Between-group comparisons</th>
<th>Within-group comparisons</th>
<th>Effect size</th>
</tr>
</thead>
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<tr>
<td></td>
<td>(Order A)</td>
<td>(Order B)</td>
<td>P-Value</td>
<td>Order A</td>
</tr>
<tr>
<td>Order Effect (Overall Difference (Eval3))</td>
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Note: Table describes mean change (SD) in kinematic parameters, p-values and effect sizes for comparisons as described in methods. Abbreviations: RPR – reach path ratio; Max_Elbow_Ext_time – time-to-maximum elbow extension; Max_Shoulder_Flex_time – time-to-maximum shoulder flexion; Peak_Hand_Vel_time – time-to-peak hand velocity time; ROM_Elbow_Ext - elbow range of motion; ROM_Shoulder_Flex – shoulder range of motion.
Figure 3-1. Study design. Summarizing the cross-over design. Participants were evaluated three times: at baseline and after each treatment block. The treatment order for Group A was FTP followed by POWER and for Group B POWER followed by FTP.
Figure 3-2. Treatment protocols. Sections A and B: Outline of the functional task practice (FTP) program. Consistent with our previous work, the FTP program addressed six global therapeutic goals A). Therapeutic activities (B) were developed on the basis of the current therapeutic goal, the nine activity categories listed in the sub-table, the participant’s functional ability and his/her personal goals. Each 90-minute treatment session involved 15 minutes of stretching and warm up, followed by practice of activities in each of the 9 categories for 8 minutes each. Specific examples of activities for high and low functioning individuals are provided. To assure consistency
across all participants, treatment was advanced to the next therapeutic goal on the timeline specified, the nine activity categories were presented in rotation, and timing of each category was adhered to. **Section C: Outline of the POWER training.** Participants performed both concentric and eccentric actions for 10 consecutive weeks. Movement speed ranged from 30 to 90 degrees per second for eccentric and from 30 to 180 degrees per second for concentric actions. Each bar represents one set of 10 repetitions at the criterion speed noted on the Y-axis. A primary goal of power training is to improve the capacity for force production in dynamic conditions. Therefore, the training prescription was progressed through advancement of the criterion movement speed. Because the neuromuscular active state differs with movement speed, the number of sets was adjusted to maintain a consistent work:rest ratio across the 10 week program. Referenced to Week 1 (3 sets of each exercise: Con 30°/s, Con 60°/s, Ecc 30°/s), the work:rest averaged 1.07 (±.08, range 0.97 – 1.27). Each set involved 10 repetitions
Figure 3-3. Key kinematic parameters of functional reach-to-grasp reveal effects of FTP and Power. Left panel describes Treatment effect (differences following treatment 1). Graphs describe mean and standard errors of mean velocity (Panel A), elbow extension ROM (Panel B) and trunk displacement (Panel C) at baseline, and after first and second treatments. Group A (FTP followed by POWER) corresponds to white bars, Group B (POWER followed by FTP) to gray bars. Graphs show significant effect in elbow extension ROM (Left Panel B) and Trunk displacement (Left Panel C). Right panel describes Period effect (difference in magnitude of Block1 and Block2 change scores). Graphs describe change scores after first and second treatments. Results show significant effect in mean velocity (Right Panel A) and trunk displacement (Right Panel C).
CHAPTER 4
POWER TRAINING ENHANCES ELBOW STRETCH REFLEX MODULATION POST-STROKE

4.1. Background

Between 20-40% of persons post-stroke experience spasticity\textsuperscript{225}. Spasticity is a symptom of impaired motor control commonly observed in the upper-extremity\textsuperscript{226} which may interfere with normal movement post-stroke. Classically defined, spasticity is a velocity-dependent involuntary resistance to passive muscle stretch\textsuperscript{11}. The phenomenon of spasticity involves two components: hypertonia – increased mechanical resistance to stretch, and hyperreflexia – exaggerated reflex activity in resting muscles. Both hypertonia and hyperreflexia can be quantified using passive stretches imposed under controlled velocity conditions\textsuperscript{227, 228}. Torques obtained from the passive stretch paradigm characterize hypertonia and provide information that parallels the clinical Ashworth Scale, while electromyographic responses (EMG) obtained concurrently with passive stretches characterize hyperreflexia\textsuperscript{228}.

Traditional clinical perspectives on neurorehabilitation\textsuperscript{13} argued that spasticity imposed the greatest impairment to motor function and represented the most significant limitation to motor recovery. Moreover, spasticity appeared to be exacerbated with exertion, therefore, any form of high-effort activity, including muscle strengthening, was strictly proscribed in neurorehabilitation\textsuperscript{13}

In contrast, some authors have demonstrated that weakness, rather than spasticity, is the primary cause of dysfunctional movement post-stroke\textsuperscript{229}. Several studies fail to demonstrate a significant functional relationship between spasticity and functional motor performance\textsuperscript{12}. Thilmann et al.\textsuperscript{17} studied stretch-induced EMG responses and found that, compared with controls, persons post-stroke had increased resistance to limb displacement at rest but not when the arm was actively moving, suggesting that spasticity does not contribute to motor-control abnormalities in hemiparesis. In another study, Thilmann et al. studied both the stretch-induced EMG (hypereflexia) and torque (hypertonia) responses\textsuperscript{17,68}. They found that hypertonia was associated with muscle contracture rather than with reflex hyperexcitability, and detected no relationship between hypertonia and either weakness or loss of dexterity. Another study on 95 post-stroke patients showed that severe functional disability occurred almost equally either in the presence or absence of spasticity\textsuperscript{225}.

A contemporary review of evidence suggests that high-exertion training, such as resistance training, improves upper-limb function without exacerbating muscle spasticity\textsuperscript{16}. In support of the importance of resistance training post-stroke, a recent review\textsuperscript{19} confirmed: 1) that the presence of weakness post-stroke could aggravate spasticity in many ways including: reduced traffic in descending pathways responsible for voluntary movement; muscle fiber atrophy and contracture; changes in the spatial and temporal patterns of muscle activation, causing an inefficient EMG-torque relationship; loss of functional motor units and changes in the properties of remaining units producing a decrease in maximal force due to activation on a suboptimal portion of the force-length relationship\textsuperscript{24}; 2) that strengthening can positively increase strength,
promote functional improvement and, potentially change quality of life without increasing spasticity\textsuperscript{19}.

Our research team conducted a set of studies that contributes to the evidence that resistance training as an intervention post-stroke can induce restoration of more normal movement patterns and promote appropriate activity in neural circuits\textsuperscript{18, 60, 61}. First, Patten et al.\textsuperscript{60} conducted a randomized clinical trial of upper-extremity rehabilitation to compare the effects of functional task practice, and a hybrid intervention of functional task practice combined with dynamic high-intensity resistance training post-stroke. Further, Patten et al.\textsuperscript{18} compared the effects of high-intensity resistance training and hybrid training during stretch-reflex modulation. The findings of this study suggested that: first, upper-extremity rehabilitation involving high-exertion activity did not exacerbate either the hyperreflexic or hypertonic components of spasticity in adults post-stroke. Second, they illustrate that high-intensity resistance training promoted a more appropriate modulation of stretch-induced EMG responses. These neurophysiologic adaptations were associated with upper-extremity motor function improvement evaluated with the Wolf Motor Function Test – Functional Ability Scores (FAS).

In our previous work, we compared\textsuperscript{61} power training (i.e., dynamic high-intensity resistance training) with functional-task-practice training on a battery of clinical scales and on kinematics during a reaching task. We demonstrated that, although clinical evaluation did not reveal any differential effect of treatment, kinematic improvements following power training revealed a restoration of more normal movement patterns, while improvement after functional-task-practice suggested reinforcement of
compensatory strategies. Specifically, following functional-task practice, hemiparetic participants demonstrated increased mean velocity during reaching, but reduced shoulder flexion and elbow extension range of motion, which were compensated by increased trunk displacement. In contrast, following power training, participants increased shoulder flexion and elbow extension range of motion and reduced associated trunk displacement. This study showed that power training is effective in inducing behavioral recovery; however it did not evaluate neural adaptation of power training.

Here, we compare the effects of POWER and FTP on stretch-reflex modulation. The aims of this study are: 1) to test the differential effects of POWER and FTP interventions, and 2) to test the effect of treatment order on stretch-reflex modulation. We hypothesize that POWER will reveal greater improvements in stretch-reflex modulation due to increased cortical drive and that the treatment order of FTP preceded by POWER would reveal greater behavioral motor improvements because FTP would be more effective following restoration of neuromechanical function.

4.2. Methods

4.2.1. Participants

The study population was comprised of sixteen participants (mean age 59.80 ±15.01 yrs, 2 female) who suffered a single stroke (time since onset 15.22±6.67 months). Inclusion criteria for the parent study involved: clinical presentation of a single, unilateral stroke; freedom from significant upper-extremity joint pain, range of motion limitations, or major sensory deficits as evidenced by absent proprioception at the elbow or shoulder joints. Additionally, participants were required to demonstrate: 1) ability to move the elbow and shoulder in the horizontal plane corresponding to a poor
(2/5) manual muscle test grade\textsuperscript{204} in the major shoulder and elbow agonists, 2) at least $10^\circ$ of active wrist extension, $10^\circ$ active thumb abduction, and $10^\circ$ active extension of any two digits, three times within one minute\textsuperscript{230} and 3) ability to relax the biceps brachii (i.e., silent EMG) with the arm positioned in elbow flexion out of the plane of gravity.

Participants were screened using the Neurobehavioral Cognitive Status Exam (Cognistat)\textsuperscript{231} to assess their capacity to comprehend and follow three-step commands. All aspects of the study described here were approved by the Stanford University panel on human participants in medical research and all participants provided informed consent in accordance with the Declaration of Helsinki.

4.2.2. Procedure

After providing written informed consent, all participants were enrolled in a two stage cross-over design (Figure 4-1). Participants were randomized to either treatment Order A (FTP followed by POWER) or B (POWER followed by FTP). Each treatment block (either FTP or POWER) lasted ten weeks and included 3 (90 minutes) sessions per week. Thus, each participant received a total of 60 sessions (i.e. 180 hours) of one-on-one treatment delivered by a licensed physical therapy. The treatment blocks were separated by two weeks of inactivity. Participants underwent to four evaluations: 1) at baseline, 2) after the first and 3) second treatment blocks and 4) at 6 months follow up (retention). Both, the participants and the assessors were blinded to the order randomization.

4.2.3. Intervention

The treatment algorithms have been previously described in detail\textsuperscript{61}. All participants received either FTP or POWER interventions in separate bouts to allow comparison of individual treatment effects. FTP involved practice of functional tasks
using a progression of six therapeutic goals and nine activity categories. Specific therapeutic tasks were chosen from these activity categories based on participant-specific goals and baseline functional level and practiced on a structured rotation within the framework of the overriding therapeutic goals. POWER involved five reciprocal upper-extremity movements: shoulder abduction/adduction, shoulder flexion/extension, shoulder external/internal rotation, transverse plane elbow flexion/extension and wrist flexion/extension, which were trained using a commercially available dynamometer. Custom-designed attachments to enable participants with impaired grasp to engage the dynamometer were used by all participants. POWER involved a standardized progression in which movement speed and the number of training sets (i.e., 10 repetitions each) were adjusted to maintain a constant period of active muscle work within each session.

4.2.4. Evaluations

Stretch Reflex testing was performed using ramp-and-hold elbow extensions applied using a commercially available dynamometer operated in passive mode. Surface electromyography (EMG) was recorded from the biceps brachii using pre-amplified electrodes. Elbow extensions covered a 100-degree range ending at the participant’s full anatomical range of motion. Each trial was comprised of four phases: a 10 second static hold in elbow flexion; passive elbow extension at criterion speed; a 5 second static hold in full extension; and a passive return to elbow flexion at 30°/s. Two conditions were performed: passive, in which subjects were instructed to relax as the

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limb was moved through the full range of elbow motion by the dynamometer; and
preloaded, in which the subjects sustained an isometric contraction of elbow flexor
muscle at 20% of MVIC before and during passive elbow extension stretches. Data
were collected at four criterion speeds (i.e., 90°/s, 150°/s, 210°/s and 270°/s). To
quantify passive joint torques, two additional trials were performed at 10°/s. The
reliability of both EMG and torque responses was already been established for ramp-
and-hold stretches obtained using this paradigm228.

4.2.5. Stretch Reflex Analysis

The slow (10 deg/s) passive torque response at each position was subtracted from
the torque measured during stretches imposed at all speeds. EMG activity was
evaluated as the mean amplitude calculated over a 100 ms sliding window. For each
trial, EMG was defined as active when the mean amplitude exceeded threshold (i.e.,
mean baseline, resting EMG plus 2.5 standard deviations). EMG data were used to
obtain the following parameters indicative of stretch reflex modulation:

- **EMG Burst Duration.** The percentage of the movement time during which EMG
  activity will be present.

- **Position Threshold.** The joint angle, expressed in degrees of elbow flexion, at
  which muscle activity will be first identified.

- **Burst Intensity.** The mean amplitude of EMG activity when the muscle will be
  active minus the baseline resting activity.

4.2.6. Statistical Analysis

For each parameter (i.e. EMG burst duration, position threshold and burst
intensity), comparisons were performed to evaluate treatment-specific changes between
FTP and POWER, the treatment order (A=FTP>POWER vs. B=POWER>FTP) (Figure
4-1) and the retention effect. We calculated the difference scores between:
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- **Baseline and Block 1 Evaluations.** To test the first-block treatment effect, either POWER or FTP, depending on treatment order (Order A vs. Order B).

- **Block 1 and Block 2 Evaluations.** To test the second-block treatment effect.

- **Block 2 and Block 3 Evaluations.** To test the retention effect, at 6 month follow-up.

- **Block 3 and Baseline Evaluations.** To test the order effect.

Statistical analysis was performed with JMP 9 software\textsuperscript{20}. Kolmogorov-Smirnov test revealed normally distributed data (p >.05). We performed analysis of variance including the following factors: orders (i.e., Order A or Order B), condition (i.e., Passive or Preloaded), block (i.e., 1, 2, or 3), treatment (i.e., FTP, POWER and Retention) and speed (i.e., 90°/s, 150°/s, 210°/s and 270°/s). We evaluated the interactions between the factors for each stretch reflex parameter (i.e., EMG burst duration, position threshold and burst intensity). Unless otherwise noted, statistical significance was set at p <.05. P-values were corrected for multiple comparisons using a Bonferroni correction.

### 4.3. Results

We did not find differences among reflex responses across criterion velocities (p>0.05) for all three stretch-reflex parameters. Therefore, data from all four criterion velocities were collapsed. Further, we did not find differences between passive and preloaded conditions (p>0.05).

#### 4.3.1. Treatment Effect

POWER produced significantly greater improvement in stretch reflexes modulation in all three parameters (all p-values < 0.01) (Figure 4-3 –Top row). POWER produced a 350 ms (SD±30) decrease in burst duration, 21.73° (SD ±3.89) decrease in position.

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threshold (i.e., EMG onset occurred at greater elbow extension by 21.73°) and 89.62 ms (SD ±21.08) increase in EMG onset latency. In contrast, FTP produced only 10 ms (SD±20) decrease in burst duration, 4.30° (SD±2.97) decrease in position threshold and 1.49 ms (SD±15.87) increase in EMG latency.

4.3.2. Retention Effect

In general, at retention, improvements in stretch reflex modulation were partially maintained: 10 ms (SD±30) increase in burst duration, 11.17° (SD±4.26) decrease in position threshold and 25.11 ms (SD±18.43) increase in EMG onset latency ((Figure 4-3 –Top row).

4.3.3. Period Effect (Treatment Block by Group)

Independently of its position in the treatment order, POWER produced significantly greater improvements in stretch reflex modulation in all three parameters (all p-values < 0.01) (Figure 4-3 – Middle row). After POWER, burst duration decreased of 450 ms (SD±40) in the first block treatment and 240 ms (SD±50) in the second block treatment. Instead, after FTP, burst duration decreased by 80 ms (SD±20) in the first block treatment and increased (i.e., worsening) by 60 ms (SD±40) in the second block treatment. After POWER, position threshold decreased 33.02° (SD±4.88) in the first treatment block and 10.24° (SD±5.73) in the second treatment block. After POWER, EMG onset latency increased by 152.78 ms (SD±34.31) in the first treatment block and of 26.47 ms (SD±21.71) in the second treatment block. After FTP, EMG onset latency increased by 18.30 ms (SD±22.72) in the first treatment block, but decreased (i.e. worsening) in the second treatment block.
4.3.4. Order Effect

When POWER was followed by FTP (Group B), overall outcomes were significantly greater for burst duration and latency (p-values < 0.05) (Figure 4-3 – bottom row). Overall, burst duration decreased by 410 ms (SD±50) in Group B but only 290 ms (SD±50) in Group A; position threshold decreased by 30.10⁰ (SD±8.30) in Group B and only 20.31⁰ (SD±5.56) in Group A; EMG onset latency increased by 136.36 ms (SD±34.03) in Group B and only 41.46 ms (SD±24.13) in Group A.

4.4. Discussion

Primary effects. We compared the effects of POWER and FTP training on stretch-reflex modulation. The primary aims of this study were to test: 1) the differential effects of POWER and FTP interventions, and 2) the effect of treatment order on stretch-reflex modulation. We hypothesized that POWER would reveal greater improvements in stretch-reflex modulation due to enhanced afferent regulation and that the treatment order FTP proceeded by POWER would reveal greater behavioral motor improvements because FTP would be more effective following restoration of neuromechanical function.

As hypothesized, POWER produced greater improvements of stretch-reflex modulation than FTP for all parameters: EMG burst duration, position threshold and burst intensity. These findings indicate that POWER constitutes a potent form of neuromotor training. Besides adaptation in the muscle itself, profound neural adaptations after resistance training are well recognized⁵¹-⁵³. The primary mechanisms for force production and force control reside supraspinally and in the spinal circuitry. Findings of this study suggest that POWER induces restoration of mechanisms
controlling spinal motoneuron discharge\textsuperscript{17,68,187,189}. These mechanisms are likely mediated by improved descending (supraspinal) control of pre-synaptic Ia inhibition\textsuperscript{187} and enhanced post-activation (spinal) depression\textsuperscript{187,189}.

We addressed our secondary aim, understanding the effect of treatment order, using a crossover design. As hypothesized, our data reveal that POWER followed by FTP produced greater improvements, most significantly for EMG burst duration and EMG latency. Changes in position threshold failed to reach statistical significance difference between treatment Order A and B.

**Influence of voluntary activation and speed.** The study design included passive and preloaded conditions with the attempt to discriminate between supraspinal and spinal adaptations. The preloaded condition was implemented to stimulate the voluntary supraspinal descending control by means of an isometric contraction of elbow flexor muscle before and during passive elbow extension stretches\textsuperscript{232}. In an intact nervous system, one of the major inhibitory circuitry regulating the excitability of the spinal motoneurons is the Ia inhibitory interneuron pool\textsuperscript{232}. These interneurons receive input from Ia afferent and supraspinal center and are responsible for reciprocal inhibition of antagonist muscle\textsuperscript{232}. Therefore, as a consequence of antagonist contraction, we were expecting a reduction of the stretch reflex responses by increase of disynaptic reciprocal inhibition and pre-synaptic inhibition of Ia afferents. In contrast to our hypothesis, our data suggest that the post-intervention adaptation effects did not differ between the two conditions in any of the stretch reflex parameters. This lack of differential effects between passive and preloaded conditions may suggest that both the passive and pre-loaded conditions are testing the same neurophysiologic function or
that participants of this study had an inappropriate depression of the inhibitory mechanisms controlling the stretch reflex$^{232}$.

Further, this study evaluated stretch reflex modulation at different velocities (i.e., 90°/s, 150°/s, 210°/s and 270°/s). Our findings suggest that treatment effects did not differ between velocities. Previous work also found that stretch reflex responses are weakly dependent on stretch reflex velocity. Wolf et al$^{233}$ demonstrated that position threshold is not affected by speed (1.0 radian/s) in post-stroke individuals and suggested that the speed used in their study may not have been fast enough to induce a speed effect. Further, Powers et al$^{227, 234}$ demonstrated that the stretch-evoked torque was not dependent on stretch reflex velocity. The authors suggested that the individual stretch reflex threshold may influence the relationship between the stretch reflex responses and the stretch speed. Thus, failure to detect a statistically significant effect does not necessary indicate a lack of speed effect. Further research should address the relationship between individual stretch reflex threshold and a wider range of speeds.

**Neuromechanisms.** Many spinal pathways control the excitability of the stretch reflex and a malfunction in any of them could theoretically produce an exaggeration of the stretch reflex including Ib inhibition, recurrent inhibition, disynaptic reciprocal Ia inhibition and presynaptic mechanisms. However, the main two mechanisms that have been postulated to influence the stretch reflex modulation post-stroke are: 1) impaired (decreased) presynaptic Ia inhibition$^{184,129,187,232}$ and 2) decreased post-activation depression (homosynaptic depression)$^{184,129,187,232}$. The argument that presynaptic Ia inhibition may be decreased spastic individuals, emerges from observation of decreased H-reflex depression induced by tonic vibration applied to the antagonist
The fact that the depression is associated to a motor discharge (the tonic vibration response), authors suggested that it must have a presynaptic influence. However, when tonic vibration was applied to the homonymous tendon, it also induced H-reflex depression due to post-activation depression evoked by repetitive synaptic activation. Post-activation depression also contributes to the vibratory-induced depression of the reflex and it can be attributed to the repetitive activation of the Ia-motoneurone synapses. It is well recognized that resistance training induces change within the nervous system. However, the argument for whether these changes affect both the spinal and the supraspinal circuitries is still open. Enoka described phenomena that show evidence of neural adaptation after strengthening in non-disabled individuals, such as an increase in a muscle's strength in the absence of muscular adaptations, strength changes in the limb contralateral to the trained muscle, and specificity of strength adaptations to the training movements. Carroll et al. suggested that resistance training is associated with an increase in short-term motor-unit synchrony, which is argued to result from changes in synaptic efficacy within the motoneuron pool. These observations imply that after resistance training the number, or the strength, of the connections to the motoneurons of trained muscles may increase which suggests that resistance training may improve the synaptic efficacy between the cortico-spinal cells and spinal motoneurons. However recently, Falvo et al. demonstrated that three weeks of resistance training elicited significant strength gains which were accompanied by neural adaptation at the level of the cortex. The authors were able to demonstrate supraspinal adaptations using movement-related cortical potentials (MRCP). Following training, the authors found MRCP amplitude was
attenuated at several scalp sites overlying motor-related cortical areas and the onset of MRCP was anticipated. Furthermore, Kokotilo et al.\textsuperscript{50} conducted a systematic review of neuroimaging studies that examined reorganization of brain function during force production and force modulation after stroke. Their review includes a number of imaging modalities, including functional magnetic resonance (fMRI), TMS, electroencephalography (EEG) and magnetoencephalography (MEG). They conclude that motor reorganization occurs with respect to force generation and modulation after stroke. Key findings across studies were that during force production, increased activation in motor areas, including the undamaged contralesional hemisphere, occurred in people with more severe stroke, and recruitment of these motor areas often diminished as motor function recovered. With respect to force modulation, increased activation in motor areas occurred with greater force generation in people with stroke, and those with more severe stroke showed greater activation with increasing force-production levels.

One of the purposes of this study was to evaluate the potential effect of POWER training on the descending cortical drive. The preloaded condition was implemented to evaluate the presynaptic, descending cortical influence and the passive condition was implemented to evaluate the putative monosynaptic spinal reflexes. In contrast to our hypothesis, our data did not allow us to discriminate between spinal and supraspinal (presynaptic) influences by using the preloaded condition. Future studies with more sophisticated techniques such as transcranial magnetic stimulation (TMS) and H-reflex should further investigate the origin of neuroadaptations after resistance training. These techniques will allow to study the supraspinal involvement and to explore the relative
contributions of presynaptic Ia inhibition and postactivation depression to the malfunction of the arc reflex post-stroke.

Our hypothesis is that POWER induces neuroadaptations at spinal (including presynaptic and monosynaptic inhibitory pathways) and supraspinal levels. Specifically, it increases the central neural drive leading to enhanced recruitment of the spinal circuitry and consequent improved control of the force required for execution of complex multi-segmental tasks.

**Relevance.** We directly compared two intervention approaches with the aim of demonstrating differential mechanisms of neuromotor recovery. Our findings demonstrate that POWER promotes greater improvements of stretch reflex modulation and better retention of these improvements at follow-up six months following intervention. Further, POWER followed by FTP induced greater improvement in stretch reflex parameters than vice versa, which may result from increased neural drive from the impaired hemisphere. Importantly, our results confirm the lack of deleterious effects of high-intensity activities in persons with neurological disorders\textsuperscript{14, 15}. Taken together, our results offer novel insight for identifying effective UE rehabilitation interventions that promote restoration of normal motor function, including stretch reflex modulation, post-stroke. Further experimental studies are necessary to 1) better identify the physiological mechanisms that underlie improved reflex modulation, such as the contribution of presynaptic and monosynaptic inhibitory pathways after POWER training and 2) explore the effect of POWER training on the impaired cortical descending inhibitory control.
Figure 4-1. Study design. Summarizing the cross-over design. Participants were evaluated 4 times: at baseline, after each treatment block and at 6 months follow up. The treatment order for Group A was FTP followed by POWER and for Group B POWER followed by FTP.
Figure 4-2. Passive stretch reflex. Top row shows treatment effects. Middle row shows group by block effect. Bottom Raw shows Order effect. Black columns indicate FTP treatment, gray columns indicate POWER treatment and light gray columns indicate retention. Black columns with gray borders indicate FTP preceded POWER (Order A). Gray columns with black borders indicate POWER preceded FTP (Order B).
CHAPTER 5
UPPER-EXTREMITY REHABILITATION REDUCES INTER-HEMISPHERIC
COMPETITION POST-STROKE

5.1. Background

Limited recovery of upper extremity function continues to be one of the greatest challenges faced in neurorehabilitation for persons post-stroke. As a result, there is an urgent unmet need to identify effective approaches to drive upper-extremity (UE) recovery. Contemporary approaches to motor rehabilitation are based on evidence that practice and experience drives cortical reorganization following neural injury\textsuperscript{100, 236}. Current UE treatment approaches focus on repetitive execution of functional movements, ostensibly to facilitate neural plasticity\textsuperscript{237}. However, while these therapeutic methods show promise in improving UE function post-stroke, most of the work to date documents improvements through clinical or gross behavioral measures, which emphasize task accomplishment more than motor control or neuroplastic changes\textsuperscript{36}. Thus, there remains a significant knowledge gap between means required to induce positive neurobiological and behavioral change that constitutes functional recovery in humans post-stroke. This discrepancy suggests that repetitive execution of functional movements alone may not be sufficient to drive the necessary cortical reorganization and effect functional improvement following stroke. Therefore, there is a clear need to augment or potentiate the behavioral effects derived from experience-driven therapies for this clinical population.

\begin{itemize}
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Traditionally, UE behavioral treatment approaches have focused on repetition of functional movements (i.e. task practice), which is argued to facilitate neural plasticity\textsuperscript{237}. Despite the presence of profound weakness, strengthening has been proscribed in neurorehabilitation because it is assumed to exacerbate spasticity and impair motor performance\textsuperscript{13}. Mainstream therapeutic interventions, such as constraint-induced movement therapy (CIMT)\textsuperscript{237} and functional task-practice (FTP)\textsuperscript{237}, show promise at promoting improved UE function, however the metrics of improvement are gauged by clinical scales or gross behavioral measures that emphasize task accomplishment over reacquisition of appropriate motor strategies or neuroplastic changes\textsuperscript{36}. Importantly, assessing task completion fails to distinguish compensatory (i.e., maladaptive) strategies from restoration (i.e., strategies used by non-disabled individuals) at either the behavioral or neural levels\textsuperscript{78}. Our research team has completed a set of studies demonstrating that high-intensity resistance training (i.e. POWER training), performed either in isolation or in combination with FTP (i.e. HYBRID training)\textsuperscript{61}, can induce restoration of more normal movement by improving neuromechanical function. These positive outcomes can most likely be attributed to profound, well-recognized neural adaptations that occur at the level of the spinal cord and motor cortex\textsuperscript{53}. While our studies to date demonstrate that POWER is an effective treatment at the behavioral level, we have not had the opportunity to measure neuroplastic changes that may occur in the brain, or elsewhere in the neuraxis, concurrently with behavioral and neuromechanical recovery.
Following stroke, activity in the affected hemisphere (AH) is disrupted; not only by the infarct itself, but also by inhibition from the unaffected hemisphere (UH) which further reduces the excitability of the AH. As first described by Ward and Cohen\textsuperscript{63} and more recently stated by Nowak’s\textsuperscript{64} hypothesis of inter-hemispheric competition post-stroke, the primary motor cortex of the UH becomes disinhibited and exerts exaggerated inhibition onto the primary motor cortex of the AH.

Among several innovative, non-invasive techniques for improving motor recovery post-stroke, repetitive transcranial magnetic stimulation (rTMS) shows considerable promise\textsuperscript{73}. rTMS involves focused magnetic stimulation applied to the skull to target a particular brain area\textsuperscript{75}. In healthy adults, rTMS at frequencies less than 1Hz can suppress excitability of the motor cortex, causing an inhibitory effect, while at higher frequencies (e.g., >1Hz) rTMS can increase cortical excitability, causing facilitation\textsuperscript{72}. The capacity for rTMS to influence cortical excitability contributes to the rationale for its use as a therapeutic adjuvant that may improve the efficacy of rehabilitation strategies for persons post-stroke\textsuperscript{64, 76}. Modulation of cortical excitability with rTMS may induce synaptic plasticity and potentially limit development of maladaptive neural strategies\textsuperscript{63, 64}. Asymmetric cortical excitability resulting from stroke may enable maladaptive neuromotor strategies, disrupting physiological activity in transcallosal pathways and producing an imbalance in the reciprocal inhibitory projections between hemispheres\textsuperscript{63, 64}. In this context, rTMS has been also been proposed as a theoretical approach to restore the balance of inter-hemispheric inhibition post-stroke (e.g., reduce inter-hemispheric competition)\textsuperscript{63, 64, 63, 64, 73}. 
The current literature reveals positive effects of rTMS post-stroke including: modulation of cortical excitability (e.g., MEP amplitude, recruitment curves, motor threshold) suggesting improved inter-hemispheric balance. However, it is important to note that no studies to date have directly investigated the effects of rTMS on IHI. Thus, support for the theoretical explanation that rTMS rebalances inter-hemispheric inhibition remains to be demonstrated. The current working hypothesis holds that inhibitory rTMS over the unaffected hemisphere (UH) reduces transcallosal inhibition from the unaffected to the affected/ipsilesional hemisphere and facilitatory rTMS over the affected hemisphere (AH) increases excitability of the AH and increases transcallosal inhibition from the affected to the unaffected/contralesional hemisphere. Consistent with effects noted in healthy individuals, constant high-frequency rTMS (trains of stimuli separated by inter-trains intervals) has been used in two ways in persons post-stroke: low-frequency (e.g., ≤ 1Hz) stimulation of the UH to reduce hyper-excitability of the contralesional hemisphere, or high-frequency (e.g., >1 Hz) stimulation of the AH to increase excitability of the ipsilesional hemisphere\textsuperscript{70}. Some investigators favor low-frequency rTMS to the UH over high-frequency rTMS to the AH because of its wider toleration and fewer potential risks of inducing seizures\textsuperscript{61}, although review of the current literature does not support these concerns (Appendix A).

This study addressed the gap between inducing neurobiological and behavioral change that constitutes functional recovery by examining combined behavioral and neurobiological approaches that represent potential drivers of cortical reorganization.
We combined behavioral therapies that improve strength (POWER) and motor skill (FTP) with therapeutic inhibitory repetitive transcranial magnetic stimulation (rTMS).

Specifically, the aims of this study were to: 1) test the hypothesis of inter-hemispheric competition post-stroke; 2) test whether it was possible to restore a balance of inter-hemispheric competition; and 3) test whether rTMS combined with POWER training resulted in better functional, biomechanical and neurophysiological outcomes than rTMS combined with FTP.

Consistent with Nowak’s assumption, we hypothesized that: 1) the primary motor cortex of the UH would be disinhibited and would exert exaggerated inhibition onto the primary motor cortex of the AH; 2) inter-hemispheric competition could be reduced; and 3) based on our previous studies, the combination of inhibitory rTMS on the UH with POWER training of the affected arm would reveal reduced hemispheric competition and improved motor behavior.

5.2. Methods

5.2.1. Subject Characteristics

Here we report two single case designs.

Case 1. The patient was a 59-year-old, left hand dominant, white male who was enrolled in the present study 6-months following a lacunar infarction of the right putamen and periventricular white matter with consequent left hemiparesis affecting both the upper and lower extremities. Baseline clinical scores revealed low level of spasticity measured by Modified Ashworth Scale (MAS) (composite score, 3 out of 32), a medium level of motor impairment measure by Fugl-Meyer Upper-Extremity
Motor Score (UEFMMMS)\textsuperscript{93} (47 out of 66) and no sensory impairment by the sensory portion of the UEFMMMS\textsuperscript{94} (12 out of 12).

**Case 2.** The patient was a 70-year-old, right hand dominant, white female who was enrolled 11-months following a hemorrhage in the right putamen with consequent left hemiparesis affecting both the upper and lower extremities. Baseline clinical scores revealed low level of spasticity measured by MAS\textsuperscript{25} (composite score, 1 out of 32), a medium level of motor impairment measure by UEFMMMS\textsuperscript{93} (48 out of 66) and a severe sensory impairment by the sensory portion of the UEFMMMS\textsuperscript{94} (6 out of 12).

5.2.2. Study Design

The study consisted of a multiple baseline, A-B case series design. Following repeated baseline assessments (timing), participants performed 6-weeks of affected arm POWER training followed by 6-weeks of bilateral FTP. Each treatment session was preceded by 20 minutes of inhibitory rTMS to the contralesional (unaffected) hemisphere. Assessments were conducted at baseline, after each treatment and following six months without additional intervention. The study design is described in Figure 5-1.

5.2.3. Measures

Our multimodal assessment approach provided insight into this dynamic relationship between neurobiology and motor behavior, and paid particular attention to the selection of measures that distinguish between compensation and recovery. The multimodal assessment included: clinical tests, three-dimensional motion analysis, measures of force production and transcranial magnetic stimulation (TMS). Both
participants underwent the same multimodal evaluation. Data from four healthy control volunteers (mean age 63.75±7.85 years, 1 female, all right hand dominant) were obtained to provide reference data for all measures.

**Wolf Motor Function Test (WMFT).** Our primary clinical test was the WMFT, which is one of the most used clinical tests to evaluate UE motor function post-stroke (citation). Clinometric properties of the WMFT have been established, shown to have high interrater reliability (intraclass correlation coefficients, ≥ 0.88), internal consistency (Cronbach α ≥ 0.86), and test-retest reliability (r ≥ 0.90)\textsuperscript{180}. In addition to the WMFT, we used a battery of clinical outcomes to represent a comprehensive assessment across all levels of the ICF\textsuperscript{205}. Specifically, this clinical battery included: the Modified Ashworth Scale (MAS)\textsuperscript{25}, Fugl-Meyer Upper-Extremity Motor Score (UEFMMS)\textsuperscript{93} and the sensory portion of the UEFMMS\textsuperscript{94}, the Beck Depression Inventory\textsuperscript{238} and the Late Life Function and Disability Instrument\textsuperscript{239}.

**Three-dimensional motion analysis.** Kinematics of the paretic UE were measured while participants were seated in a straight-back chair with the paretic UE resting on the ipsilateral thigh (Start position). The shoulder was positioned in neutral flexion/extension and neutral internal rotation; the elbow in 75-90 degrees of flexion with the wrist resting in pronation. Participants were instructed to reach, grasp and retrieve a full soda can positioned on a table top at 80% of arm’s length (i.e., ‘Coke can’ task\textsuperscript{180}). This functional reach-to-grasp task was selected as the study outcome task because of its status as a fundamental motor skill necessary for many daily activities. Participants completed 1-2 practice trials followed by three test trials. Three-dimensional motion
analysis data were collected using 53 reflective markers placed on the: anterior and posterior spines, base of sacrum, manubrium and body of sternum, 7th cervical vertebra, 10th thoracic vertebrae, and bilaterally on the acromion processes, medial and lateral epicondyles, ulnar and radial styloid processes, superior thirds of the upper arm and forearm (triads markers), hand and finger tips (set of 11 small size markers).

Marker data were recorded with a twelve-camera motion analysis system (Vicon 612, Oxford Metrics Inc., Oxford, U.K.) at a sampling frequency of 200 Hz. The motion analysis system expressed output data as three-dimensional, time-dependent marker coordinates in relation to a laboratory coordinate system.

**Transcranial Magnetic Stimulation (TMS).** We investigated inter-hemispheric competition by studying the combination of hemispheric cortical excitability and inter-hemispheric inhibition (IHI). Recruitment curves (RC) slopes were used to study cortical excitability. Ipsilateral silent period (iSP) was used to study IHI. RC was generated by stimulation over the motor threshold hotspot at progressively increasing intensities recording 10 stimuli in 5% increments beginning at an intensity of 10% below motor threshold. Data collection for the RC was terminated when a plateau of the sigmoidal curve was observed. The input-output curve was measured for both ipsilesional and contralesional hemispheres. The ability to reconstruct RCs depended on the ability to evoke MEPs. iSP was obtained using single pulse TMS delivered at 150% of motor threshold while the participant produced a sustained, submaximal contraction (50% maximal effort) of the FDI muscle ipsilateral to the stimulation. Twenty responses of iSP were obtained for each hemispheres.
**Measure of force production.** We investigated force/torque production by using a commercially available dynamometer\(^{21}\) during isometric and dynamic (i.e. isotonic and isokinetic) muscle contractions of elbow flexion-extension in the hemiparetic side. Three trials were collected and then averaged.

**5.2.4. Intervention**

One-on-one treatment session was delivered 3 days weekly. Both participants participated in 6 weeks (18 sessions) of power training (POWER) and 6 weeks (18 sessions) of functional task practice (FTP). POWER was performed unilaterally with the paretic/affected arm, while functional task practice included activities typically performed bilaterally, but was emphasize practice and repetition with the paretic arm. Both POWER and FTP are described elsewhere\(^{61}\). All treatments were preceded by inhibitory rTMS delivered to the contralesional hemisphere.

**5.2.4.1. Power training**

We delivered dynamic, high-intensity resistance exercise for the shoulder, elbow and wrist using an isokinetic dynamometer. The treatment protocol involved 7 exercises (shoulder flexion, shoulder abduction, shoulder external rotation, elbow flexion/extension, wrist flexion/extension), 3 sets of 10 repetitions of each exercise. The speed of movement was progressively adjusted upward over the six weeks of training. Details of POWER intensity and progression are shown in Figure 5-2.

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5.2.4.2. Functional Task Practice (FTP)

FTP involved practice of functional tasks using a progression of six therapeutic goals and nine activity categories. Specific therapeutic tasks were chosen from these activity categories based on participant-specific goals and baseline functional level and practiced on a structured rotation within the framework of the overriding therapeutic goals (Table 5-4).

5.2.4.3. Repetitive TMS (rTMS)

Inhibitory rTMS was administered over the contralesional M1 – corresponding to the hot spot for the ipsilesional/non-paretic muscle representation. In addition, participants wore a tight-fitting lycra swim cap. Skin-mounted surface electromyogram preamplifier was placed over FDI muscle contralateral to the stimulated hemisphere. Subjects were seated in the dynamometer chair adjusted such that hips, knees and ankles were maintained at 90 degrees and were asked to relax. MEP threshold was measured before and after each rTMS session using a figure-8 coil centered at the scalp vertex and connected to a Magstim® 200² high-power magnetic stimulator (Magstim® Ltd, UK). Stimulation was delivered at an intensity of 100% motor threshold, 1 Hz frequency, biphasic waveform and 1200 stimulations in a single, continuous train lasting 20:00¹⁷².

5.3. Analysis

5.3.1. Clinical Tests

For the 15 total items of the WMFT, we calculated the number of items that improved or worsened. Improvement was defined as at least 10% reduction in task
execution time and worsening was defined as at least 10% increase in task execution
time. In addition, we calculated the change in the sum of task execution time for all
tasks (Total Time) between baseline and the first block of intervention (or post-POWER,
i.e. rTMS+POWER), between the first and the second block of intervention (or post-
FTP, i.e. rTMS + FTP) and between the second block intervention and follow-up (or
Retention). For all other clinical tests, we reported the raw score at each evaluation (i.e.
Baseline, post-POWER, post-FTP and Retention).

5.3.2. Three-Dimensional Motion Analysis

Marker data were labeled using Vicon Nexus\textsuperscript{22} and modeled using Visual3D\textsuperscript{23}. Kinematic trajectories, extracted from Visual3D, were analyzed using custom-written
MATLAB\textsuperscript{\textregistered}, scripts\textsuperscript{24}. Kinematic data were low-pass filtered (12 Hz cutoff) using a bi-
directional 4\textsuperscript{th} order Butterworth filter. The start-of-movement (SOM) was defined as the
first point at which the velocity of the marker on the third metacarpophalangeal joint
exceeded 5% peak velocity and the end-of-movement (EOM) as the last point at which
velocity of this marker fell below 5% peak\textsuperscript{43,181}.

Our primary kinematic outcomes were shoulder and elbow range of motion and
trunk displacement to quantify movement execution. Total movement time and reach-
path-ratio (RPR) were used as secondary outcomes to quantify speed and movement
accuracy.

\textsuperscript{22} Copyright\textsuperscript{\textcopyright} Vicon 612, Oxford Metrics, Oxford, UK

\textsuperscript{23} Copyright\textsuperscript{\textcopyright} 2010 C-Motion, Version 4.00.19, Inc C-Motion, Germantown, Maryland

\textsuperscript{24} MathWorks\textsuperscript{\textregistered}, Inc., Version R2011b, Massachusetts, USA
Range of motion (ROM) was calculated for shoulder flexion and elbow extension as the difference, in degrees, between the maximum and minimum joint angle achieved. Trunk displacement was defined as the displacement of the sternum marker, in centimeters, in the sagittal plane. Movement time was defined as the time between SOM and EOM. Reach-path-ratio was defined as the ratio of the actual path and the direct path lengths of the hand marker. The actual path is defined as the three-dimensional displacement of the hand marker path during the reach task, and the direct path is defined as the three-dimensional distance between the hand marker at onset and the hand marker at offset.

5.3.3. Transcranial Magnetic Stimulation (TMS)

5.3.3.1. Recruitment curve (RC)

For each stimulus intensity the average of 10 stimuli was evaluated. Peak amplitude and area of the averaged MEP signal were calculated. We considered the presence of MEP if the peak-to-peak amplitude of the averaged signal was ≥ 50 μV. The MEP onset was defined as last crossing of the mean baseline EMG level before the MEP peak and the MEP offset as the first crossing of the mean baseline EMG level after the MEP peak. The area of the mean MEP was normalized to the maximal MEP area. The data were fit using a non-linear regression to the Boltzmann Equation followed by a linear regression fit to the modeled data in the steepest portion of the range. We report motor threshold (MT) as the stimulation level at which the slope of the fitted line intersects the abscissa.
5.3.3.2. Ipsilateral silent period (iSP)

The EMG signals were rectified and averaged over 20 stimuli. The mean and the standard (SD) deviation of the EMG level for 100 ms prior to TMS stimulus were determined from the averaged signal. We considered the presence of an ipsilateral MEP (iMEP) if the post-stimulus EMG exceeded the pre-stimulus mean baseline EMG by >1 SD for ≥5 ms\textsuperscript{186}. iMEP onset was defined as the last crossing of the pre-stimulus mean baseline EMG before the MEP peak and the iMEP offset as the first crossing of the pre-stimulus mean baseline EMG after the iMEP peak. iMEP area was calculated between the iMEP onset and offset (iMEP duration). Similarly, we considered the presence of an iSP if the post-stimulus EMG fell below the pre-stimulus mean baseline EMG by ≥1 SD for >5 ms. The iSP onset was defined as the first crossing of the pre-stimulus mean baseline EMG after the MEP peak and the iMEP offset as the first crossing of the pre-stimulus mean baseline EMG after the iSP onset for at least 5 ms\textsuperscript{186}. The iSP duration was defined as the time between the onset and the offset values. We also calculated the laterality index (LI) for the iSP duration as \((A-B)/(B+A)\), where \(A\) corresponds to the dominant hemisphere (DH) for the healthy controls and to the unaffected hemisphere (UH) for the stroke participants, and \(B\) corresponds to the nondominant hemisphere (NDH) for the healthy control and to the affected hemisphere (AH) for the stroke participants.

5.3.4. Force Production.

For each contraction, peak torque (for isometric contractions) and peak power (for isotonic and isokinetic contractions) were calculated. The average of three trials was...
reported for both elbow flexion and extension movements. During isometric contraction peak torques were calculated at 55° (for movements in flexion) and 75° (for movements in extension) starting from the fully extended position of the elbow (i.e. 0°). During isotonic and isokinetic contractions peak powers were calculated during the range 0-120°.

5.4. Results

5.4.1. Clinical Tests

Case 1. The WMFT, after the first intervention block (post-POWER), revealed a specific number of improved and a specific number of worsened timed items in both, the affected (AA) and the unaffected (UA) arms. Compared to the second intervention block (post-FTP), a greater number of improved items and fewer worsened items were detected following POWER. At follow-up, there was a further increase of improved items and a further decrease of worsened timed items in both AA and UH (Table 5-1).

Change revealed an improvement (decrease) in the sum of task execution time in the AA after the first intervention block (post-POWER) and a worsening (increase) in the sum of task execution time in the second intervention block (post-FTP). However a similar improvement was revealed after both interventions and follow-up in the UA (Figure 5-3).

Case 2. The second intervention block (post-FTP) revealed a specific number of improved and a specific number of worsened timed items in both, the AA and the UA arms compared to the first intervention block (post-POWER). At follow-up, there were a
lower number of improved items and a greater number of worsened timed items compared to the previous evaluation (Table 5-1).

Change scores revealed an improvement (decrease) in task execution time in both the AA and UA after the second intervention block (post-FTP) but an increased task execution time in both the AA and AU after the first block intervention (post-POWER). At follow-up there was a further improvement in the AA, while the UA did not show any change (Figure 5-3).

Raw scores of Fugl-Meyer Upper extremity scale score (UEFMMMS) and its sensory portion, Beck Depression Inventory (BDI), Modified Ashworth Scale (MAS) and late life function and disability instrument for both participants, are reported in Table 5-2 and 5-3.

5.4.2. Kinematics

Case 1. Shoulder flexion and elbow extension range of motion increased post-POWER (change score: 3.25° for shoulder and 6.09° for elbow), but decreased post-FTP (change score: -4.36° (shoulder) and -3.31° (elbow). At follow-up, both shoulder flexion and elbow extension increased (change scores: 6.20° for shoulder and .90° for elbow). Trunk displacement decreased post-POWER (change score: -3.65 cm) and continued to decrease post-FTP (change score: -7.41 cm) and at follow-up (change score: - 6.50 cm (Figure 5-4).

Case 2. POWER revealed unchanged shoulder excursion and reduced elbow excursion (change score: -0.62° at the shoulder and -7.63° at the elbow), associated with a small reduction of trunk displacement (change score: -1.93 cm). Instead, FTP
increased shoulder and elbow excursion (change score: 6.45° (shoulder) and 13.83° (elbow). At follow-up, the shoulder ROM did not change (change score: 0.92°) and the elbow ROM decreased (change score: -10°). Further, trunk displacement reduced somewhat following both treatments, POWER (change score: -2.0 cm) and FTP (change score: -16.0 cm). However, trunk displacement was worse at follow-up (change score: 20.21 cm) (Figure 5-4).

The secondary outcomes total movement time and index of curvature for both participants, are described in Figure 5-5.

5.4.3. Transcranial Magnetic Stimulation (TMS)

5.4.3.1. Recruitment curve (RC)

In healthy controls, the average of the recruitment curve slopes was 0.05 (±0.006) for the dominant hemisphere and 0.03 (± 0.01) for the nondominant hemisphere.

**Case 1.** At baseline (Figure 5-8), the recruitment curve slope was 0.01 for the UH, In the AH, we stimulated up to 100% of stimulator output without eliciting MEPs, therefore a recruitment curve could not be constructed. Post-POWER, the recruitment curve slope shifted towards normal values, 0.05 for the UH. In the AH there was an emergence of MEPs from which it was possible to construct a recruitment curve, which had slope of 0.05. Post-FTP, the recruitment curve slope was 0.06 for the UH and was not possible to construct a recruitment curve for the AH since the MEPs were complex and below threshold (Figure 5-9). At follow-up, it was possible to construct recruitment curves for both hemispheres with slopes of 0.05 for the unaffected hemisphere and 0.03 for the affected hemisphere.
Case 2. At baseline (Figure 5-8), the recruitment curves for the two hemispheres were symmetrical and both slopes were 0.03. Post-POWER, the slopes remained similar with a value of 0.04. Post-FTP, the recruitment curve slope for the unaffected hemisphere remained at 0.04. However, the slope of the affected hemisphere dropped to 0.01. At follow-up, both slopes increased reaching a value of 0.09 for the unaffected hemisphere and 0.04 for the affected hemisphere.

5.4.3.2. Ipsilateral silent period (iSP)

In healthy controls, the average duration of ipsilateral silent period (iSP) from the dominant hemisphere (DH) to the nondominant hemisphere (NDH) (iSP while stimulating the dominant hemisphere) was 37.92 (±5.77) ms, and the average duration of the ipsilateral silent period (iSP) from the NDH to the DH (iSP while stimulating the nondominant hemisphere) was 24.91 (±0.9) ms (Figure 5-10). The laterality index for the iSP duration ((DH-NDH)/(DH+NDH)) was 0.20 (±0.72), indicating a slight predominance of interhemispheric inhibition from the dominant hemisphere (Figure 5-11).

Case 1. At baseline, the iSP duration from the AH to the UH (iSP while stimulating the affected hemisphere) was shorter (23.20 ms) than the healthy controls; instead, the iSP duration from the UH to the AH (iSP while stimulating the unaffected hemisphere) was longer (91.13 ms) than healthy controls. Post-POWER, the duration of IHI from the AH to the UH increased (59.44ms) and from the UH to the AH decreased (71.66 ms). Post-FTP, the duration of IHI from the UH to the AH continued to decrease (65 ms). We were unable to generate sufficient responses, therefore, data relative to
interhemispheric inhibition from the affected hemisphere to the unaffected hemisphere were unavailable. At follow-up, the duration of IHI from the AH to the UH continued to increase (65 ms) and the duration of the interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere continued to decrease (48.85 ms) (Figure 5-10). The laterality index for the iSP duration ((AH-UH)/(AH+UH)) was 0.59 at baseline, 0.09 post-POWER, 1 post-FTP and -0.14 at Follow-up (Figure 5-11).

**Case 2.** At baseline, the duration of IHI from the affected hemisphere to the unaffected hemisphere (iSP while stimulating the affected hemisphere) was longer (138.43 ms) than the healthy controls; instead, the duration of the interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere (iSP while stimulating the unaffected hemisphere) was shorter (60 ms) than the opposite hemisphere but longer than healthy controls. Post-POWER, the duration of the interhemispheric inhibition from the affected hemisphere to the unaffected hemisphere reduced (87.94 ms) and the duration of the interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere increased (93.64 ms). Post-FTP, the duration of iSP from the affected hemisphere to the unaffected hemisphere continued to decrease (79.80 ms); the duration of the iSP from the affected hemisphere to the unaffected hemisphere remained stable (93.64 ms). At follow-up, the duration of the iSP from the affected hemisphere to the unaffected hemisphere continued to increase (59.60 ms); the duration of the iSP from the unaffected hemisphere to the affected hemisphere continued to increase (111.40 ms) (Figure 5-10). The laterality index for the iSP duration ((AH-UH)/(AH+UH)) was -0.39 at baseline – indicating a predominance of
interhemispheric inhibition from the AH to the UH, however it normalized in response to intervention: 0.03 post-POWER, 0.07 post-FTP and 0.30 at Follow-up (Figure 5-11).

5.4.4. Force Measurements

**Case 1.** POWER improved torque/power improvements in all contraction modes: isometric elbow flexion (change score: 7.82±0.04) and extension (change score: 10.16±1.44); isotonic elbow flexion (change score: 13.17±0.54) and extension (change score: 15.65±0); isokinetic elbow flexion (change score: 7.63±2.60) and extension (change score: 12.21±0.46). FTP improved all elbow flexion contractions: isometric (change score: 5.91±0.75), isotonic (change score: 11.34±1.08) and isokinetic (change score: 0.39±2.68). However, force production in all the extension contractions was worse after FTP: isometric (change score: -12.46±2.26), isotonic (change score: -6.4±6.68) and isokinetic (change score: -5.84±2.14). At follow up, isometric elbow flexion (change score: -8.82±0.94), isotonic elbow extension (change score: -5.31), isokinetic elbow flexion (change score: -5.05±0.15) and extension (change score: -0.62±2.40) were worse. Only isometric elbow extension (change score: 6.45±1.69) and isotonic elbow flexion (change score: 4.85±2.16) improved at follow-up (Figure 5-12).

**Case 2.** POWER showed torque/power improvements in all contraction modes: isometric elbow flexion (change score: 0.97±0.62) and extension (change score: 3.49±0.19); isotonic elbow flexion (change score: 2.74±1.25); isokinetic elbow flexion (change score: 10.42) and extension (change score: 10.88±2.10) except for isotonic elbow extension (change score: -0.31±0.45). FTP improved only isometric elbow flexion (change score: 0.97±0.62) and isokinetic elbow extension (change score: 1.28±0.58).
Force production in all other contraction conditions was worse: isometric elbow extension (change score: -7.19±0.84), isotonic elbow flexion (change score: -0.98±2.20) and extension (change score: -0.16±0.21) and isokinetic elbow flexion (change score: -13.43±0.01). At follow-up, isometric elbow extension (change score: 435±0.70), isotonic elbow flexion (change score: 1.06±0.70) and extension (change score: 2.17±0.05) and isokinetic elbow flexion (change score: 3.35±0.10) improved. Instead, isometric elbow flexion (change score: -0.48±0.10) and isokinetic elbow extension (change score: -0.62±2.40) worse (Figure 5-12).

5.5. Discussion

This study aimed to address the gap between inducing neurobiological change and detecting positive behavioral change that constitutes functional recovery in persons post-stroke. We examined combined behavioral and neurobiological approaches to better understand mechanisms of functional recovery. We combined behavioral therapies that improve strength, POWER, and motor skill, FTP, with inhibitory therapeutic repetitive transcranial magnetic stimulation (rTMS) to the UH.

Hypothesis of inter-hemispheric competition. Our first aim was to test the hypothesis of interhemispheric competition post-stroke. As we hypothesized, at baseline Case 1 showed presence of interhemispheric competition, consistent with Nowak’s hypothesis. Interhemispheric competition was revealed as an imbalance in the iSP duration between the two hemispheres. The prolonged duration of the unaffected hemisphere iSP suggests that the unaffected hemisphere may be disinhibited and exerts exaggerated inhibition onto the affected hemisphere. The exaggerated laterality
index (LI) indicates the predominance of the unaffected hemisphere meaning of inter-hemispheric competition as described by Nowak. In addition, at baseline we were unable to elicit MEPS in the AH in Case 1. The inability to evoke MEPs post-stroke is considered a poor prognostic indicator\textsuperscript{241, 242}. Our study however suggests that the presence or absence of MEPs as a prognostic indicator should not be used in isolation. Case 1 showed improvements of the cortical excitability (reappearance of MEPs and ability to reconstruct RC) and IHI even in absence of MEPs at baseline evaluation.

Case 2 also, showed an imbalance of IHI. Surprisingly, at baseline this imbalance was not consistent with Nowak's hypothesis. Hemispheric competition was revealed as prolonged iSP duration from the affected compared to the unaffected hemisphere. The prolonged duration of the affected hemisphere iSP suggests that the affected hemisphere exerts greater inhibition onto the unaffected hemisphere. The negative laterality index (LI) indicates the predominance of the affected hemisphere. In contrast to Case 1, it was possible to elicit MEPs in both hemispheres at baseline evaluation in Case 2. Moreover, at baseline evaluation recruitment curve slopes were similar between the two hemispheres, and close to normal values. An important note regarding the reversed inter-hemispheric competition is that Case 2 had disputable hand laterality. The participant revealed that she was naturally left-handed, but was forced to right hand laterality during childhood. This forced laterality may have affected the direction of IHI and the LI at baseline. Of note, in Case 1, the affected hemisphere was the dominant hemisphere and the LI showed predominance of the unaffected hemisphere.
Restoring balance of inter-hemispheric competition. Our second aim was to determine if it is possible to restore a balance of inter-hemispheric competition. In Case 1, POWER training produced reduction of inter-hemispheric competition as shown by balanced duration of iSP and normalization of the LI. In addition, POWER showed emergence of MEPs. This may indicate a normalization of the cortical excitability both within and between the two hemispheres. We cannot draw conclusions about IHI after FTP treatment since data were not available. Although, as suggested by disappearance of effective MEPs in the AH and increased recruitment curve slope in the UH, it does appear that improvements in cortical excitability revealed by POWER training were lost following FTP indicating a return to the baseline state. In Case 2, POWER also showed reduction of inter-hemispheric competition as shown by balanced duration of iSP between the two hemispheres and normalization towards positive values of the LI. These results were maintained after FTP. POWER induced an increase of the recruitment curve slopes of both hemispheres, bringing the cortical excitability within the normal range.

Effects of POWER training. Our third aim was to test whether rTMS combined with POWER training resulted in better functional, biomechanical and neurophysiological outcomes than rTMS combined with FTP. In Case 1, motor function, as indicated by WMFT, revealed a greater number of improved and a lower number of worsened timed items in the affected hand post-POWER training. Further, POWER induced improvement (decrease) in the WOLF score (e.g., sum of task execution time). In addition, POWER produced improvements in joint excursion at the elbow and
shoulder, associated with reduced trunk displacement. These outcomes are consistent with improved motor strategies in response to POWER demonstrated in our previous work. At the neurophysiologic level, POWER produced reduced inter-hemispheric competition as shown by balanced LI and positive changes in cortical excitability, including emergence of MEPs in the affected hemisphere. In summary, POWER showed positive behavioral and neural effects consistent with our hypothesis of increased central drive in the ipsilesional hemisphere.

Conversely, in Case 2 FTP showed improvements in the WOLF score as indicated by a greater number of improved and a lower number of worsened timed items in the affected hand. Further, FTP induced improvement (decrease) in the WOLF score (e.g., sum of task execution time). In addition, FTP produced improvements in joint excursion at the elbow and shoulder, associated with reduced in trunk displacement. At the neurophysiological level, POWER produced normalization of inter-hemispheric competition, as indicated by positive direction of the LI, and FTP produced negative changes in cortical excitability, as indicated by increased asymmetry in recruitment curve slopes. In summary, in Case 2 POWER did not appear to be as effective at the behavioral level as it was for Case 1, however it still induced positive neural changes. It is important to note that the two individuals had similarity in clinical evaluation at baseline and lesion location. However, they had opposite responses in clinical and behavioral motor outcomes. One important clinical difference at baseline was that Case 2 had a sensory impairment as indicated by the sensory component of the UEFMMS (Table 5-2). The severe sensory impairment could have affected the potential benefit
from POWER training. It has been described the negative association between sensory impairment and motor ability\textsuperscript{243}. Normal movement relies both on an intact motor system and also on sensory information\textsuperscript{244}. Carey et al\textsuperscript{245} stated the primary importance of sensation is to provide the feedback needed to guide motor acts. It is possible that Case 2 had benefit more from FTP than POWER because of the presence of visual feedback during the execution and accomplishment of functional tasks. Therefore, it could be possible that the motor output of Case 2 during POWER training was inadequate, as consequence of sensory impairment, and therefore ineffective to induce positive motor behavioral changes.

**Limitations.** We recognize that this study included only two individuals, which are not enough to draw definitely conclusions about the heterogeneous post-stroke population. However, the purpose and the innovation of this case series were to demonstrate the possibility to induce neural changes at the supraspinal level as an effect of rehabilitation intervention. Another limitation of this study is the use of iSP as a measure IHI. IHI is usually studied by a paired-pulse protocol with the conditioning stimulus delivered to one M1 and the test stimulus delivered to the other M1 10ms later (S-IHI)\textsuperscript{246}. The activity in the M1 receiving the conditioning stimulus, facilitates inhibition of the MEP elicited by the test stimulus. It has been suggested\textsuperscript{246} that this inhibition is produced at cortical level via transcallosal pathways. However, an alternative method used to study interhemipsheric inhibition involves a short attenuation, or interruption, of ongoing voluntary EMG activity induced by TMS of the ipsilateral M1\textsuperscript{247}. This ipsilateral silent period (iSP) has a latency of 30-40ms post-stimulus and lasts around 25ms.
Meyer et al. indicated that iSP is mediated by interhemispheric cortico-cortical inhibitory pathways including fibres passing through the posterior half of the trunk of the corpus callosum. Chen et al. suggested that iSP and S-IHI are mediated by different neural mechanisms (i.e., pathways). For this reason, the iSP is currently considered as a measure that provides complementary, but not identical, information regarding interhemispheric inhibition compared to S-IHI. However, several authors have used the iSP instead of the S-IHI to provide an estimation of IHI. The advantage of using the iSP in persons post-stroke consists of the fact that it allows estimation of IHI even in the absence of MEPs in the ipsilesional hemisphere when it would not be possible to induce S-IHI.

**Conclusions.** In general, our findings suggest that it is possible to induce neurobiological change associated with behavioral change that constitutes functional recovery. Our findings support our hypothesis that POWER promotes enhanced central neural drive in the ipsilesional hemisphere and may represent potential driver of cortical reorganization. Our results compel us to investigate these mechanisms with future larger scale research studies, which may inform how individual characteristics interact with mechanisms of neural recovery.
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Table 5-2. Clinical scales

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<th>Fugl Meyer Upper Extremity Scale Motor (66)</th>
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Table 5-3. Late life function and disability instrument

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Table 5-4. Functional task practice (FTP).

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<td>Incorporate gravity</td>
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<td>Pour into taller vessels.</td>
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<td>Elevate table surface</td>
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<td>2-4 weeks</td>
<td>Incorporate shoulder external rotation and stretch to long finger flexors</td>
<td>Catch/Release</td>
<td>Release ball into hoop using long reach</td>
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<td>Incorporate bilateral hand movement</td>
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<td>Alternate bounce/catch/release with both hands</td>
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<td>4-6 weeks</td>
<td>Incorporate reaching and manipulation through hand-directed movements</td>
<td>Feeding/Cooking</td>
<td>Feed self with spoon</td>
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<tr>
<td></td>
<td>Incorporate controlled elbow movement</td>
<td></td>
<td>Grasp jars from table and place on shelf</td>
</tr>
</tbody>
</table>

Note: Consistent with our previous work, the FTP program addressed six global therapeutic goals. Therapeutic activities were developed on the basis of the specific therapeutic goal. There were nine activity categories: water tasks, catch-release, feeding and cooking, games, painting and drawing, laundry, sport, computer keyboarding and tool tasks. Each 90-minute treatment session involved 15 minutes of stretching and warm up, followed by practice of activities in each of the 9 categories for 8 minutes each. Table reports specific examples of activities. Difficulty of activities was adjusted based on level of function of each individual. To assure consistency across all participants, treatment was advanced to the next therapeutic goal on the timeline specified and the nine activity categories were presented in rotation.
Figure 5-1. Study design. Participants were evaluated 4 times: at baseline, after 6 weeks of rTMS and POWER training; after 6 weeks of rTMS and FTP training; and at 6 months follow up.
Participants performed both concentric and eccentric actions for 6 consecutive weeks. Movement speed ranged from 30 to 75 degrees per second for eccentric and from 30 to 180 degrees per second for concentric actions. Each bar represents two sets of 10 repetitions at the criterion speed noted on the Y-axis. A primary goal of power training is to improve the capacity for force production in dynamic conditions.
Figure 5.3. Wolf motor function test. Change score of task execution time (total time) between baseline and the first block of intervention (post-POWER), between the first and the second blocks of intervention (post-FTP) and at retention. Upward bars indicate worsening (increase) and downward bars indicate improvement (decrease) in task execution time.
Figure 5-4. Key kinematic parameters of functional reach-to-grasp. Top chart describes range of motion (in degrees) of shoulder and elbow joints. Bottom chart describes trunk excursion (in millimeters). Baseline post-POWER and post-FTP evaluations are shown for case 1 and 2. Data from a healthy control are shown for comparison.
Figure 5-6. Speed and index of curvature of functional reach-to-grasp.
Figure 5-8. Recruitment curve slopes.
Figure 5-9. Motor evoked potentials (MEPs). At baseline evaluation we were not able to induce MEPs in the ipsilesional hemisphere. Top panel shows the reappearance of MEPs after POWER. MEPs are maintained after FTP and Follow-up evaluations. However, after FTP we were not able to reconstruct a RC since the MEPs were complex and below threshold. The MEP latency (~40 ms for all evaluations) looks most consistent at follow-up. The scale is the same for all three evaluations.
Figure 5-10. Ipsilateral silent period duration. Duration of inhibition from the affected to the unaffected hemisphere (white columns) and from the unaffected to the affected hemisphere (black columns), at baseline, after first (Post-POWER) and second (Post-FTP) block of interventions and at follow-up. Horizontal lines indicate average iSP duration in four healthy controls. Top line indicates inhibition from dominant to non-dominant hemisphere and bottom line indicates inhibition from non-dominant to dominant hemisphere.
Figure 5-11. Laterality index for iSP duration.
Figure 5-12. Force production. Flexion movements (left column) and extension movements (right column). Top row illustrates isometric contractions, middle row describe isotonic contractions and bottom row isokinetic contractions (eccentric contraction at the speed of 120deg/s). Case 1 is represented in white and Case 2 is represented in black. Each plot represents the change in force/torque/power after POWER, after FTP and at follow-up.
CHAPTER 6
POWER TRAINING POST-STROKE ENGAGES NEURAL CIRCUITS AT SPINAL AND SUPRASPINAL LEVELS

6.1. Background

Current upper-extremity (UE) treatment approaches post-stroke focus on repetitive execution of functional movements, ostensibly to facilitate neural plasticity. High intensity activities, especially strengthening, have traditionally been avoided because they are assumed to increase spasticity and impair motor performance in neurological disorders. Among the currently accepted therapeutic approaches are constraint-induced movement therapy (CIMT)\textsuperscript{138}, task-oriented and repetitive training\textsuperscript{137} and more recently, robotic therapies\textsuperscript{135}. While these therapeutic methods show promise in improving UE function post-stroke, most of the work to date documents improvements through clinical or gross behavioral measures, which emphasize task accomplishment more than motor control or neuroplastic changes\textsuperscript{36}. Due to the gross nature of discernment, these metrics are not able to distinguish restoration from compensatory movements at either the behavioral or the neural level.

Our research team has conducted a set of studies that contributes to the contemporary evidence that resistance training as an intervention post-stroke can induce restoration of more normal activation in neural circuits and movement patterns. First, Patten et al.\textsuperscript{18, 60} conducted a randomized clinical trial of UE rehabilitation to compare the effects of functional task practice (FTP), and a hybrid intervention of FTP combined with dynamic high-intensity resistance training post-stroke. This clinical trial revealed that the hybrid intervention produced more significant gains in both clinical

indicators of motor recovery and neuromechanical parameters, including: isometric maximal voluntary force, dynamic isovelocity torques and neuromuscular activation, as revealed using EMG\textsuperscript{18,60}. Further, Patten et al.\textsuperscript{18} compared the effects of these two intervention approaches on stretch reflex modulation. Results of this study indicate: first, that UE rehabilitation involving high-exertion activity does not exacerbate either the hyperreflexic or hypertonic components of spasticity in adults post-stroke; second, dynamic, high-intensity resistance training (e.g., power training) promoted more appropriate modulation of stretch-induced EMG responses; third, these neurophysiologic adaptations were associated with improved UE motor function improvement as evaluated with the Wolf Motor Function Test – Functional Ability Scores (FAS). Finally, clinical improvements in response to the 22.5 hours of hybrid intervention exceeded those in response to 60 hours of CIMT as reported from the ExCITE trial\textsuperscript{230}. Subsequently, Corti et al\textsuperscript{61} compared power training, performed in isolation, against FTP on a battery of clinical scales and kinematics of unconstrained reaching. In contrast to clinical scales, UE kinematics obtained through 3D motion capture afford a sensitive, quantitative and reproducible assessment that enables discernment between compensatory and recovery strategies\textsuperscript{62}. Although clinical evaluations conducted by Corti et al\textsuperscript{61} did not reveal differential treatment effects, kinematic improvements following POWER training revealed restoration of more normal movement patterns, while performance after FTP indicated refinement of compensatory movement strategies. Specifically, following FTP, hemiparetic participants demonstrated increased mean velocity during reaching, but reduced shoulder flexion and elbow extension range of motion, which were compensated with increased trunk displacement. In contrast,
following POWER training, participants increased shoulder flexion and elbow extension range of motion and significantly reduced associated trunk displacement. Further, the use of a crossover design revealed that these treatment effects were greater when POWER training preceded FTP training than vice versa.

These positive outcomes of POWER can most likely be attributed to: a) the well recognized and profound neural adaptations induced by resistance training\(^{51, 53, 55}\), and b) therapeutic intensity, which promotes improvement by challenging the subject’s capacity. Neural adaptations induced by resistance training occur: 1) at the level of the spinal cord, potentially including short-term motor unit synchronization, which is caused by changes in synaptic efficacy within the motoneuron pool, and 2) at the supraspinal level, including adaptations within the cortical circuitry. While our combined work to date suggests that POWER and HYBRID are effective treatments and may induce neuromechanical changes, we have not measured the effect of therapeutic intervention involving POWER training on neural circuits at the supraspinal level.

Technological developments have led to the introduction of electrophysiological techniques that provide substantial insight into the adaptive changes of neurophysiologic networks associated with plasticity and recovery post-stroke\(^{92, 153, 253-255}\). These technologies include transcranial magnetic stimulation (TMS) and H-reflexes, which are two of these non-invasive tools, to measure therapeutically induced neuroplasticity post-stroke at supra-spinal and spinal levels, respectively.

The H-reflex is the electrical analogue of the spinal stretch reflex and tests the monosynaptic reflex pathways and associated activity in the spinal circuitry\(^{187}\). Literature suggests that H-reflex amplitude and slope are greater in the paretic versus non-paretic
arm post-stroke and the paretic arm versus non-disabled group\textsuperscript{256}. Recently, the H-reflex has been used to selectively study spinal inhibitory pathways including: presynaptic Ia inhibition and post-activation depression (PAD). Presynaptic Ia inhibition is responsible for a late inhibition (i.e., D1 inhibition) and is typically assessed using a conditioned H-reflex. Presynaptic Ia inhibition of the flexor carpi radialis (FCR) is elicited by electrical stimuli applied to the nerve supplying antagonist muscles\textsuperscript{184 129}. PAD is explored by varying the time interval between repeated H-reflexes\textsuperscript{129}. Aymard demonstrated that both D1 inhibition and PAD were reduced in the affected arm post-stroke as compared to a group of non-disabled individuals\textsuperscript{184}.

TMS involves non-invasive brain stimulation by magnetic field pulses that induce a flow of current in the tissue, leading to the excitation of neurons\textsuperscript{257}. Stimulation of the hand-representation area of a healthy motor cortex induces motor evoked potentials (MEP) in the contralateral hand muscles, which manifest as muscle contractions or twitches.

The recruitment curve (RC) obtained using TMS is a commonly used indicator of cortical excitability\textsuperscript{258}. Decreased activity of the ipsilesional cortex has been observed after stroke by using electrophysiological recordings\textsuperscript{65}, cortical stimulation\textsuperscript{66} and functional neural imaging studies\textsuperscript{67}. This decreased cortical excitability has been attributed to damage from glutamate receptor expression from neurons in the infarct zone.

In the healthy brain, neural activity in the motor areas is equally balanced in terms of mutual inhibitory control between hemispheres\textsuperscript{64}. Movements of one hand are associated with enhanced neural activity in contralateral motor areas of the brain.
Activated contralateral motor areas produce inhibition on homologous areas of the ipsilateral hemisphere. Stroke affects activity in this circuitry and disrupts this balance of IHI. As a result, the primary motor cortex of the unaffected (contralesional) hemisphere becomes disinhibited and thus exerts exaggerated inhibition to the primary motor cortex of the affected (ipsilesional) hemisphere. This phenomenon is known as Nowak’s hypothesis of inter-hemispheric competition post-stroke\(^\text{64}\). Murase et al.\(^\text{259}\) demonstrated that the amount of inhibition exerted from the unaffected to the affected hemisphere is positively correlated with the severity of the functional impairment of the affected hand as measured by finger tapping. One way to study IHI is by measuring the symmetry of inhibition between the two hemispheres via the ipsilateral silent period (iSP)\(^\text{250-252}\). The ipsilateral silent period refers to a reduction in background EMG in a contracting muscle ipsilateral to TMS stimulation following a supra-threshold stimulus\(^\text{250-252}\).

Experimental studies suggest that plastic changes usually require the down regulation of local inhibitory circuits within M1 and that local disinhibition can unmask latent intracortical connections contributing to cortical reorganization\(^\text{252, 260-263}\). Three types of inhibitory phenomena involving cortical mechanisms are usually studied using TMS: 1) the cortical (contralateral) silent period (cSP)\(^\text{262}\) 2) suppression of voluntary EMG (SVC or Davey’s technique)\(^\text{264}\) and 3) short intracortical inhibition (SICI)\(^\text{265}\). The cSP refers to suppression of the voluntary muscle activity of the contralateral hand following suprathreshold TMS\(^\text{262}\). cSP is commonly interpreted to result from inhibitory activity in intracortical circuits likely mediated by the inhibitory neurotransmitter GABA\(_b\)\(^\text{262}\). Recent studies suggest that cSP in the ipsilesional hemisphere is significantly
prolonged when compared to either the unaffected hemisphere of patients post-stroke or to healthy controls. SVC, or Davey's technique, refers to suppression of the voluntary muscle activity of the contralateral hand by sub-threshold TMS without any prior excitatory response (i.e., MEP). Davey et al proposed that SVC activates corticofugal neurons, which, via collaterals, excite inhibitory interneurons that inhibit corticospinal activity. Pathways involved in SVC could include a longer route, such as the inhibitory loop via the thalamus, which would explain the longer latency of SVC compared to cSP. Since SVC is evoked in response to subthreshold TMS, the structures responsible for the EMG suppression are likely superficial (i.e., cortical surface, closer to the stimulating coil). Indeed, Jones (1975) reported that inhibitory GABAergic neurons are located predominantly in the most superficial layers of the motor cortex. Thus, EMG suppression induced by sub-threshold TMS during motor activity is argued to confirm the presence of corticomotor involvement. SVC has never been studied in persons post-stroke, however Davey studied SVC in spinal cord subjects and suggested that SVC has a longer latency compared to healthy control group. This phenomenon may reflect a weak or absent early component of cortical inhibition in the spinal cord injured population. SICI is commonly used to test intracortical inhibitory circuits likely mediated by GABA. Studies investigating SICI in people with stroke have found reduced intracortical inhibition in the affected hemisphere.

The effect of therapeutic intervention involving POWER training post-stroke on excitatory and inhibitory networks at either spinal and supraspinal levels has never been addressed. Therefore, the overall objective of this single-subject design was to improve
our understanding of mechanisms underlying recovery post-stroke by using a multimodal investigative approach that provides insight into the dynamic relationship between neurophysiology and motor behavior and pays particular attention to the selection of measures that distinguish between recovery and compensation. This study evaluated the effect of 2-weeks of HYBRID training (POWER + FTP) using clinical tests and three-dimensional motion-analysis of functional task performance to measure motor control; H-reflexes to test the spinal circuitry, and TMS to measure cortical networks (i.e. excitatory and inhibitory), and IHI. Our central hypothesis was that an intervention involving POWER would increase central neural drive during functional voluntary movement, which would be revealed by improvements in both motor behavioral and neural outcomes.

In this study, we used TMS to study cortical excitability, inter-hemispheric inhibition (IHI) and cortical inhibitory networks. The first aim of this study consisted of evaluating the effect of the HYBRID training at the behavioral level. To address this aim, we used clinical tests to measure motor impairment and activity levels, and three-dimensional motion-analysis of functional upper-extremity tasks to measure behavioral motor control. Consistent with our previous studies, we hypothesized that clinical tests would fail to detect differences after treatment, while kinematics would reveal post-treatment effects. The second aim of this study evaluated the excitability and inhibitory networks at the spinal and supra-spinal levels. At the spinal level, we hypothesized that HYBRID training would induce reduced excitability of the affected upper-limb motor pools as revealed by increased presynaptic inhibition (i.e., D1 inhibition) and post-activation depression (PAD) (i.e., homosynaptic depression). At the supraspinal level, we
hypothesized that HYBRID training would induce increased cortical excitability of the affected hemisphere and rebalancing of IHI. Further, we expected that HYBRID training would induce improved modulation of the inhibitory pathways, which would be revealed by shortened cSP duration, increased magnitude of SVC and increased SICI, towards normal.

6.4. Research Design and Methods

6.4.1. Inclusion and exclusion Criteria

The participant was included on the basis of the following inclusion and exclusion criteria: 1) clinical presentation of at least one, and no more than three, strokes on the same side of the brain (confirmed by CT or MRI); 2) demonstrated ability to move the upper extremity in the horizontal plane corresponding to a poor (2/5) manual muscle test grade in the major shoulder and elbow agonists 3) at least 10-degrees of active wrist extension, 10-degrees of active abduction of the thumb, and 10-degrees of active extension of any two digits, three times within one minute 4) freedom from significant UE joint pain, passive range of motion limitations, and marked sensory deficits as evidenced by absent proprioception at the elbow or shoulder joints. The exclusion criteria were: 1) use of medications that may lower seizure threshold; 2) history of epilepsy, brain tumor, learning disorder, mental retardation, drug or alcohol abuse, dementia, major head trauma, or major psychiatric illness; 3) evidence of epileptiform activity on electroencephalography obtained prior to screening; 4) history or radiographic evidence of arteriovenous malformation, intracortical hemorrhage, subarachnoid hemorrhage, or bilateral cerebrovascular disease; 5) history of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull;
6) pregnancy; 7) inability to understand 3-step directions; 8) impaired corrected vision that would alter kinematics of reaching.

6.4.2. Participant characteristics

Participant was 66-year-old, right hand dominant, white female who was enrolled in the present study 5-months following a venous infarction associated with cortical vein thrombosis involving the arm-hand knob region and the subcortical posterior half of white matter (including the corona radiata and posterior limb of internal capsule). The lesion resulted in left hemiparesis affecting mainly the upper extremity with absence of cognitive impairment. The participant was identified during acute inpatient rehabilitation at Brooks Rehabilitation Hospital in Jacksonville, FL and she was enrolled in this study after discharge from all formal, supervised inpatient and outpatient rehabilitation.

6.4.2. Experimental Design

This single-subject design involved two weeks of HYBRID (POWER + FTP) therapy at Brooks Center for Rehabilitation Studies in Jacksonville, FL. Prior to, immediately following and one-month following, the participant underwent a multimodal evaluation at the VA Rehab R&D Brain Rehabilitation Research Center (BRRRC) in Gainesville, FL (Figure 6-1).

6.4.3. Outcome Measures

The multimodal evaluation included behavioral and neurophysiological measures.

6.4.3.1. Behavioral measures

Behavioral measures included clinical tests and three-dimensional motion analysis.

Clinical tests. Clinical tests were comprised of the: 1) upper-extremity subsection of the Fugl-Meyer Assessment 93 (including the total score and its motor portion) to
measure upper-extremity motor impairment; 2) Modified Ashworth Scale (MAS) for shoulder flexors/extensors, abductors/adductors, external/internal rotators, elbow and wrist flexor/extensor muscles to measure hypertonia; 3) Wolf Motor Function Test (WMFT), to measure motor activity; 4) muscle strength measurements of five reciprocal upper-extremity movements using a hand-held myometer.

**Three-dimensional motion analysis.** Kinematics of the paretic UE were measured while the participant was positioned in sitting in a straight-back chair with the paretic UE resting on the ipsilateral thigh (Start position). The shoulder was positioned in neutral flexion/extension and neutral internal rotation; the elbow in 75-90 degrees of flexion with the wrist resting in pronation. The participants was instructed to reach, grasp and retrieve a full soda can positioned on a table top at 80% of arm’s length (i.e., ‘Coke can’ task). This functional reach-to-grasp task was selected as the study outcome task because of its status as a fundamental motor skill necessary for many daily activities. Subjects completed 1-2 practice trials followed by three test trials. Three-dimensional motion analysis data were collected using 53 reflective markers placed on the: anterior and posterior spines, base of sacrum, manubrium and body of sternum, 7th cervical vertebra, 10th thoracic vertebrae, and bilaterally on the acromion processes, medial and lateral epicondyles, ulnar and radial styloid processes, superior thirds of the upper arm and forearm (triads), hand and finger tips (set of 11 small size markers).

Data were recorded with a twelve-camera motion analysis system (Vicon 612, Oxford Metrics Inc., Oxford, U.K.) at a sampling frequency of 200 Hz. The motion

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analysis system expressed output data as three-dimensional, time-dependent marker coordinates relative to a laboratory coordinate system.

6.4.3.2. Neurophysiologic measures.

**H-reflex.** We conducted three sets of experiments: 1) unconditioned H-reflexes to establish a recruitment curve and slope for the flexor carpi radialis (FCR)\(^{184}\) 2) D1 inhibition, conditioning of the FCR H-reflex with median nerve stimulation to study pre-synaptic inhibition\(^{184}\), and 3) repeated H-reflexes at varying interstimulus intervals to study post-activation or homosynaptic depression\(^{184}\). In all sets of experiments, the participant was seated with the forearm pronated, with wrist in neutral flexion/extension position and elbow at 45-degrees flexion; shoulder was in neutral rotation and slightly abducted and flexed to allow access to the median nerve.

H and M-waves were electrically evoked using a constant current stimulator\(^{27}\) Conditioning stimuli were delivered using a second stimulator (Grass technologies, West Warwick, RI, USA). For the unconditioned H-reflex and D1 inhibition, we used a surface electromyography electrode placed over the belly of the flexor carpi radialis to record the H and M-wave and a stimulating bipolar electrode placed in the medial bicapital groove to stimulate the median nerve. For post-activation depression (PAD), we used an additional electromyography electrode on the belly of the extensor carpi radialis and a stimulating electrode above and lateral to the elbow to stimulate the radial nerve. Data were collected at a sampling rate of 10kHz using a PowerLab analog-to-digital converter and LabChart Software\(^{28}\).

\(^{27}\)Digitimer DS7A, Digitimer Ltd., Hertfordshire, England

\(^{28}\)PowerLab analog-to-digital converter and LabChart Software Version 7.3, ADInstruments, Colorado Springs, CO, USA
Once the stimulation site for the median nerve was located, FCR H-reflex recruitment curves were obtained. The stimulation intensity at the median nerve was sequentially increased (typically by 0.5 mA increments) from sub-H-reflex threshold intensity to the point when H-reflex amplitude reached the maximum and began to decline; thereafter, current intensity was increased at a faster rate (1 mA) until a maximum M-wave (Mmax) was elicited.

Pre-synaptic Ia or D1 inhibition was performed by median nerve stimulation (unconditioned stimulus) preceded by a conditioning stimulus at the radial nerve (conditioned stimulus). Unconditioned responses were elicited at the stimulation intensity level that produced an M-wave equal to 20% of Mmax (ascending curve of the M-wave). The radial nerve conditioning stimulus was delivered at 0.95 motor threshold at an interstimulus interval of 13 ms (conditioning stimulus preceded test by 13 ms). We performed 20 stimuli randomly alternating conditioned and unconditioned stimuli.

Post-activation or monosynaptic depression (PAD) was tested by randomly stimulating the median nerve at interstimulus intervals (ISIs) between 1-12 seconds. Five stimuli were repeated at each ISI at an intensity level that produced an H-wave equal to Hmax/2.

**Transcranial magnetic stimulation (TMS).** We conducted four sets of experiments to study cortical excitability, interhemispheric inhibition (IHI) and activity in cortical inhibitory networks. During TMS testing, the participant was seated comfortably in a semi-reclined chair. Stimulation was delivered using one or two Magstim® 200 stimulators connected through a Bi-stim module to a figure-eight coil (Magstim®) while

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29 The Magstim® Company LTD, Whitland, Wales, UK
recording MEPs from the contralateral first dorsal interosseous (FDI) muscle by means of pre-amplified EMG electrodes (MA-311, Motion Lab Systems, Baton Rouge, LA, USA). The coil was placed tangentially over the scalp, with the handle pointing backwards and laterally at a 45° angle away from the midline, inducing a posterior-anterior current in the target hemisphere.

We studied cortical excitability by calculating the slope of the active input-output curve, also known as the active recruitment curve (RC). The slope of the RC provides a measure of the excitability of cortical motor areas. Active RC was generated by stimulation over the motor threshold hotspot during background contraction (10% of the maximal effort) of the first dorsal interosseous (FDI). Responses were elicited at progressively increasing intensities over a range from 10% below motor threshold until maximal MEP amplitude was obtained. 10 stimuli were recorded at each intensity and stimulation intensity was increased in 5% increments. The maximum FDI M-wave was evoked and the peak-to-peak amplitude used to normalize MEP amplitude for construction of the RC. RC was measured for both ipsilesional and contralesional hemispheres.

We used the duration of ipsilateral silent period (iSP) to study inter-hemispheric inhibition (IHI). iSP was obtained using single pulse TMS delivered at 150% of motor threshold while the participant produced a background contraction (10% of the maximal effort) of the FDI muscle ipsilateral to the stimulation. 10 trials of iSP were obtained for each hemisphere.

We studied cortical inhibitory networks by measuring the cortical silent period (cSP), the suppression of voluntary contraction without an excitatory response (SVC or
Davey’s technique) and short intracortical inhibition (SICI). The cSP consists of suppression of the voluntary muscle activity of the contralateral hand by a supra-threshold TMS after prior excitatory response (MEP). We studied the cSP simultaneously with MEP amplitude during the RC experiment. 10 cSP trials were obtained at each stimulus intensity for each hemisphere. The SVC, or Davey’s technique, consists of suppression of the voluntary muscle activity of the contralateral hand by a sub-threshold (i.e., ~20% below motor threshold) TMS without any prior excitatory response. 50 trials of SVC were obtained for each hemisphere. SICI consists of a reduction in the amplitude of the excitatory response (MEP) to a suprathreshold test stimulus (intensity producing MEPs of ~1mV) by a subthreshold conditioning stimulus (80% of active motor threshold) at interstimulus intervals ranging from 1 to 6 ms. 5 paired-pulse stimuli were delivered at each ISI to quantify SICI in each hemisphere.

6.4.4. Therapeutic Interventions

HYBRID intervention consisted of combined POWER training followed by FTP for 3 hours daily, 5 days per week, for two weeks. The treatment algorithms was developed on the basis of the results of our previous studies and adapted for a shorter treatment period. POWER involved five reciprocal upper-limb movements: shoulder abduction/adduction, shoulder flexion/extension, shoulder external/internal rotation, transverse plane elbow flexion/extension and wrist flexion/extension. All movements were trained using a commercially available dynamometer and custom fabricated attachments to accommodate the hemiparetic upper-extremity (Table 6-1). FTP involved practice of functional tasks using a progression of six therapeutic goals and

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30 Biodex, Copyright © 2012, Biodex Biomedical System 3.2, Shirley, NY, USA
nine activity categories. Specific therapeutic tasks were chosen from a list of activity categories based on participant-specific goals and baseline functional level and practiced on a structured rotation within the framework of the therapeutic goal (Table 6-2).

6.5. Analysis

6.5.1. Clinical Tests

For MAS, we calculated the composite score for shoulder flexion/extension, abduction/adduction, external/internal rotation, elbow and wrist flexion/extension. For Fugl-Meyer Assessment, we calculated the total score (total score) and the motor portion (motor score). For WMFT, we calculated the sum and the mean of the total execution time for both affected and unaffected sides. WMFT was compared to normal data\(^\text{270}\). For muscle strength measurements, we calculated the change score between baseline and post-HYBRID and between post-HYBRID and follow-up for each UE movement.

6.5.1. Three-Dimensional Motion Analysis

Marker data were labeled using Vicon Nexus\(^\text{31}\) and modeled using Visual3D\(^\text{32}\). Kinematic trajectories, extracted from Visual3D, were analyzed using custom-written Matlab\(^\text{33}\) scripts. Kinematic data were low-pass filtered (12 Hz cutoff) using a bi-directional 4\(^\text{th}\) order Butterworth filter. The start-of-movement (SOM) was defined as the first point at which the velocity of the marker on the third metacarpophalangeal joint

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\(^{31}\) Vicon© 612, Oxford Metrics, Oxford, UK

\(^{32}\) Copyright© 2010 C-Motion, Version 4.00.19, Inc C-Motion, Germantown, Maryland

\(^{33}\) MathWorks®, Version R2011b, Inc., Massachusetts, USA
exceeded 5% peak velocity and the end-of-motion (EOM) as the last point at which velocity of this marker fell below 5% peak.\

Our primary kinematic outcomes were shoulder and elbow range of motion and trunk displacement to quantify movement execution. Reach-path-ratio (RPR) was used as a secondary outcome to quantify movement accuracy.

Range of motion (ROM) was calculated for shoulder flexion and elbow extension as the difference, in degrees, between the maximum and minimum joint angle achieved. Trunk displacement was defined as the displacement of the sternum marker, in millimeters, in the sagittal plane. Reach-path-ratio was defined as the ratio of the actual path and the direct path length of the hand marker. The actual path is defined as the three-dimensional displacement of the hand marker path during the reach task, and the direct path is defined as the three-dimensional distance between the hand marker at onset and the hand marker at offset.

6.5.2. H-reflex

The peak-to-peak amplitude of both, H- and M-waves were normalized to Mmax. Using the range of H- and M-responses, H- and M- recruitment curves were plotted. Maximum values for H- and M- of the recruitment curves were calculated and the Hmax/Mmax ratio was assessed. Linear regressions were calculated for both H- and M-wave recruitment curves to obtain the H- and M-slope. The slope of the H-reflex recruitment curve (Hslp) was calculated on the ascending limb defined as a range from 10-85% of maximum H-reflex amplitude. Similarly, the M-slope (Mslp) was calculated for the M-wave recruitment curve. Hslp was normalized to Mslp, expressed as the ratio - Hslp/Mslp. This ratio has been reported as an effective and sensitive method to detect changes in spinal excitability. For conditioned stimuli, the amplitude of the
conditioned H-reflex was expressed as relative to the unconditioned H-reflex. The amplitude of the H-reflex following repeated stimulation was expressed relative to H-reflex amplitude at the 12 s ISI\textsuperscript{184}.

6.5.3. Transcranial Magnetic Stimulation (TMS)

The area of the average, rectified MEP response was calculated at each stimulus intensity. MEP areas were normalized to M-wave area and the stimulus-response curve of MEP area against stimulus intensity (i.e. recruitment curve, RC) was constructed. A non-linear regression fit of the data was performed using the Boltzmann Equation, followed by a linear regression fit of the modeled data in the steepest portion of the range. The slope of the fitted line was reported.

For cortical silent period (cSP), ipsilateral silent period (iSP) and EMG suppression (a.k.a. Davey’s technique): EMG data were rectified and averaged over multiple trials. The mean and the standard (SD) deviation of the baseline EMG level for 100 ms before TMS stimulus was determined from the averaged signal. We considered the presence of an MEP (either ipsilateral or contralateral) if the post-stimulus EMG exceeded the pre-stimulus mean baseline EMG by > 1 SD for ≥ 5 ms. MEP onset was defined as the last crossing of the pre-stimulus mean baseline EMG before the MEP peak and the MEP offset as the first crossing of the pre-stimulus mean baseline EMG after the MEP peak. MEP area was calculated between the MEP onset and offset (MEP duration). Similarly, we considered the presence of an SP (either cSP and iSP) if the post-stimulus EMG fell below the pre-stimulus mean baseline EMG by ≥ 1 SD for > 5 ms. The SP onset was defined as the first crossing of the pre-stimulus mean baseline EMG after the MEP peak and the MEP offset as the first crossing of the pre-stimulus mean baseline EMG after the SP onset for at least 5 ms\textsuperscript{186}. The SP duration was the time between the
onset and the offset values. For each ISI, signal averaging of multiple stimuli was performed. The peak amplitude was calculated and normalized relative to the single-pulse (unconditioned) MEP amplitude. The stimulus-response curve of cSP against stimulus intensity (i.e. recruitment curve, RC) was constructed using a non-linear regression fit of the data to the Boltzmann Equation, followed by a linear regression fit of the modeled data in the steepest portion of the range. The slope of the fitted line was reported.

6.6. Results

6.6.1. Clinical Tests

Clinical tests are summarized in Table 6-3 and 6-4. At baseline, MAS indicated a slight increase in muscle tone in 5 out of 7 tested muscles (composite score, 5). MAS improved progressively after HYBRID treatment (composite score, 2) and at follow-up (composite score, 0). At baseline, Fugl-Meyer assessment indicated a very mild impairment (total score, 118 out of 126 and motor score, 62 out of 66). After HYBRID, Fugl-Meyer reached the maximum value for both total score and motor score (respectively, 126 out of 126 and 66 out of 66), these scores were maintained at follow-up. At baseline, Wolf motor function test for both the unaffected arm (sum, 25.49±1.19 and mean, 1.70±1.19) and affected arm (sum, 26.57±1.20 and mean, 1.77±1.20) were similar to normal data for the age-matched population (mean for right 1.30±0.3 and for left 1.30±0.3)\textsuperscript{270}. These values remained stable after HYBRID (sum for unaffected, 23.71±1.09 and for affected, 23.61±1.35) and at follow-up (sum for unaffected, 24.70±1.02 and for affected, 23.93±0.99). At baseline, muscle strength measurements revealed an asymmetry between unaffected (muscle strength average, 18.22lb) and affected (muscle strength average, 11.69lb) arms in favor of the unaffected arm. After
HYBRID, there was a larger improvement in the affected arm (average change score, 4.81lb) versus the unaffected arm (average change score, 0.56lb. At follow-up, the affected arm continued to improve (average change score, 1.59lb).

**6.6.3. Kinematics**

Kinematics of the affected arm were compared to the unaffected arm during the same functional reaching task (Figure 6-2). At baseline, the affected arm had less range of motion at the shoulder and elbow (shoulder, 18.87±1.45° and elbow, 11.70±1.66°) than the unaffected arm (shoulder, 22.46±1.01° and elbow, 21.82±1.39°). After HYBRID, range of motion of the affected arm had a small increase at shoulder flexion (change score: 2±0.9°) and a greater increase at elbow extension (change score: 5.83±0.5°). At follow-up these improvements were lost at the shoulder (change score: -3.54±0.04°) but maintained at the elbow (1±0.3°). Trunk excursion during affected arm movement was lower (17±2.01mm) than during unaffected arm movement (20.25±1.22mm) at baseline and it increased progressively post-HYBRID (19.51±2mm) and at follow-up (25.14±1.28mm). The reach-path ratio of the affected arm (1.03±0.09) did not differ from the reach-path ratio of the unaffected arm (1.04±0.01) at baseline and remained constant at all the evaluations (Figure 6-2).

**6.6.4. H-reflex**

**Unconditioned test.** The $H_{\text{max}}/M_{\text{max}}$ ratio at baseline was greater (0.77) than the value reported for non-disabled older adults (~0.4)$^{256}$ and decreased progressively after HYBRID treatment (0.35) and at follow-up (0.16) (Figure 6-2). Similarly, the $H_{\text{slope}}/M_{\text{slope}}$ ratio was greater at baseline (0.74) than the value reported for non-disabled older adults.
and decreased progressively after HYBRID treatment (0.66) and at follow-up (0.50) (Figure 6-2).

**Pre-synaptic Ia or D1 inhibition (conditioned test).** At baseline, the conditioned D1 test induced an abnormal facilitation of the H-reflex response (154.46±2.7% of unconditioned value) instead of inhibition as observed in non-disabled individuals\(^\text{184}\). After HYBRID treatment, this abnormal facilitation was somewhat reduced (114.17±2.84% of unconditioned value) and became inhibition at follow-up (93.73±12.70 of unconditioned value) (Figure 6-4).

**Homosynaptic or post-activation depression (PAD) (repeated test).** Figure 6-5 illustrates the post-activation depression when the inter-stimulus interval (ISI) was varied from 1 to 12 seconds. H-reflex size at ISI of 12 seconds was used as reference value (i.e. 100%)\(^\text{184}\). At baseline, for ISIs ranging between 1 to 5 seconds, the amplitude of the H-reflex increased when the ISIs increased with a similar pattern as observed in non-disabled subjects\(^\text{184}\). To quantify the total post-activation depression, the area under the PAD curve at ISIs ranging between 1 and 12 seconds was calculated. At baseline the area (1005) was greater than after HYBRID training (890.30) and at follow-up (580.50), indicating a progressive increase of total PAD.

**6.6.5. Transcranial Magnetic Stimulation**

**6.6.5.1. Recruitment curve**

At baseline, the recruitment curve slope was greater in the unaffected hemisphere (9.07) than in the affected hemisphere (4.56) (Figure 6-7). After HYBRID treatment, the slope in the unaffected hemisphere decreased (5.36) and increased in the affected hemisphere (5.76). At follow-up the slope in the unaffected hemisphere continued to decrease (2.55), while it remained stable in the affected hemisphere (5.01). These
results indicate a decreased excitability in the unaffected hemisphere and a concurrent increased excitability in the affected hemisphere.

6.6.5.2. Silent period (SP)

We constructed the stimulus-response (S-R) curves of SP duration against stimulus intensity (Figure 6-11). At baseline, the linear slopes in the steepest range of the sigmoidal curves were similar in the unaffected (7.52±0.16) and affected (6.07±0.28) sides. After HYBRID treatment, the slopes reduced in both sides (unaffected, 3.81±1.36 and affected, 3.43±1.30) and they both increased at follow-up (unaffected, 12.42±3.08 and affected, 5.82±1.90). Further, the duration of the silent period decreased after HYBRID treatment, versus baseline, for stimulation intensities greater than 50% in the unaffected side and decreased after HYBRID and at follow-up for stimulation intensities greater than 45% in the affected side (Figure 6-11).

6.6.5.3. Ipsilateral silent period (iSP)

At baseline, IHI from the affected to the unaffected hemisphere (iSP duration while stimulating the affected hemisphere) was shorter than IHI from the unaffected to the affected hemisphere (iSP duration while stimulating the unaffected hemisphere) (34 and 42 ms, respectively). After HYBRID treatment, IHI from the affected to the unaffected hemisphere increased (42.99 ms) and from the unaffected to the affected hemisphere decreased (37.38 ms). At follow-up, IHI was reduced in both hemispheres (from the affected to the unaffected hemisphere, 37.13ms and from the unaffected to the affected hemisphere, 26.38ms) and reached values of non-disabled healthy controls (Figure 6-6). The laterality index for the iSP duration ((AH-UH)/(AH+UH)) was 0.10 at baseline, -0.06 after HYBRID treatment and -0.16 at follow-up (Figure 6-6).
6.6.5.4. **Short Intracortical inhibition (SICI)**

At baseline, the affected hemisphere revealed less SICI compared to the unaffected hemisphere for ISIs less than 3ms. These data are consistent with previous work\textsuperscript{265}. After HYBRID, SICI increased in the affected hemisphere and decreased in the unaffected hemisphere. SICI after HYBRID was greater in the affected versus the unaffected hemisphere for ISIs ranging 1-6ms. At follow-up, SICI increased in both hemispheres and became more symmetrical (Figure 6-7).

6.6.5.5. **Suppression of voluntary contraction (SVC).**

We were able to show suppression of the voluntary contraction (SVC) after sub-threshold TMS for both affected and unaffected sides (Figure 6-10). At baseline, the percent of inhibition normalized to the prestimulus EMG in the affected FDI (22.07%) was slightly smaller than the unaffected hemisphere (30%). After Hybrid training, the % of inhibition remained constant in both affected (21.50%) and unaffected (25%) hemispheres. At follow-up, there was a slight decrease in inhibition in both affected (18.82%) and unaffected (19.15%).

6.7. **Conclusion**

This study evaluated the effect of 2-weeks of HYBRID training (POWER + FTP) using clinical tests and three-dimensional motion-analysis during a functional task to measure motor control, H-reflexes to test spinal circuitry, TMS to measure cortical networks (i.e. excitatory and inhibitory), and IHI. Table 6-5 summarizes the results for each neurophysiologic technique and the corresponding neurological pathways. Our central hypothesis was that an intervention involving POWER would increase central neural drive during functional voluntary movement, which would be revealed by improvements in both motor behavioral and neural outcomes.
**Behavioral level.** Baseline evaluation for all clinical tests of the affected arm, with exception of muscle strength measurements, showed minimal motor impairment. Either after HYBRID or at follow-up, MAS and Fugl-Meyer Assessment reached the maximum scores and WMFT reached normative values for age-matched non-disabled population (Table 6-3). Strength measurements revealed asymmetry between arms in favor of the unaffected arm (~7lb difference). HYBRID training increased strength in all muscles of the unaffected arm except for wrist extensors. The greater strength improvements were at elbow flexors/extensors, shoulder internal rotators and flexors. Of note, baseline evaluation revealed greater weakness in proximal relative to distal muscles, and this weakness was in accordance with the participant’s self-report of motor impairment. Total muscle strength in the affected arm progressively improved after HYBRID and at follow-up, while muscle strength remained constant in the unaffected arm.

Similarly to clinical tests, kinematic data indicated that the motor control strategy in the affected arm was very similar to the unaffected arm during UE reaching task. After HYBRID, shoulder and elbow ROM and trunk displacement improved (reaching unaffected arm values); at follow-up, these improvements were maintained at elbow ROM, but they were lost at shoulder ROM and trunk displacement.

**Spinal Circuits.** Baseline evaluation for both $H_{max}/M_{max}$ and $H_{slope}/M_{slope}$ ratios are in accordance with values reported previously for post-stroke individuals$^{256}$. Our results reveal progressively reduced $H_{max}/M_{max}$ and $H_{slope}/M_{slope}$ ratios post-HYBRID and at follow-up. Interestingly, after HYBRID both these ratios reached values reported for non-disabled older adults$^{256}$. These findings suggest normalization of spinal excitability, which is normally found to be increased in the affected upper-limb post-stroke$^{256}$. 
Further, we evaluated presynaptic inhibition (i.e., D1 inhibition) and post-activation depression (PAD) (i.e. homosynaptic depression). Both PAD and D1 increased progressively post-HYBRID and at follow-up. Therefore, our results suggest that HYBRID training induces improved modulation of the spinal mechanisms controlling homosynaptic (PAD) and presynaptic (D1) pathways of the monosynaptic reflex arc. Improvements in modulation of the homosynaptic reflex arc (PAD) may suggest improvement in the efficacy of the Ia fibre-motoneurone synapse. Improvements in the presynaptic (D1) mechanisms may suggest improvement of the descending inhibitory control from supraspinal structures post-stroke. Our results at spinal level, including both excitatory and inhibitory pathways, are in accordance with our hypothesis of positive neural changes post-HYBRID.

**Supraspinal level.**

First, we evaluated the slope of the stimulus-response curve of MEP area vs. stimulus intensity, which offers information regarding the excitability of the motor cortex and the strength and integrity of the corticospinal pathways\textsuperscript{271, 272}. Our data indicate that HYBRID increased RC slopes in the affected hemisphere and reduced RC slopes in the unaffected hemisphere. These findings suggest an increase of the cortical excitability in the affected hemisphere and a concurrent decrease of the cortical excitability in the unaffected hemisphere.

Second, we evaluated interhemispheric inhibition (IHI). IHI is commonly studied by a paired-pulse protocol with the conditioning stimulus delivered to one M1 and the test stimulus delivered to the other M1 10ms later (S-IHI)\textsuperscript{246}. Specifically, the activity in the M1 receiving the conditioning stimulus, facilitates inhibition of the MEP elicited by the
test stimulus. Ferbert et al suggested that the inhibition was produced at cortical level via transcallosal route. Besides S-IHI, interhemipsheric inhibition can also be studied by a short interruption of ongoing voluntary EMG activity induced by focal TMS of the ipsilateral M1. This ipsilateral silent period (iSP) has a latency of 30-40ms post-stimulus and lasts around 25ms. Meyer at al indicated that iSP reflects interhemipsheric cortico-cortical inhibitory mechanisms mediated by fibres passing through the posterior half of the trunk of the corpus callosum. Chen et al suggested that the neural mechanisms underlying the iSP differ from those responsible for S-IHI. For this reason, the iSP is currently considered as a measure that provides complementary, but not identical, information on interhemispheric inhibition compared to S-IHI. Several authors have used the iSP instead of the S-IHI to provide an estimation of interhemispheric inhibition. The advantage of using the iSP in persons post-stroke is that it allows estimation of IHI even in the absence of MEPs in the ipsilesional hemisphere. Our data indicate that HYBRID increased the iSP from the affected to the unaffected hemisphere, and reduced the iSP from the unaffected to the affected hemisphere. At follow-up, the iSP in both affected and unaffected hemispheres reduced and reached values of healthy controls. These findings indicate rebalancing of IHI following therapeutic intervention. The laterality index of the iSP indicated a slight predominance of the unaffected hemisphere at baseline and a reversed condition in favor of the affected hemisphere after HYRBID and at follow-up.

We also evaluated the short-intracortical inhibitory network (SICI). Consistent with previous studies, our results indicated reduced SICI in the affected hemisphere compared to the unaffected hemisphere at baseline. After HYBRID, SICI increased in
the affected hemisphere and reduced in the unaffected hemisphere, resulting in greater intracortical inhibition in the affected hemisphere. At follow-up, SICI increased in both hemispheres and become more symmetrical. Some authors\textsuperscript{185, 273} suggested that the asymmetry in SICI of the affected and unaffected hemispheres is a maladaptive process. It has been suggested that the reduced inhibition in the affected hemisphere could be due to persistent reduction in the intracortical inhibitory GABA\textsubscript{A}ergic circuits within M1 or to an increased excitability and lowered threshold for activation of those interneurons responsible for the excitatory effects at short ISIs. Cincinelli\textsuperscript{185}, suggested there is an enhanced intracortical excitability of the affected hemisphere as a result of reduced (defective) SICI. As the author suggested, it is important to clarify that there are different excitable elements in motor cortex, thus increased excitability to paired stimuli might reflect to reduced activity of inhibitory M1 intracortical circuits, and the decreased excitability to single stimuli is probably related to loss of excitable elements. Therefore, our findings suggest HYRBID training was able to improve the modulation of the GABA\textsubscript{A}ergic circuits within M1 or the interneurons responsible for excitatory effects at short ISIs. These results are in accordance with our hypothesis.

Lastly, we studied the suppression of voluntary contraction (i.e., SVC or Davey’s technique). Our data did not indicate any changes in the depth of EMG suppression after either HYBRID or follow-up evaluations in either the affected and unaffected hemispheres. SVC reveals suppression of the ongoing EMG by a sub-threshold TMS pulse and is known to occur as a result of activating superficial cortico-cortical inhibitory interneurons, argued to be mediated by GABA\textsubscript{A}ergic receptors. The resulting EMG suppression induced during motor activity reflects the presence of corticomotor
involvement. At all evaluations, we were able to elicit EMG suppression with sub-threshold TMS pulse indicating corticomotor involvement in the voluntary FDI contraction (10% of MVIC). A visual analysis of EMG (Figure 6-10) could lead to the interpretation that HYBRID training increased SVC in both the affected and unaffected hemispheres. However, when the suppression is normalized to the prestimulus EMG activity, the magnitude of inhibition is similar. It is possible that HYBRID treatment did not have any effect on the mechanisms controlling SVC, however it also possible that HYBRID did increase the amount of suppression as revealed by the EMG visual inspection and that the amount of inhibition as % of the prestimulus EMG cannot be interpreted as meaningful. In support of this interpretation, Barthelemy and Nielsen suggested that the suppression of the EMG can only be used to provide confirmation of the contribution of corticospinal drive to the ongoing EMG, but it cannot be used to draw conclusions regarding the magnitude of that drive, how significant it is for the EMG activity or for differences in the drive during two tasks.

Taken together our findings support our hypothesis that POWER training promotes enhanced central neural drive in the ipsilesional hemisphere and may represent a potential driver of cortical reorganization including modulation of intracortical and interhemipsherric inhibition. The intensity of the HYBRID treatment may have indirectly improved the impaired modulation of the cortical inhibitory pathways by engaging increased participation of the nervous system and eliciting greater voluntary cortical drive. Further, our data reveal that it is possible to induce concurrent neurophysiologic changes at spinal and supraspinal levels, associated with behavioral change that constitutes functional recovery. The positive outcomes of HYBRID training can most
likely be attributed to: a) the well-recognized and profound neural adaptations induced by POWER training, and b) therapeutic intensity, which promotes improvements by challenging the subject’s capacity and by engaging increased participation of the nervous system. This is the first study to address the effects of therapeutic intervention involving POWER training post-stroke concurrently on spinal and on supra-spinal excitatory and inhibitory networks. Our results compel us to investigate these mechanisms with future larger scale research studies, which may inform how individual characteristics interact with mechanisms of neural recovery.
Figure 6-1. Single-subject design. Participant underwent to two weeks of HYBRID (POWER + FTP) therapy and was assessed with a multimodal evaluation, including clinical tests, behavioral and neurophysiologic measures prior to and immediately following two weeks of treatment, and at one-month follow-up.
<table>
<thead>
<tr>
<th>Week 1</th>
<th>Number of sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speeds</td>
<td>-30</td>
</tr>
<tr>
<td>Shoulder flexion</td>
<td>2</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>2</td>
</tr>
<tr>
<td>Shoulder extrarotation</td>
<td>2</td>
</tr>
<tr>
<td>Wrist flexion/extension</td>
<td>2</td>
</tr>
<tr>
<td>Elbow flexion/extension</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 2</th>
<th>Number of sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder flexion</td>
<td>2</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>1</td>
</tr>
<tr>
<td>Shoulder extrarotation</td>
<td>1</td>
</tr>
<tr>
<td>Wrist flexion/extension</td>
<td>2</td>
</tr>
<tr>
<td>Elbow flexion/extension</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Table indicates number of sets performed for each movement during the two weeks of training. Monday, Wednesday and Friday training involved shoulder flexion and abduction, and wrist flexion/extension. Tuesday and Thursday training involved shoulder external rotation and elbow flexion/extension.
Table 6-2. Functional task practice (FTP) of HYBRID training.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Key kinesiologic components</th>
<th>Advancing therapy</th>
<th>Therapeutic goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laundry task</td>
<td>Manipulation skills including grips, proximal stabilization/eduction required</td>
<td>Begin by smoothing out and folding a towel, focus on appropriate gleno-humeral rhythm. Advance to tasks requiring proximal stabilization with simultaneous manipulation including buttoning, zipping, tying and folding of laundry.</td>
<td>Wrist/hand</td>
</tr>
<tr>
<td>Writing/ drawing/ paint</td>
<td>Gleno-humeral rhythm &amp; stabilization with elbow control</td>
<td>This task can be advanced by raising the height and increasing the vertical angle of the work surface. Furthermore, more difficult patterns can introduced.</td>
<td>Shoulder</td>
</tr>
</tbody>
</table>

Note: Consistent with our previous work, the FTP program addressed six global therapeutic goals. Therapeutic activities were developed on the basis of the specific therapeutic goal. There were nine activity categories: water tasks, catch-release, feeding and cooking, games, painting and drawing, laundry, sport, computer keyboarding and tool tasks. Each 90-minute treatment session involved 15 minutes of stretching and warm up, followed by practice of activities in each of the 9 categories for 8 minutes each. Table reports specific examples of activities. Difficulty of activities was adjusted based on level of function of each individual. To assure consistency across all participants, treatment was advanced to the next therapeutic goal on the timeline specified and the nine activity categories were presented in rotation.

Table 6-3. Clinical scales. Numbers in parenthesis indicate scores for non-disabled.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post HYBRID</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Ashworth Scale (0)</td>
<td>5.00</td>
<td>2.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Fugl-Meyer Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (126)</td>
<td>118.00</td>
<td>126.00</td>
<td>126.00</td>
</tr>
<tr>
<td>Motor score (66)</td>
<td>62.00</td>
<td>66.00</td>
<td>66.00</td>
</tr>
<tr>
<td>Wolf Motor Function Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right - unaffected (median)</td>
<td>25.49±1.19</td>
<td>23.71±1.09</td>
<td>24.70±1.02</td>
</tr>
<tr>
<td>Left - affected (median)</td>
<td>26.57±1.20</td>
<td>23.61±1.35</td>
<td>23.93±0.99</td>
</tr>
<tr>
<td>Right (mean) (1.3±0.3)</td>
<td>1.70±1.19</td>
<td>1.58±1.09</td>
<td>1.65±1.02</td>
</tr>
<tr>
<td>Left (mean) (1.3±0.3)</td>
<td>1.77±1.20</td>
<td>1.71±1.66</td>
<td>1.60±0.99</td>
</tr>
</tbody>
</table>
### Table 6-4. Muscle strength.

<table>
<thead>
<tr>
<th>Movements</th>
<th>Change scores</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right/Unaffected side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post HYBRID</td>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder flexion (lb)</td>
<td>2.10</td>
<td>0.10</td>
<td>3.20</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td>Shoulder extension (lb)</td>
<td>0.10</td>
<td>-0.90</td>
<td>0.10</td>
<td>-1.60</td>
<td></td>
</tr>
<tr>
<td>Shoulder abduction (lb)</td>
<td>0.40</td>
<td>3.00</td>
<td>1.40</td>
<td>7.80</td>
<td></td>
</tr>
<tr>
<td>Shoulder adduction (lb)</td>
<td>-0.70</td>
<td>1.20</td>
<td>1.40</td>
<td>3.70</td>
<td></td>
</tr>
<tr>
<td>Shoulder extrarotation (lb)</td>
<td>1.40</td>
<td>0.50</td>
<td>1.90</td>
<td>-1.20</td>
<td></td>
</tr>
<tr>
<td>Shoulder intrarotation (lb)</td>
<td>0.70</td>
<td>-1.00</td>
<td>7.40</td>
<td>-0.60</td>
<td></td>
</tr>
<tr>
<td>Elbow extension (lb)</td>
<td>1.60</td>
<td>-1.10</td>
<td>14.10</td>
<td>-4.30</td>
<td></td>
</tr>
<tr>
<td>Elbow flexion (lb)</td>
<td>-0.80</td>
<td>-4.30</td>
<td>17.40</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>Wrist flexion (lb)</td>
<td>0.10</td>
<td>-2.00</td>
<td>1.80</td>
<td>2.30</td>
<td></td>
</tr>
<tr>
<td>Wrist extension (lb)</td>
<td>0.70</td>
<td>1.20</td>
<td>-0.60</td>
<td>5.30</td>
<td></td>
</tr>
<tr>
<td>Pathways</td>
<td>Technique</td>
<td>Parameters</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>Spinal excitability</td>
<td>H-reflex</td>
<td>Hmax/Mmax ratio</td>
<td>Reduced in the AA (Figure 6-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hslope/Mslope ratio</td>
<td>Reduced in the AA (Figure 6-3)</td>
<td></td>
<td></td>
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<tr>
<td>Presynaptic Iₐ inhibition</td>
<td>D1 inhibition</td>
<td></td>
<td>Increased in the AA (Figure 6-5)</td>
<td></td>
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<td>Monosynaptic inhibitory reflex arc</td>
<td>PAD</td>
<td></td>
<td>Increased in the AA (Figure 6-6)</td>
<td></td>
<td></td>
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<tr>
<td>Cortical excitability</td>
<td>TMS</td>
<td>RC slope of MEPs area</td>
<td>Reduced in the UH; increased in the AH (Figure 6-7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-hemispheric inhibitory pathways</td>
<td>iSP duration</td>
<td></td>
<td>Increased from AH to the UH; decreased from the UH to the AH (Figure 6-8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical inhibitory interneurons (GABA₆)</td>
<td>RC slope for cSP duration</td>
<td>Decreased in AH and UH (Figure -11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Inhibitory pathway (GABA₆)</td>
<td>SICI (%inhibition)</td>
<td></td>
<td>Increased in the AH; decreased in the UH (Figure 6-9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical inhibitory interneurons (GABA₆)</td>
<td>SVC duration</td>
<td></td>
<td>No change in either AH or UH (Figure 6-10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 6-2. Key kinematic parameters. Horizontal lines indicate values for the unaffected arm (black line is shoulder ROM, dash line is elbow ROM).
Figure 6.3. $\frac{H_{\text{max}}}{M_{\text{max}}}$ and $\frac{H_{\text{slope}}}{M_{\text{slope}}}$.
Figure 6-4. H-reflex recruitment curves and slopes.
Figure 6-5. Presynaptic or D1 inhibition. Values are expressed as percent of unconditioned reflex: Values greater than 100 correspond to facilitation and values smaller than 100 correspond to inhibition.

Figure 6-6. Post-activation depression (PAD). Values are expressed as percent of reflex at ISI of 12 seconds: Values greater than 100 correspond to facilitation compared to reflex at ISI of 12 seconds, and values smaller than 100 correspond to inhibition compared to reflex at ISI of 12 seconds.
Figure 6-7. TMS recruitment curve slopes.
Figure 6-8. Ipsilateral silent period (iSP) and laterality index (LI).
Figure 6-9. Short intracortical inhibition (SICI).
Figure 6-10. Suppression of voluntary contraction (SVC) or Dave’s technique. Units for x-axis are milliseconds and units for y-axis are in microvolts.
Figure 6-11. Stimulus response (S-R) curves of SP against stimulus intensity.
CHAPTER 7
CONCLUSIONS

The overall objective of this dissertation was to improve our understanding of mechanisms underlying upper-extremity recovery post-stroke by using a multimodal method of investigation that provides insight into the dynamic relationship between neurophysiology and motor behavior and pays particular attention to the selection of measures that distinguish between recovery and compensation. Chapters 3, 4, 5 and 6 of this dissertation describe individual studies we performed as an attempt to answer our research questions.

Study 1. We investigated concurrent clinical and kinematic changes following two UE rehabilitation treatments, functional task practice (FTP) and power (POWER) training, with the primary aim of understanding whether improved UE function post-stroke results from utilization of compensatory movements or restoration of more normal movement patterns. According to our hypothesis, behavioral motor improvements, as demonstrated by kinematics, reveal restoration of more normal movement function post-POWER. In contrast, behavioral changes post-FTP revealed compensatory movement strategies. While mean reaching velocity increased post-FTP, this apparent improvement involved concurrent reductions in shoulder flexion and elbow extension ROM, and increased trunk displacement – changes indicating reinforcement of compensatory movement strategies\(^5\). Following POWER, participants increased shoulder flexion and elbow extension ROM, reduced associated trunk displacement and also demonstrated greater improvements in the time to maximum shoulder flexion and elbow extension, parameters contributing to normal inter-joint coordination. As revealed by a shift toward normal across numerous kinematic parameters\(^6\), motor patterns more
similar to healthy individuals were revealed following POWER. These behavioral manifestations can be attributed to restoration or true motor recovery. By using a crossover design we were able to address a secondary aim, understanding the effect of treatment order. As hypothesized, our data reveal that POWER followed by FTP produced greater improvements, primarily significantly reduced trunk displacement, indicating a marked reduction of compensatory movements. Notably, this reduced compensation was accompanied by reappearance of normal patterns of shoulder and elbow movement present prior to stroke. Taken together, these results offer novel insight for identifying effective UE rehabilitation interventions that promote restoration of normal motor function. Further experimental studies are necessary to identify the physiological mechanisms that underlie restoration of normal movement.

**Study 2.** We compared the effects of POWER and FTP training in stretch-reflex modulation. POWER produced greater improvements of stretch-reflex modulation than FTP for all parameters (i.e. EMG burst duration, position threshold and burst Intensity). Again, by using a crossover design, we were able to address a secondary aim of understanding the effect of treatment order on stretch-reflex modulation. As hypothesized from findings of our previous study, our data reveal that POWER followed by FTP produced greater improvements, most significantly for EMG burst duration and EMG latency. Changes in the reflex position threshold were present but did not reach statistical significance. It is well recognized that resistance training induces change within the nervous system. However, the argument whether these changes affect both the spinal and the supraspinal circuitries is still open. This study design included passive and preloaded conditions with the attempt to discriminate between supraspinal
The preloaded condition was implemented to stimulate the voluntary supraspinal descending control by means of isometric contraction of elbow flexor muscles before and during passive elbow extension stretches. In contrast to our hypothesis, data suggest that the effects did not differ between the two conditions in any of the stretch reflex parameters. The explanation for the lack of differential effects between passive and preloaded conditions may be that both these conditions are testing the same neurophysiologic function.

Findings of this study may suggest that POWER induces restoration of mechanisms controlling spinal motoneurone discharge. These mechanisms are likely mediated by improved descending (supraspinal) control of motor neuron excitability at the spinal level. Our hypothesis is that improvements at the spinal levels depend on improved regulation of spinal and supraspinal mechanisms. Specifically, we believe it can increases the central neural drive leading to enhanced recruitment of the spinal circuitry and consequent improved control of the force required for execution of complex multi-segmental tasks. Future studies with more sophisticated techniques to study pre-synaptic Ia inhibition, post-activation depression and cortical excitability should be conducted to differentiate the locus of neural adaptations after resistance training.

**Study 3.** This study is based on the notion that asymmetric cortical excitability resulting from stroke may enable maladaptive neuromotor strategies, disrupting physiological activity in transcallosal pathways and producing an imbalance in the mutual inhibitory projections between hemispheres\(^{63,64}\). Following stroke, activity in the affected hemisphere is disrupted; not only by the infarct itself, but also by inhibition from the unaffected hemisphere which further reduces the excitability of the affected
hemisphere. As first described by Ward and Cohen\textsuperscript{63} and more recently stated by Nowak’s\textsuperscript{64} hypothesis of inter-hemispheric competition post-stroke, the primary motor cortex of the unaffected hemisphere becomes disinhibited and exerts exaggerated inhibition onto the primary motor cortex of the affected hemisphere.

Specifically, the aims of this study were to: 1) test the hypothesis of inter-hemispheric competition post-stroke; 2) test whether it was possible to restore a balance of inter-hemispheric competition; and 3) test whether repetitive transcranial magnetic stimulation (\textit{rTMS}) combined with POWER training resulted in better functional, biomechanical and neurophysiological outcomes than \textit{rTMS} combined with FTP.

This study included two participants with lesions in similar locations (e.g., right putamen and contiguous white matter) with consequent similar left hemiparesis affecting both the upper and lower extremities.

The outcomes for Case 1 are consistent with our hypothesis that is formulated on our previous work\textsuperscript{61,54} (i.e., better improvements after POWER training versus FTP, as revealed by increased force production in UE muscles, increased joint excursion at elbow and shoulder and associated reduction of compensatory trunk displacement.) At the neurophysiologic level, POWER produced reduced inter-hemispheric competition as shown by restored balance of inter-hemispheric inhibition (i.e., \textit{iSP} laterality index). Further, it induced positive changes in cortical excitability characterized by emergence of MEPs in the affected hemisphere. In summary, POWER showed positive behavioral and neural effects consistent with our hypothesis of increased central drive from the ipsilesional hemisphere.
Conversely, Case 2 revealed better improvements after FTP in joint excursion at elbow and shoulder, associated with improvements in trunk displacement. Further, she did not reveal any change in force production of UE muscles after either POWER training or FTP. At the neurophysiological level, POWER produced normalization of inter-hemispheric competition as indicated by positive direction of the iSP laterality index. In summary, in Case 2 POWER did not seem to be as effective at the behavioral level as it was for Case 1, however it still induced positive neural changes. We believe that the sensory impairment of Case 2 could have affected the potential benefit from POWER training. It is possible that Case 2 had benefit more from FTP training than POWER training because of the presence of visual feedback during the execution and accomplishment of functional tasks and that the motor output of POWER training was inadequate, as consequence of sensory impairment, and therefore less effective for inducing positive motor behavioral changes. In support of this view, Van der Lee\textsuperscript{37} showed that constrained-induce movement therapy (CIMT), in which the patient is strongly encouraged to use only the affected arm while the unaffected arm is immobilized, was more effective in people with hemineglect.

In general, findings of this case series suggest that it is possible to induce changes in cortical excitability and interhemispheric inhibition (IHI) associated with behavioral change that constitute functional recovery post-stroke. Our findings support our hypothesis that POWER promotes enhanced central neural drive in the ipsilesional hemisphere and may represent a potential driver of cortical reorganization. Our results compel us to investigate these mechanisms with future larger scale research studies,
which may inform how individual characteristics interact with mechanisms of neural recovery.

**Study 4.** This single-subject design evaluated the effect of 2-weeks of HYBRID training\(^{54}\) (POWER + FTP) using clinical tests and three-dimensional motion-analysis during a functional task to measure behavioral motor control; H-reflexes to probe the spinal circuitry; transcranial magnetic stimulation (TMS) to measure physiological functioning of the cortical networks (i.e. excitatory and inhibitory), and interhemispheric inhibition (IHI). Our central hypothesis was that an intervention involving POWER would increase the central neural drive during functional voluntary movement, which would be revealed by improvements in both motor behavioral and neural outcomes at both the spinal and supraspinal levels. Our kinematic data suggest that HYBRID improved motor control during the functional reaching task. At the spinal level, our findings strongly suggest normalization of spinal hyperexcitability and increased presynaptic (e.g., supraspinal) and homosynaptic (spinal) inhibition of the reflex arc in the affected UE motor pools. TMS data at post-HYBRID evaluation indicated: 1) increased recruitment curve slopes in the affected hemisphere and reduced recruitment curve slopes in the unaffected hemisphere; 2) increased ipsilateral silent period from the affected hemisphere to the unaffected hemisphere, and reduced ipsilateral silent period from the unaffected hemisphere to the affected hemisphere – indicating rebalancing of IHI; 3) reduced cortical silent period (cSP) duration and its RC slope in the unaffected hemisphere – indicating improvement of intracortical inhibition mediated by GABA\(_B\) receptors\(^{252}\); 4) increased SICI in the affected hemisphere and decreased SICI in the
unaffected hemisphere – indicating improvement of intracortical inhibition mediated by GABA\textsubscript{A} receptors\textsuperscript{265}.

These positive outcomes of HYBRID training can most likely be attributed to: a) the well-recognized and profound neural adaptations induced by POWER training\textsuperscript{53, 55, 58}, and b) therapeutic intensity, which promotes improvement by challenging the subject’s capacity. Neural adaptations induced by resistance training occur: 1) at the level of the spinal cord, potentially including short-term motor unit synchronization, which is caused by changes in synaptic efficacy within the motoneuron pool\textsuperscript{53}, and 2) at the supraspinal level, including adaptations such as increased activation within the cortical circuits\textsuperscript{58, 154}. Our results suggest that HYBRID training induces improved modulation of the spinal mechanisms controlling homosynaptic (PAD) and presynaptic (D1) pathways of the monosynaptic reflex. Improvements in homosynaptic reflex modulation (PAD) suggest improvement in the efficacy of the Ia fibre-motoneurone synapse\textsuperscript{184}. Improvements in the presynaptic (D1) mechanisms suggest improvement of descending inhibitory control from higher cortical structures post-stroke\textsuperscript{184}. TMS data confirm positive treatment effects on inhibitory and excitatory supraspinal pathways.

The affected hemisphere improved its cortical excitability and its interhemispheric influence (i.e., inhibition) on the unaffected hemisphere. These findings together suggest an improved interaction between the two hemispheres. In addition, our results suggest improved modulation of the inhibitory pathways within the motor cortex mediated by GABA\textsubscript{B} (cSP) and GABA\textsubscript{A} (SICI) receptors. In accordance with previous studies, our study showed motor recovery associated with reduction of cSP duration, which is usually prolonged in the ipsilesional hemisphere post-stroke, and increased
SICI, which is usually reduced in the ipsilesional hemisphere post-stroke. As we hypothesized, the HYBRID treatment may have indirectly improved the impaired modulation of the cortical inhibitory pathways by intensely eliciting more participation of the nervous system and engaging of voluntary cortical drive.

**The power of POWER training: intensity of training.**

Studies regarding the efficacy of intervention post-stroke suggest that high intensity treatments result in better outcomes\(^\text{222, 275}\). However, definitions of treatment intensity usually focus on the duration of therapy or the number of repetitions\(^\text{222, 275}\). Therefore, based on this definition, time seems to be an important variable in post-stroke rehabilitation. However, as suggested by Wallace et al\(^\text{275}\) equal time of therapy may not reflect equal intensity of treatment, particularly if there are differences in the content of therapy and severity of the stroke. Systematic reviews of strength training after stroke have provided evidence for efficacy in reducing impairments and a generalization of these effects to increased functional activities. To obtain improvements in strength post-stroke, Patten et al recommended working at a minimum intensity of 60% of one repetition maximum\(^\text{14, 16, 44, 276}\) using three sets of 8-10 exercises with load adjusted to maintained the minimum desired training target (60-80% of one repetition maximum). Kidgell and Pearce\(^\text{154}\) demonstrated changes in cortical excitability and inhibitory cortical networks in non-disabled subjects after strength training based on heavy resistive load, manipulation of repetition and velocity. It appears that training intensity and the manner in which the repetitions are performed are important for increasing neural transmission via the corticospinal pathway\(^\text{154-156}\). Lee et al\(^\text{277}\), Carroll et al\(^\text{155}\) and Jensen et al\(^\text{157}\) reported either a decrease or no change in corticospinal
excitability after strength training. However, these studies did not provide information regarding parameters of strength training program such as training load, repetition, speeds and progression. The consistent findings between studies using high-intensity standardized strengthening protocol suggest that to maximize strengthening training via change in neural control, protocols need to focus on load, repetition and velocity. Based on these notions, we believe that positive outcomes of POWER training can most likely be attributed to the therapeutic intensity, which promotes improvements by challenging the subject’s capacity and by engaging increased participation of the nervous system. POWER improves the efficiency in descending neural pathways because of adjustments in the activation of agonists and synergists and decreases in coactivation of antagonists. These adaptations after strength training occur at: a) the supraspinal level, involving changes in corticospinal excitability and inhibition and b) the spinal level, involving changes in spinal motoneuron excitability and activity in inhibitory and excitatory interneurons\textsuperscript{154}.

**Significance.** Impairments of UE function are among the most persistent and disabling effects of stroke. While the problem is well recognized, identification of effective therapeutic interventions that restore functional UE use remains elusive. While mainstream therapeutic interventions, such as constraint-induced movement therapy (CIMT) and functional task-practice (FTP), show promise at promoting improved UE function post-stroke, the metrics of improvement are gauged by clinical scales or gross behavioral measures which emphasize task accomplishment more than motor control or neuroplastic changes\textsuperscript{36}. Importantly, assessment at the level of task completion or failure does not distinguish restoration from compensation at either the behavioral or the
neural levels. This dissertation contributes to the contemporary evidence that resistance training as an intervention post-stroke can induce restoration of more normal activation in neural circuits and movement patterns.

**Conclusions and future research.** Results of this dissertation support the idea that an intervention involving POWER facilitates restoration of impairments but also activates the process of true recovery at the behavioral and neural levels post-stroke. However, future larger scale research studies need to be conducting to better identify the neurophysiological mechanisms that underlie restoration of normal movement. The relationship between spinal and supraspinal facilitatory and inhibitory systems may be clarified by studying their interactions. The knowledge of how different cortical inhibitory and facilitatory circuits are related to each other would improve our understanding of the functional reorganization of the motor cortex and would allow better interpretation of abnormalities post-stroke and changes following therapy.

Further, our studies suggest that besides impairment of the ipsilesional hemisphere, the contralesional hemisphere may also be impaired after stroke. Specifically, the contralesional hemisphere may become disinhibited which could contribute to interhemispheric competition\(^{64}\). Our studies suggest that POWER training may induce positive neural changes affecting the excitability of both hemispheres, which may facilitate a more balanced interhemispheric relationship. Based on these notions, future research should reference responses from non-disabled healthy controls as comparison rather than from the contralesional hemisphere.

Moreover, our findings suggest that individual characteristics (such as sensory impairments, depression or physical condition pre-stroke) could interact with
mechanism of recovery. Future studies should inform how individual characteristics (such as sensory impairment, depression, motivation etc.) interact with mechanisms of recovery, which would help the identification of those individuals who could benefit most from high-intensive practice.

Lastly, more investigations need to be conducted to fully understand the effects of treatment intensity. It would be interesting to compare our 2-weeks of HYBRID training with one of the currently most applied therapeutic approaches for upper-extremity hemiparesis, such as induced movement therapy (CIMT). CIMT is a very onerous treatment in terms of both the patient’s time and health-care costs. During CIMT, the patient is strongly encouraged to use only the affected arm while the unaffected arm is immobilized. Classically, CIMT is administered for 6 hours/day over 2 weeks, resulting in a total of 60 hours of treatment. In contrast, the HYBRID intervention we proposed in this dissertation consists of 3 hours per day of therapy over two weeks resulting in a total of 30 hours of treatment. This comparison will give more insights regarding the relationship of duration and intensity of treatment.
APPENDIX A
REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OF MOTOR CORTEX AFTER STROKE: A FOCUSED REVIEW

The following hyperlink gives access to the published candidate’s review about the current safety and efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) on the primary motor cortices (M1) of the affected hemisphere in adults post-stroke (Click on OvidSP & Athens to access the article).

http://pt.wkhealth.com/pt/re/lwwgateway/landingpage.htm;jsessionid=P5GThTB3x7bhnWtWJTvzs3j6kcHvbtQLTQp3PTw1hm9GTG6gz1Gb!-459155671!181195629!8091!-1?issn=0894-9115&volume=91&issue=3&spage=254


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BIOGRAPHICAL SKETCH

After earning her bachelor’s degree in physical therapy from the University of Insubria (Varese, Italy), Manuela Corti worked at San Raffaele Hospital in Milan as a physical therapist, researcher in the Movement Analysis Laboratory and teacher in the physical therapy program at the University Vita-Salute San Raffaele. In the hospital, she worked with dozens of people with motor disabilities. Their heartbreaking stories and unflinching courage inspired her to dedicate her life to helping people with motor dysfunction. She eagerly learned about motor impairments in people with neurological disorders and developed expertise with motion analysis. While at San Raffaele, she contributed to four peer reviewed and three non-peer reviewed articles, which appear in the premiere rehabilitation medicine journal in Italy. After five years at San Raffaele, helping one patient at a time, she resolved to further her education in order to develop skills to conduct scientific research and position herself to make discoveries with broad impact for people with neuromotor dysfunction.

To achieve her goals, Manuela Corti moved from her home in Italy to enroll in the University of Florida (UF) Rehabilitation Sciences Doctoral Program, under the mentorship of Dr. Carolynn Patten. She dedicated her doctoral studies to understanding neuromotor recovery by combining physiological and behavioral techniques including: transcranial magnetic stimulation (TMS), stretch and H-reflexes, motion analysis and clinical measures.

She received her Ph.D from the University of Florida in the spring 2012. Her curriculum includes courses in neurobiology, neurophysiology and magnetic resonance imaging and spectroscopy in living systems.
Ultimately, she will pursue an academic position in clinical-translational science, directing and conducting neurological related research. The overall objective of her research lies in investigating the neuromechanics and neurobiology of neurologic disorders. The long-term goal of her research is to improve therapy and recovery for persons with neurological diseases.