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Role of corticospinal influences in post-stroke spasticity

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Résumé

Chez les personnes post-AVC (Accident Vasculaire Cérébral), spasticité, faiblesse et toute autre coactivation anormale proviennent de limitations dans la régulation de la gamme des seuils des réflexes d'étirement. Nous avons voulu savoir si les déficits dans les influences corticospinales résiduelles contribuaient à la limitation de la gamme des seuils et au développement de la spasticité chez les patients post-AVC.

La stimulation magnétique transcranienne (SMT) a été appliquée à un site du cortex moteur où se trouvent les motoneurones agissant sur les fléchisseurs et extenseurs du coude. Des potentiels évoqués moteurs (PEM) ont été enregistrés en position de flexion et d'extension du coude. Afin d'exclure l'influence provenant de l'excitabilité motoneuronale sur l'évaluation des influences corticospinales, les PEM ont été suscités lors de la période silencieuse des signaux électromyographiques (EMG) correspondant à un bref raccourcissement musculaire juste avant l'enclenchement de la SMT.

Chez les sujets contrôles, il y avait un patron réciproque d'influences corticospinales (PEM supérieurs en position d'extension dans les extenseurs et vice-versa pour les fléchisseurs). Quant à la plupart des sujets post-AVC ayant un niveau clinique élevé de spasticité, la facilitation corticospinale dans les motoneurones des fléchisseurs et extenseurs était supérieure en position de flexion (patron de co-facilitation). Les résultats démontrent que la spasticité est associée à des changements substantiels des influences corticospinales sur les motoneurones des fléchisseurs et des extenseurs du coude.

Mots-clés : influences corticospinales, spasticité, AVC, SMT

Abstract

In post-stroke patients, spasticity, weakness and abnormal coactivation result from limitations in the range of regulation of stretch reflex thresholds. We investigated whether the deficits in residual corticospinal influences contribute to the limitation in the regulation of those thresholds and as a result to spasticity in post-stroke subjects.

A single-pulse transcranial magnetic stimulation (TMS) was applied to the site of the motor cortex projecting to motoneurons of elbow flexors and extensors. Responses to TMS (motor evoked potentials or MEPs) were recorded at a flexion and an extension position of the elbow joint. To exclude the influence of background motoneuronal excitability on the evaluation of corticospinal influences, MEPs were elicited during the electromyographic (EMG) silent period produced by brief muscle shortening prior to TMS.

In control subjects, corticospinal facilitation of flexor motoneurons was usually larger whereas that of extensor motoneurons was smaller during actively maintained flexion than when the extension position was maintained (reciprocal pattern of position-related changes in flexor and extensor MEPs). In most post-stroke subjects with high clinical spasticity scores, corticospinal facilitation of both flexor and extensor motoneurons was greater at the actively established flexion position (co-facilitation pattern). Results show that spasticity is associated with substantial changes in the corticospinal influences on flexor and extensor motoneurons. Corticospinal co-facilitation of the two groups of motoneurons may be related to the necessity to overcome resistance of spastic muscles during active changes in the elbow joint angle.

Keywords: corticospinal influences, spasticity, stroke, TMS

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List of abbreviations

AP	Antero-posterior
CNS	Central nervous system
CVA	Cerebrovascular accident
IC	Invariant characteristic
EMF	Electromotive force
EP	Equilibrium Point (hypothesis)
M1	Motor cortex
MAS	Modified Ashworth Scale
MEP	Motor evoked potential
MoCA	Montreal Cognitive Assessment
MT	Motor threshold
PA	Postero-anterior
PIC	Persistent inward currents
R	Range of reciprocal muscle activation
rTMS	Repetitive transcranial magnetic stimulation
SII	Secondary somatosensory cortex
tDCS	Transcranial direct current stimulation
TES	Transcranial electric stimulation
TMS	Transcranial magnetic stimulation
SR	Stretch reflex
TSRT (λ)	Tonic stretch reflex threshold
UMN	Upper motor neuron

BB	Biceps brachii
BR	Brachioradialis
TL	Triceps lateralis
TM	Triceps medialis

To my mother,

and to the giants of Ancient Greece,
on whose shoulders science stands today.

Acknowledgements

Throughout my time spent as a Master's student at the IRGLM, I have had the opportunity to cross paths with many individuals who have collaborated with me on common projects and enriched my academic experience. I now take the time to pay tribute to those I am indebted to.

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1. INTRODUCTION

Stroke, or cerebrovascular accident (CVA), is a major public health concern since over 300.000 Canadians are affected by it and are living with its devastating consequences. This is notably the case for frequent impairment of upper limb movements which leads to a loss of functional independence. This is why a major issue in stroke rehabilitation is in determining which strategies are most effective in optimizing recovery of arm function.

Spasticity, characterized by abnormal muscle activity, is a common occurrence in individuals with neurologic disorders such as spinal cord injury, multiple sclerosis, traumatic brain injury, stroke, and in children with cerebral palsy. Following a lesion to the motor cortex after CVA, spasticity can set in and cause motor impairments. Its onset is unpredictable but usually occurs within the first year post-stroke. At the outset it can translate, to varying degrees, to an inability to control limb movements. This can considerably interfere with a person's ability to conduct normal day-to-day activities, especially if it is accompanied with considerable pain.

Spasticity can manifest itself as an over-activation of a particular set of muscles. It is a common sign of the upper motor neuron (UMN) syndrome. UMNs refer to neurons that originate in the motor cortex and end in the spinal cord, where they synapse with lower motor neurons (LMN) that innervate muscles. Damage to UMN disrupts normal functioning of spinal reflex arcs controlling muscle tone resulting in tight, stiff muscles often producing jerky movements.

The incidence of spasticity following first stroke is approximately 20% and it causes a four-fold increase in direct costs in care as compared to stroke survivors without it. In addition, work productivity in patients with spasticity is reduced up to 89%. Mitigating these extra costs and the physical and emotional well-being of patients constitute strong reasons for refining our understanding of the origins of spasticity, in the hope of improving current available treatments.

The aim of our present study is to attempt to explain how the motor cortex influences arm movements in individuals who have developed spasticity in the arm after a stroke. The

time of spasticity onset is of no particular importance as long as it corresponds to the typical delays varying from weeks to a full year post-stroke. We seek to outline whether there are any differences in the cortex modulation of movement in healthy and post-stroke individuals and to discover any underlying mechanisms that offer an explanation to such differences.

To provide a context to our study's objectives, we shall first present a neurophysiological basis of movement in healthy individuals before discussing spasticity in more detail. Current motor control theories as well as the method of transcranial magnetic stimulation (TMS) of the motor cortex will be reviewed. The literature review will be followed by a chapter on the methods used to prepare the experiments designed to study corticospinal influences on the movement of the arm. The next chapter outlines the results obtained from the experiments, by measuring muscle activity in voluntary and passive movements. The last chapter provides a discussion to summarize the results found and to confirm our main hypothesis. Finally, a conclusion outlines our findings along with its implications in the clinical realm.

2. LITERATURE REVIEW

2.1 Neurophysiological basis of movement

Muscles are at the foundation of all movements. Commands issued from the motor cortex or spinal cord are transmitted to α-motoneurons, which relay electrical impulses to muscles that respond by a contraction the intensity of which depends on the frequency of the impulses and the number of activated α-motoneurons.

2.1.1 Stretch reflex

The muscle spindle is the centerpiece of proper functioning of the stretch reflex (SR). The spindle is a sensory receptor embedded in each muscle, composed of 8-10 intrafusal fibres structured in parallel with muscle contractile (extrafusal) fibres. When muscle fibres are stretched, the spindle stretches along with them and excites afferent nerves mediating rapid reflex adjustments of muscle activity (Figure 2.1). Its ability to track changes in muscle length allow group Ia sensory afferents to increase their activity, directly affecting motoneuronal and hence muscular activity. The spindle is innervated by *gamma motor neurons*, small diameter myelinated motor endings that connect onto the polar ends of intrafusal fibers. The activation of gamma motor neurons leads to an increase in firing rate of the sensory endings, translating into a greater likelihood that the stretch of a muscle causes sensory afferents to fire. The stretch reflex therefore acts to resist muscle lengthening by contracting the agonist muscle and simultaneously inhibiting the antagonist muscles via Ia inhibitory interneurons. It has been empirically confirmed that the reflex pathway is monosynaptic since the latency between the afferent volley and excitatory post-synaptic potential in the motor neuron is practically equal to the duration of signal transmission across a single synapse (Kandel, 2000).

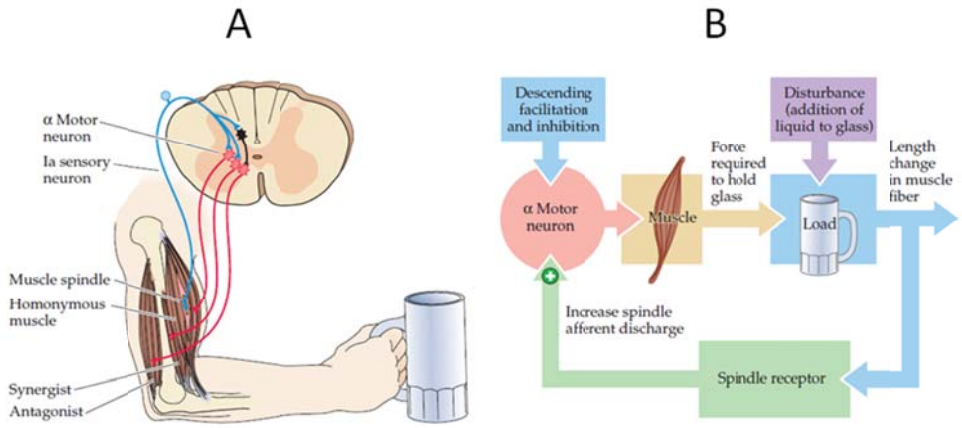

FIG. 2.1 Stretch reflex mechanism. (A) The lines in blue represent the Ia sensory neurons which fire when the muscle spindle is stretched. The lines in red are the α-motoneurons that innervate the muscle, which contracts if Ia firing depolarizes the motoneurons' membrane potentials. (B) Negative feedback loop model of the stretch reflex. Taken from Purves et al., 2004, p.380.

In engineering terms, the stretch arc reflex acts as a negative feedback loop. When a spindle stretches, Ia afferents increase their firing rate, the excitatory connections to α-motoneurons that innervate homonymous and synergist muscles are provoked into a muscle contraction (Kandel, 2000). The spindle is innervated by γ motor neurons, the role of which consists in adjusting the sensitivity of the muscle spindle to muscle length changes. During an active contraction, the γ motoneurons allow the spindle to be under tension and keep the feedback loop active. Without some degree of tension, the spindle would not be able to signal further changes in length (Hunt, 1951). It was previously thought that hyperactivity of γ motoneurons was linked to spasticity. While this hyperactivity may be present in some cases of spasticity, it is also worthy to look at the potential contribution from the higher centers.

2.1.2 Cortical projections

The cell bodies of UMNs (Upper Motor Neurons) are present in the cortex and in several brainstem centers such as the superior colliculus and the reticular formation. Those found in the motor cortex in particular, are known to influence the generation of movement by directly affecting the activity of local circuits in the brainstem and spinal cord. A desired motor action may take one of several routes to accomplish the task of creating limb movement. One pathway consists of a direct cortical projection: motor planning originates in the motor cortex, conducts impulses down the corticospinal tract to the spinal cord, where

UMNs connect via local circuits to the LMNs (Lower Motor Neurons or α-motoneurons) that ferry the signal towards the targeted muscles responsible for generating the desired movement. Another pathway, an indirect cortical projection, employs the corticoreticulospinal tract, a combination of corticospinal and reticulospinal tracts starting at the reticular formation and ending at the spinal cord (Figure 2.2).

Following an UMN injury, a brief period of very low muscle tone in the affected muscles ensues. Spinal shock, named in reference to this period, sets in and is marked by a decreased activity in spinal circuits which are suddenly deprived of input from the higher centers. Several days later, the spinal cord circuits regain their function, but along with the recovery appear novel motor signs and symptoms (Table 2.1).

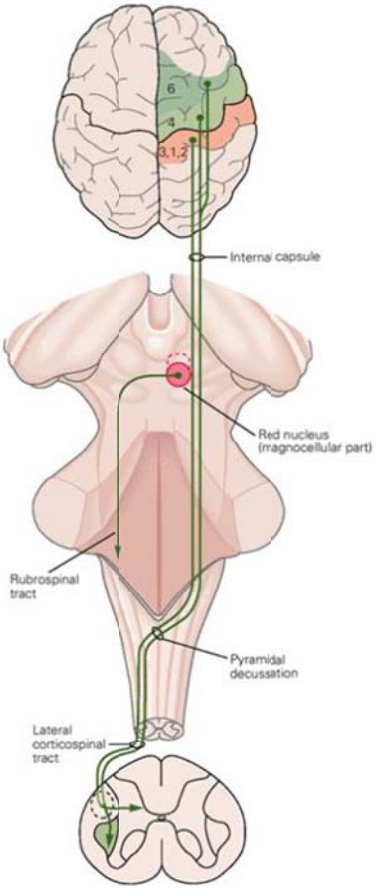

FIG. 2.2 Motor pathways. Most voluntary movements originate in the primary motor cortex (area 4, in light green) as well as the sensory areas 1, 2 & 3 (in orange). The corticospinal tract is represented by the green lines descending into the spinal cord. Taken from: Kandel et al., 2001, p.671.

TABLE 2.1 Signs and symptoms of upper and lower motor neuron lesions. Note the several symptoms that can characterize spasticity. Taken from Purves et al., 2004, p.413.

Upper Motor Neuron Syndrome	*Lower Motor Neuron Syndrome*
Weakness	Weakness or paralysis
Spasticity	Decreased superficial reflexes
Increased tone	Hypoactive deep reflexes
Hyperactive deep reflexes	Decreased tone
Clonus	Fasciculations and fibrillations
Babinski's sign	Severe muscle atrophy
Loss of fine voluntary movements	

Abnormal corticospinal transmission could be suspected in cases of UMN damage. A study found that reciprocal inhibition is diminished or absent in patients with spasticity (Crone, 2004). To sum up, cortical projections translate a desired movement into a series of impulses travelling to the spinal cord. We now turn our attention to how such impulses influence alpha motor neurons.

2.1.3. Neuronal activation

Neurons are essentially threshold elements with non-linear characteristics (Latash, 2012). Changes in the input are not necessarily translated into output changes. The generation of action potentials as a result of cell membrane depolarization obeys the *all-or-none* law: they either occur or they do not at all. An action potential only appears when the input reaches a certain minimum in stimulus; if below this threshold, nothing is generated. Above threshold, an action potential emerges and its amplitude remains the same irrespective of input stimulus. However, if the input remains above threshold, both the frequency of spikes and motoneuronal recruitment increase with increasing input.

Subthreshold depolarization is the change in the value of the current membrane potential with respect to the membrane's threshold potential. In a simplified model (Figure 2.3), an afferent input from the muscle and a central input from the motor cortex may constitute all sources of inputs. The contribution of the central input alone may be sufficient to generate an action potential. In other instances, it may need the contribution of the afferent input to provoke membrane depolarization (Latash, 2012). Other studies managed to quantify the difference between the increased excitability of the corticospinal tract and the already present activity of motoneurons resulting from its proprioceptive influences (Todd, 2003).

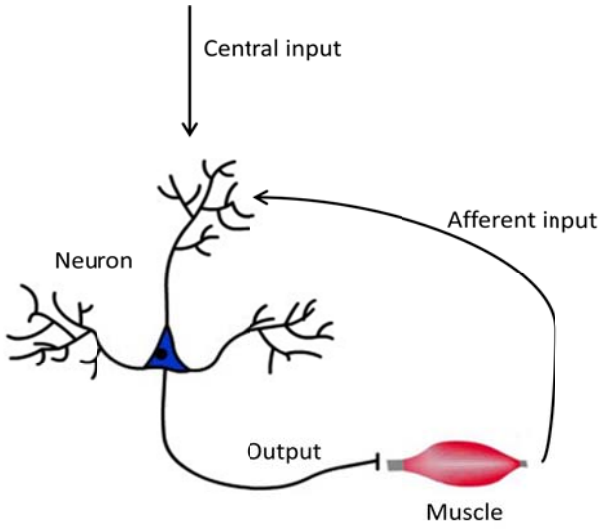

FIG. 2.3 Simplified motor circuit comprising of a motoneuron and a muscle. The diagram depicts the contributions of the central and afferent inputs (indicated by the arrows) of the neuron's activation.

2.1.4 Persistent inward currents

Persistent inward currents (PICs) are sustained positive currents primarily generated in motoneuron dendrites that can depolarize a cell's membrane. They are produced by voltage-sensitive channels that cannot deactivate despite a lack of input; this explains the persistent, looping effect of the phenomenon. Above-threshold voltage in the cell membrane can be maintained until an inhibitory input terminates motoneuronal firing. The tonic state of the resulting muscle activation is not necessarily undesirable; it may actually be of great use, especially in sustaining long-lasting muscle contraction, as for instance during postural tasks (Heckman, 2005).

An important study (McPherson, 2008) provides a link between hyperactive stretch reflexes in paretic post-stroke patients and the development of persistent inward currents. Hyperactive stretch reflexes may result from an increased reliance on monoaminergic-bulbospinal pathways following stroke-induced losses of corticospinal projections. Such pathways would provide more powerful control of motoneurons, either by increasing their excitability or by reducing their subthreshold depolarization level. PICs may be increased by tendon vibration (the tonic vibration reflex) eliciting sustained firing of motoneurons during several seconds after the termination of vibration. The response shows a correlation between the presence of PICs and augmented joint torque and EMG levels of a paretic limb with

respect to a non-paretic limb. PICs may possibly be implicated in spasticity, as the increased tone in the affected limbs seems to go hand in hand with PIC presence.

2.2 Spasticity

2.2.1 Definition

The most widely quoted and accepted definition of spasticity to this day, states that it is a "motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper excitability of the stretch reflexes, as one component of the upper motoneuron syndrome" (Lance, 1980). According to this definition, increased excitability of stretch reflexes is responsible for spasticity. Tonic stretch reflexes constitute a normal mechanism in the nervous system; the phenomenon is well identified in postural reflexes in the leg muscles that allow a person to sustain a balanced position while standing for long periods of time. Spasticity is also velocity-dependent. A slow stretch of the muscle in a relaxed state does not evoke a reflex in a healthy individual; a very high speed is needed to achieve this end (via a quick tendon tap).

Understanding spasticity is a challenging task, both for clinician and patient, as it is a complex, multi-faceted phenomenon involving different neural structures, varying between individuals (Bhimani, 2012; Grimm, 1983). There exists a large difference in how spasticity management is approached between clinicians and patients. On one hand, clinicians run through a standardized protocol to assess spasticity in a one size-fits-all approach. On the other hand, patients resort to a myriad of strategies to cope with the varied manifestations of their sensory experiences (Mahoney, 2007).

While spasticity can be alleviated through regular physiotherapy and medication (Baclofen being among the interventions), its symptoms never truly disappear. Also, spasticity can vary over time. It may manifest itself more strongly in the morning, when the prolonged inactivity of the body following sleep leads to tighter muscles. Changes in temperature, especially towards colder environments, seem to worsen spasticity. Stress can exacerbate spasticity as well. Such considerations are taken into account by patients in order to minimize the negative consequences of spasticity and optimize their ability to perform

activities of daily living. At the clinical level, treatment should be tailored to the individual's needs, by addressing the symptoms on a case by case basis, rather than through a group approach. The realities of clinical settings, as they stand today, may however be insufficient to meet this challenge, unless a restructuring of clinical practice takes place.

2.2.2 Controversies in the definition of spasticity

Lance's definition of spasticity has two aspects. First, spasticity is associated with an enhanced tonic stretch reflex. Second, spasticity is velocity-dependent and the use of several speeds of muscle stretches is needed to correctly assess the degree of spasticity. Spasticity is likely associated with disorders in the control of voluntary movements (Calota, 2009). Few studies have tackled the connection between spasticity and voluntary movement deficits. Instead, the emphasis had primarily been put in characterizing spasticity in terms of biomechanical variables, which are most likely consequences, not causes of spasticity. Muscle contractures are the oft-cited consequence of spasticity, although it has been claimed that the reverse is also true (O'Dwyer, 1996). These are characterized by a shortening of muscle fiber length, causing a rearrangement of muscle-joint interaction (Gracies, 2001). This can also include changes in the properties of soft tissues such as ligaments and tendons in the joint.

Recently, spasticity was defines as "a disordered sensor-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" (Pandyan, 2005). The apparent lack of a consensual definition confirms the notion that spasticity is not a single phenomenon; there are several possible manifestations of post-stroke spasticity. An interpretation of the definition of spasticity may focus on the alterations in the central processing of sensory inputs as being the likely causes of its generation; much less attention is directed to the structural changes in the muscles such as contractures. Prime focus is aimed at the study of imbalances of inhibitory and excitatory impulses that lead to motor disorders such as spasticity (Ward, 2011). However, it is important to introduce at this point the current methods of measuring spasticity before establishing which one we have adopted in our study.

2.2.3 Spasticity measurement

Tools used to measure the severity of spasticity, such as the Ashworth or Modified Ashworth Scale (MAS) which assesses the level of muscle tone, have their utility in the clinical world but are insufficient in determining the correct diagnosis among clinical signs such as spasticity, dystonia, clonus, spasms, hyperreflexia, and other muscle tone disorders. Spasticity is not simply characterized by the changes in passive muscle properties; these are usually consequences of spasticity which may in turn contribute towards its worsening. Consequently, contractures in the affected joint may greatly impact spasticity but they could not serve as a basis for establishing its neurologic origin. A neuronal contribution brought on by the hyper-excitability of group II pathways, a distinct group of sensory fibers that act as stretch receptors in the muscle spindle, may be at the root of the neurologic origin of spasticity (Pizzi, 2005).

2.2.4 MAS reliability

It can thus be difficult to distinguish between what may seem as an increased hypertonia due to passive muscular changes or active reflex mediated changes. It was demonstrated that a correlation exists between a high MAS score and the time following the onset of stroke (Pizzi, 2005). That is, the longer time elapsed from the date of stroke, the higher the MAS score, confirming the idea that spasticity develops in time, indicating its adaptive process. Additionally, a positive correlation was found between MAS score and the Hmax/Mmax ratio, which measures the proportion of motoneurons activated by eliciting a muscle reflex following electrical stimulation of Ia afferent fibers (H-reflex) compared with those activated directly (M-wave). The finding shows an eased excitability of the H-reflex in patients with spasticity, possibly due to a decreased inhibitory control of lower motoneurons or to an increased excitability of the stretch reflex (Pizzi, 2005). Another major finding concluded that contractures can provoke spasticity generation; a correction in contractures can potentially reduce the occurrence of spasticity.

According to a neurophysiological approach, which measures EMG muscle activity, 87% of a sample of 100 post-stroke patients (average onset time 3 weeks) were found to have spasticity-like symptoms. Surprisingly, the clinical approach using the MAS considered that

only 44% of the sample had spasticity. The large difference in the diagnosis of spasticity between the two approaches causes confusion as to which of the two is most likely correct. On the other hand, among those deemed to be non-spastic by the MAS, 79% showed involuntary muscle activity, a definite marker of spasticity (Malhotra, 2008). However, an increase in activity does not necessarily produce a consistent change in muscle tone.

Overall, the lack of concordance between existing definitions and what is seen in clinical practice is an issue that remains unresolved and demands a convergence of the many interpretations of spasticity into a more universal diagnosis. A review of several studies evaluating the effectiveness of the MAS in the measure of spasticity shows it is insufficiently reliable or valid as a measure (Pandyan, 1999). This is why the direct measure of muscle activity via EMG may remain for now the best approach for discerning spasticity. Nevertheless, the emotional state and awareness of the post-stroke candidate under study is rarely taken into account when assessing spasticity, factors that may well under or overemphasize its presence (Bhimani, 2012).

2.2.5 Biomechanical approaches to spasticity measurement

Lance's definition emphasizes passive motion as a method to produce and observe the enhanced stretch reflexes incurred in people with spasticity. The accrued motor responses are mediated by afferent fibres and uninhibited reflexes (Wood, 2005). In clinical practice however, spasticity is interpreted as the resulting motor behavior, as a collection of motor program disturbances. It becomes challenging to develop appropriate measures of spasticity as its interpretation changes depending on the clinical setting. The common thread to all interpretations is that it consists in the resistance of muscle to stretching. Existing biomechanical methods of spasticity measurement are generally divided as: manual, controlled displacement, tendon tap and voluntary methods.

The manual method is based on the passive rotation (performed by a clinician) of a limb around its joint in order to elicit tonic stretch reflexes. Although the method is effective in providing a muscular response, it is not very robust; neither speed nor amplitude of motion can be standardized.

The controlled displacement method solves this shortcoming, through the use of a servo-controlled motor to drive joint movement. Repeatable movement is guaranteed and

combines with EMG recording to determine the onset of hyperactivity. The one disadvantage lies in the complexity of the setup, which may be too impractical and unfeasible to carry out in a clinical environment.

The tendon tap method more readily elicits tendon jerks in people with spasticity, which provides a means to quantify the magnitude of the phenomenon (Vattanasilp, 1999). Since duration of the stretch is very short, it only elicits phasic reflexes. The advantage of the method avoids the confusion over neural and/or mechanical contributions to spasticity. The drawback is that it cannot account for abnormal muscle activation in voluntary movement. It remains useful nonetheless as a diagnostic tool.

The voluntary method attempts to elicit thresholds while the limb is actively moved by the patient, reflecting behavior in functional tasks. The approach is often used in a controlled displacement setting which also tracks the EMG responses.

2.2.6. Problems with biomechanical measures

Many factors require corrections in the interpretations of spasticity that currently exist. The use of confusing terminology can lead to a misunderstanding of what does or does not constitute spasticity. A distinction between neural and non-neural components should also be clearly outlined. Consistent protocols should be established for clinical measurement and procuring aged-matched controls is a must to ensure the credibility of the findings. To sum up, biomechanical approaches alone are insufficient in accurately assessing spasticity; these ought to be complemented with EMG recordings to determine the onset of increased muscular activity to passive stretch (Wood, 2005).

Several studies (Powers, 1988; Jobin, 2000) basing their analyses on several angular speed landmarks enabled clinicians to determine the stretch reflex threshold when the spastic limb is at rest, through the computation of a linear regression of the sampled stretch reflex thresholds at the different velocities used. Although this technique for evaluating spasticity has been proven effective in the clinical realm, a neurologic measure would provide insights into how and why spasticity occurs. A neurologic measure should also be supported by a conceptual model that attempts to explain how movements are mediated by the corticospinal tract. The following motor theories attempt to provide a basis for the origin of body movements and its associated deficits.

2.3 Motor Control Theories

2.3.1 Basic theories

Central among some of the leading motor control theories are the notions of state and control variables. These represent specific tasks sent out by the CNS, interpreted by a controller which resends the command to an object. This descending pattern can be generally divided in two groups: feed-forward and feedback control mechanisms. Both types are integral mechanisms used by the CNS to control movement.

A feed-forward system takes the form as shown in the left of Figure 2.4 while a feedback loop, on the other hand, is depicted on the right. A feed-forward system is more expedient than one with feedback. No loops are present in such a system, less routing is needed to conduct the impulses destined to the controlled object. Both models assume task formulation to originate in the motor planning centers of the brain, which specifies a desired state of the controlled object, $X_{DES}(t)$. A command is then generated by the controller, C(t), whose role is to attempt to match the resulting outcome X(t) to the desired value.

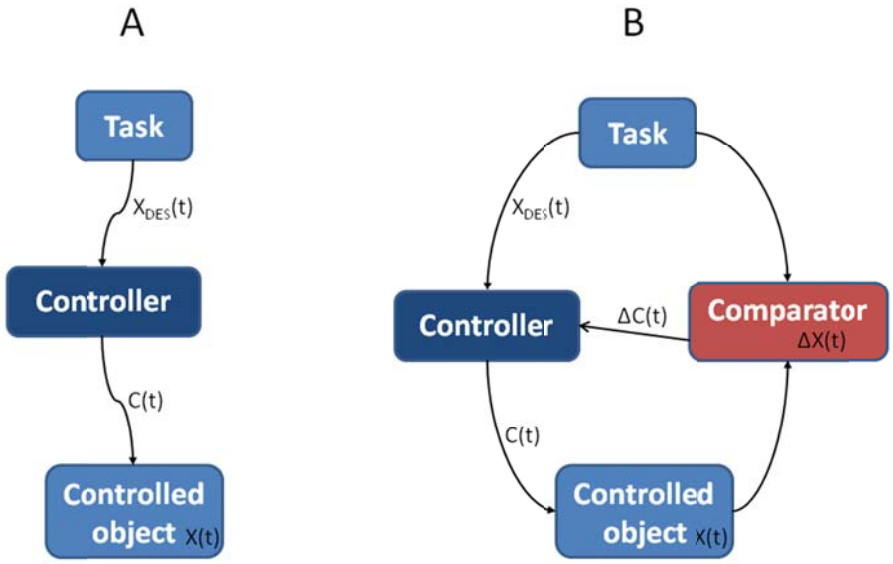

FIG. 2.4 A simplified motor system consisting of a controller and a controlled object. (A) Feed-forward control. The controller sends a command C(t) to change the state of the object to match the desired state $X_{DES}(t)$. (B) Feedback control. The comparator continuously corrects X(t) via changes in the command ΔC(t). Based on Latash, 2012, p.115.

The feedback mechanism adds an extra element which compares final outcome to desired state. The difference results in a modification of the controller's command by introducing a correction $\Delta C(t)$. The feedback loop will iterate until $X(t) \approx X_{DES}(t)$. If the speed of a task is vital, a feed-forward control model is preferred (e.g. catching a ball thrown at high velocity). If accuracy is prized over timeliness, feedback control provides the best result (e.g. pianist's rearrangement of fine finger movements).

2.3.2 Servo hypothesis

Introduced by Merton in the1950's, the servo-hypothesis model combines feed-forward and feedback control loops. Theoretically, only the smallest of errors would emerge and instantly be corrected in such system. Merton believed that voluntary muscle activation was mediated by descending commands to γ-motoneurons that changed the sensitivity of muscle spindles to muscle length. The hypothesis, however, suffers from a major shortcoming. Conduction velocities of γ-motoneurons are quite slow, meaning that a stretch reflex may take in the hundreds of milliseconds to complete in the servo model, contrary to what was measured in experimentation. It was later confirmed that α and γ motoneuronal activity happened simultaneously in a phenomenon called α-γ coactivation. The model was swiftly disqualified as a viable model for motor control (Latash, 2012).

2.3.3 Internal Models

Internal models are theoretical constructs, adopted extensively throughout the scientific community as viable mechanisms that help explain the production of motor actions, especially in what concerns planned voluntary movements. In essence, they are viewed as neural mechanisms that can mimic the input and output characteristics of the motor apparatus (Kawato, 1999). This concept originated from the fields of control theory and robotics, which eventually led to two ideas that have become prominent in the computational modeling of motor control: forward internal models and inverse dynamics.

2.3.3.1 Forward models

Although feedback models would provide good accuracy in motor output, the long delays incurred in the biological feedback loop would make any movement impractically

slow. Forward internal models can be compared to fast-time simulators able to anticipate sensory consequences of control actions and make the necessary adjustments to achieve the desired trajectory. Feed-forward models generate variables in a predictive manner. Errors between predicted and desired trajectories can be used to update the model to reduce the error gap. This is the mechanism believed to enable motor learning (Jordan, 1992). Acquiring internal models through learning may seem tedious but it is proposed that a forward model in conjunction with inverse dynamics and feedback control may allow an adaptation by generating motor commands based on desired states of motor output (Wolpert, 2000).

2.3.3.2 Inverse models

Internal models assume that the brain is equipped with an inverse dynamics model which computes values of torque based on kinematics to control a desired object (e.g. the hand). A feed-forward approach takes over following motor learning. In an inverse dynamics model, the system uses an internal representation of dynamical equations of motion which can interpret the body's interaction with the environment. A desired movement is first planned in terms of spatial coordinates. In order to carry out this planned motion, the kinematic coordinates are transformed, via the dynamical equations of motion, into the necessary joint torques to perform movement (Hollerbach, 1982).

It is thought that the brain does not memorize the association between movement instances and motor commands. The brain relies instead on an internal memory of the motor apparatus and of the environment, taking the form of an inverse dynamics model extrapolating motor command values via a functional map from the state-space input point (Kawato, 1999). Internal models are thought to be located in all areas of the brain having synaptic plasticity, but there seems to be a consensus that they are stored in the cerebellum (Doya, 1999). It is claimed that certain patterns in cerebellar Purkinje cell activity, with spike-firing patterns seen in reflex eye movement, could be reconstructed from the equations of motion pertaining to the eye (Kawano, 1996). This led to the conclusion that the cerebellum is a possible site of forward models of the limbs and other brain regions (Kawato, 1999). Although the firing frequency of Purkinje cells can be related to eye position and speed of motion, there is no solid evidence that this activity can be expressed as a function of kinematics.

2.3.3.3 Force control hypothesis

Force control hypothesis is a combination of forward and inverse internal models, with the added notion of a central specification of forces. It espouses the view that the CNS sets force levels, calculated via inverse dynamics, following which predictive control mechanisms create voluntary movements (mainly through forward internal models). This concept, along with its suggestion that forces are naturally encoded as EMG signals, was formulated some thirty years ago (Hollerbach, 1982).

However, many studies have experimentally observed that variables other than EMG signal levels are responsible for the specification of limb position. When arm movement was moved to a new position, the EMG responses of the arms muscles showed a slight increase in activity during motion but quickly resettled back to their initial level once the arm rested into its final position (Suzuki, 2001), as seen in Figure 2.5. This indicates that variables other than EMG signals are responsible for the specification of arm position.

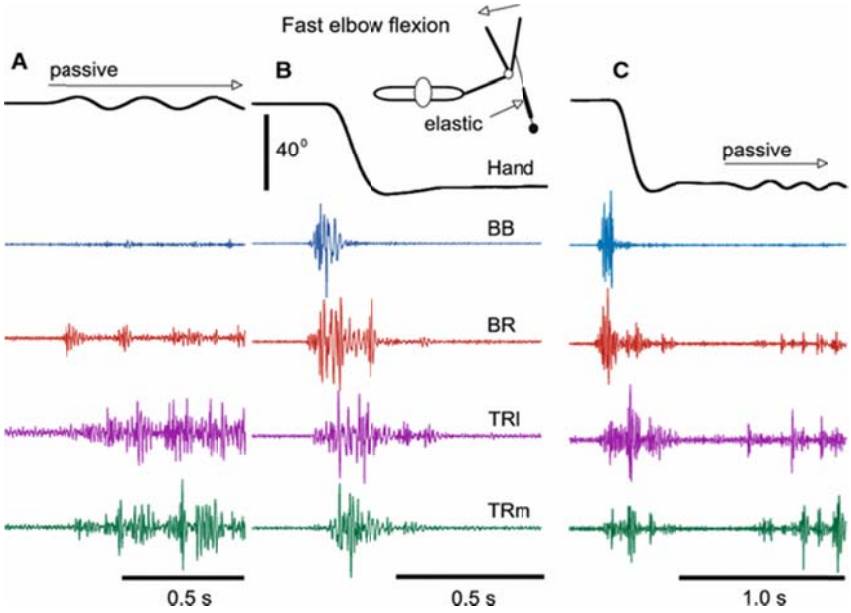

FIG. 2.5 Experimental observation showing elbow joint muscle activity returning to pre-movement levels. (A) Responses during slight passive oscillations maintained at initial position (extension). (B) Responses following fast elbow flexion. (C) Responses during passive oscillations maintained at final position (flexion). Taken from: *Exp Brain Res* (vol. 194, p. 42), AG Feldman, 2009.

2.3.3.4 The posture-movement paradox

Exposed by Von Holst and Mittelstaedt in 1950, it uncovered a problem concerning two elements seemingly at odds with one another: postural maintenance and the production of intentional movements. Powerful neuromuscular mechanisms, known as posture reflexes or posture-stabilizing structures, generate the necessary forces to resist or counter perturbations that create an imbalance in the body. Any perturbation deflecting the body's initial position is swiftly brought back through those mechanisms, ensuring the system's equilibrium. Within such a framework, how may volitional movements ever be achieved by displacing the body without triggering this resistance? The dilemma captures the posture-movement paradox.

It was initially thought that the problem could be resolved if the resistive reflexes were suppressed by the CNS at the moment the body segment deviated from its initial position, but this was disproved through experimental observation. The force control model fails to address the paradox, as the generation of forces and motion would provoke resistive postural mechanisms, requiring additional force to counteract the resistance and maintain the new position. In its attempt to integrate muscle mechanical properties into its model, the force control hypothesis cannot rise to meet the challenge posed by the posture-movement paradox without making the human motor system appear inefficient in its production of voluntary movement (Ostry, 2003).

2.4 Equilibrium Point hypothesis

2.4.1 Lambda model

The Equilibrium-Point (EP) hypothesis solves the posture-movement problem by resetting the activation thresholds of motoneurons as the limb is actively moved. By resetting the activation threshold of a muscle at rest, its motoneurons are excited at levels above threshold. This causes the muscle to contract and provoke a movement of the limb to a new position. The limb relaxes into the new position when the length of the muscle corresponds to the new activation threshold. The state of motoneurons is reset to sub-threshold, and minimal muscle activity is restored. The near-zero EMG levels of muscles at rest following voluntary movement in different positions is clearly shown in experimentation (Feldman, 2009).

EP theory rests on the idea that muscle activity can be reset whenever a new position is reached. Viewed from the posture-movement paradox perspective, the resetting of activation thresholds allows the system to view the initial position as a deviation from the future final position. The postural mechanisms that normally oppose deviations from initial posture become the driving force of voluntary motion once the new position is specified (Figure 2.6).

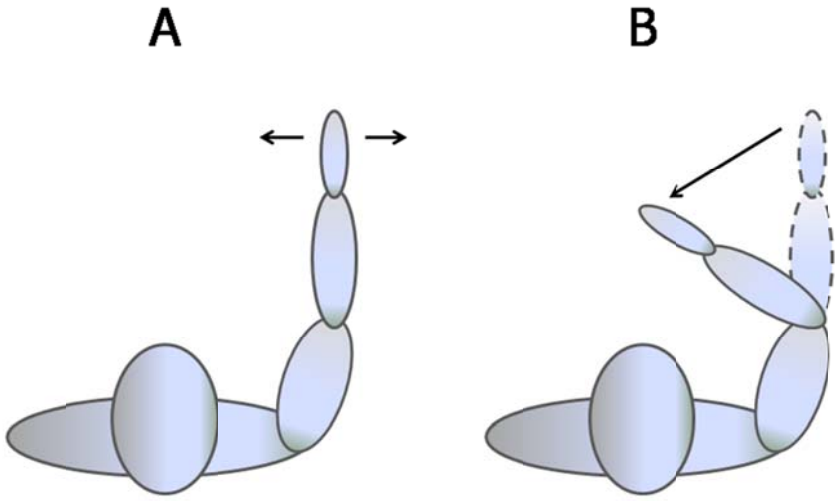

FIG. 2.6 Posture movement paradox. (A) Arm position is stabilized: muscles and reflexes resist changes in position. (B) Intentional change in arm position: muscles and reflexes do not resist intentional changes in position. The nervous system resets the activation threshold of elbow flexor muscles to allow for voluntary movement to a new position.

EP theory, otherwise known as the λ-model, was introduced nearly fifty years ago by Asatryan and Feldman (1965). It provides an elegant rationalization for the changes in stretch reflex thresholds that are modulated by the CNS. The CNS controls certain threshold variables for the activation of neuronal pools. Voluntary and involuntary movements are accounted for, as facilitation or inhibition of muscles is achieved through the CNS's regulation of tonic stretch reflex thresholds (Latash, 2010).

The EP hypothesis states that any given muscle can reach a state of equilibrium as a function of force versus muscle length. An invariant characteristic (IC) curve describes the relationship between muscle force and length, for a given value of the tonic stretch reflex threshold (λ). Upwards or downwards displacements of the equilibrium point along the curve indicate that a muscle is being subjected to loading or unloading mechanisms. A shift of the curve to the left or right indicates a resetting of λ, achieved via changes in membrane potentials in motoneurons (Feldman & Orlovsky, 1972). A shift of the curve to the left

translates into flexor muscle activation, as λ is set by the CNS to shorter flexor length (or angle of the joint) than its actual length (Figure 2.7). Conversely, if λ is set to a longer flexor length, the curve shifts to the right, indicating a relaxation of the muscle. The corticospinal tract's role as the regulator of the range of stretch reflex thresholds is the foundation of EP theory.

No direct computation of mechanical variables is assumed in the EP model. Muscular activity simply emerges as the difference between actual and threshold body configuration. Intentional motor actions are performed through descending electrochemical influences which turn into changes λ.

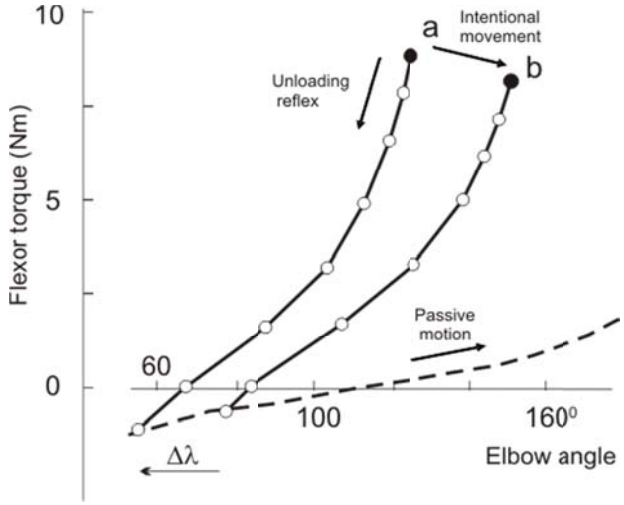

FIG. 2.7 Equilibrium-Point model. Voluntary movement corresponds to a central shift of the IC curve (a → b, black dots). Natural unloading simply resets the new EP to other points along the curve (white circles). Taken from Medicina (vol. 46, p.384), ML Latash et al., 2010.

The R parameter refers to the angular range of regulation (with R- and R+ constituting the extreme limits). This spectrum is larger than the one describing the biomechanical joint range. The R range is essentially conceptual, rather than of physiological nature. By having an R range exceed physiological boundaries of the joint, the CNS is able to set a stretch reflex threshold that can ensure a full relaxation or contraction of a muscle throughout the whole range of the biomechanical joint.

2.4.1.1 Spasticity and EP theory

The EP model not only serves to explain how voluntary movement is initiated in healthy individuals, it can also interpret movement deficits. Studies among the ones endorsing

the EP model confirmed that spasticity is related to problems in stretch reflex thresholds in specific muscles. One study extends previous findings relating to stretch reflex threshold regulation in a single muscle in passive and active movement conditions. It found spasticity is most likely to develop in the physiological flexor muscles (Levin, 2000). The agonist/antagonist muscle pair may undergo significant changes in motor unit properties following a CNS lesion, which can worsen the symptoms of spasticity.

Through experimentation, the onset of spasticity is found whenever EMG activity is considerably above the average baseline level. As expounded earlier, the λ-model asserts that stretch reflects thresholds are contained within the limits of the R range (R- & R+), which are beyond the limits of the physiological range in healthy individuals. In the case of post-stroke patients with spasticity, these limits are located within the physiological range; this is especially the case with ${}_{flex}\lambda^{+}$, the uppermost limit of the stretch reflex threshold in flexors.

A negative correlation describes the relationship between composite spasticity score and the SR thresholds of the flexor muscle; the higher the score (i.e. the stronger the impairment) the lower the value of ${}_{flex}\lambda^{+}$, the upper limit of the flexor stretch reflex threshold (Levin, 2000). An individual with spasticity is capable of moving a limb beyond a threshold, despite spasticity in the agonist muscles. This is possible because the contraction of the antagonist muscle is sufficient enough to overcome the spastic contraction of the agonist muscle. This simultaneous contraction of both agonist and antagonist muscles is called coactivation. Damage to descending pathways is the likely cause of abnormal muscle synergies (Figure 2.8).

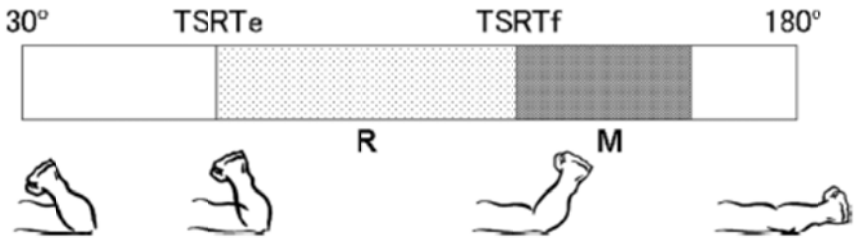

FIG. 2.8 Range of regulation of the elbow joint in patient with spasticity. The biomechanical angle of the joint spans 150°. Range R (light gray area) corresponds to the angular range where reciprocal muscle activation can occur (between flexor and extensor TSRT). Range M (dark grey area) indicates muscle coactivation. The white areas represent either no movement or unidirectional movement zones. Taken from: *Top Stroke Rehabil* (vol. 16, p.185), A Calota & MF Levin, 2009.

Several studies have made headway in the analysis of the CNS's neurophysiological parameters using cortical stimulation techniques. By stimulating areas of the motor cortex, influences stemming from the corticospinal tract can be elicited in the EMG patterns of targeted muscles. One way to stimulate the brain in a non-invasive manner is through transcranial magnetic stimulation (TMS). Although other methods do exist, it is the most efficient and widely used method to stimulate the brain. In this study, we shall look into corticospinal tract damage, as a result of stroke, to assess its influence on spasticity. We used TMS to obtain the signals encoding the corticospinal tract's influences.

2.5 Transcranial Magnetic Stimulation (TMS)

The cortex has the capacity to reorganize itself when inputs are removed. Such would be the case following the amputation of a limb or cutting of afferent nerve fibres. The areas of the cortex originally occupied by the former input would now respond to inputs coming from other parts of the body's surface. This is one example of brain plasticity.

The functional topography of the motor cortex (M1) can be modified following one of many events: a cortical lesion, electrical stimulation, pharmacological manipulations and experience. In the case of lesions following stroke, M1 representations undergo a rapid reorganization within hours upon onset (Sanes, 1990). Since electrical stimulation was found to have a depolarizing effect on the brain's cells depending on the location of stimulation, the scientific community was driven to use some form of electrical stimulation as a means for mapping the motor cortex with a higher degree of precision.

2.5.1 A brief chronology of TMS

The origins of magnetic stimulation date back to more than two centuries ago. Italian physician Luigi Galvani may be credited with the discovery of bioelectricity. He effectively proved that nerves were conductors of electrical signals across the nervous system. Alessandro Volta, a prominent physicist and contemporary of Galvani, repeated Galvani's experiments carried out on animals and provided an alternative explanation to the observed muscle twitches by claiming that the source of electricity was external to the body, not internal

as Galvani had professed. In a bid to prove this alternate view, he built the first known battery, capable of providing a sustained electric current (Sabbatini, 1998).

Those distant beginnings eventually led to the advances in electromagnetism made by Michael Faraday, with his celebrated work on electromagnetic induction. What Faraday accomplished empirically was confirmed mathematically through James Clerk Maxwell's fundamental equations which effectively proved mutual induction and showed that it was driven by a change in magnetic field over time rather than by its strength (Martens, 2012).

In the late 19th century, Fritsch and Ferrier electrically stimulated the animal motor cortex and obtained motor responses on contralateral limb muscles. Bartholow was first to attempt electrical stimulation on an exposed human cortex. In the mid-20th century, Penfield and Jasper stimulated the human brain during surgery, leading to their well-known illustrated schematic motor representation of the body parts, known as the homunculus. In 1980, Merton and Morton brought forward the first clinically applicable method of transcranial electric stimulation (TES), whose mechanism involved a high-voltage discharge that caused muscles to twitch when the stimulation was aimed on the area of the scalp corresponding to the motor cortex. Despite its viability in mapping the motor cortex, it remained too painful for the user to sustain for lengthy periods of time (Terao, 2002).

In an effort to bring a painless form of stimulation, Barker et al. introduced the first TMS device in 1985, and it has since become a technique employed in widespread use across research facilities. This ushered in a new era in the use of non-invasive and virtually painless methods for studying the human motor cortex (Butler, 2007). TES was soon dropped in favour of TMS, although it has resurged in a new form, termed tDCS (transcranial direct current stimulation), using a much lower intensity of current, and thus eliminating pain. A comparison between TMS and tDCS reveals much in common, but it is yet unclear what advantages or disadvantages each incur with respect to a particular clinical application. A more complex analysis and discussion of the use of tDCS is however beyond the scope of this thesis.

2.5.2 The electromagnetics of TMS

The basic mechanism involves a power source capable of generating an electric current through a coil of copper wire. The temporary blast in current intensity flowing through the

coil generates a magnetic field perpendicular to the plane of the coil; the resulting time varying magnetic field travels through the aperture of the circular coil carrying the current. Its vertical descent from coil down to the scalp and through the skull is practically seamless, as the cranium is very permeable to magnetic fields and the permeability of the softer biological tissues is such that it produces no effect on the magnetic field (Malmivuo & Plonsey, 1995). If it were otherwise, local currents would be induced on the scalp and cranium, causing sharp pain in the area. Although the cranium does retain a small amount of the energy induced by the magnetic field, twitch-like sensations are minimal, and virtually painless.

The time-varying nature of the magnetic flux rushing through the loop of the coil evokes an electromotive force (EMF), which in turn induces an eddy current that flows in the tissues of the brain. The electromotive force can be defined by the following equation:

$$EMF = -\frac{dF}{dt}$$

The above equation stems from the Faraday-Henry law, which states that a current is induced in the presence of a change over time in magnetic flux (F). Lenz's law takes this idea one step further by claiming that an induced current will be such that it opposes the change in the magnetic flux that induces it. Thus, the negative sign in the equation accounts for the opposing induced magnetic flux (to the original magnetic flux evoked by the current in the coil). The opposite induced magnetic flux induces an electric field in the brain which lies in a plane parallel to the coil but reversed in its orientation as depicted in Figure 2.9.

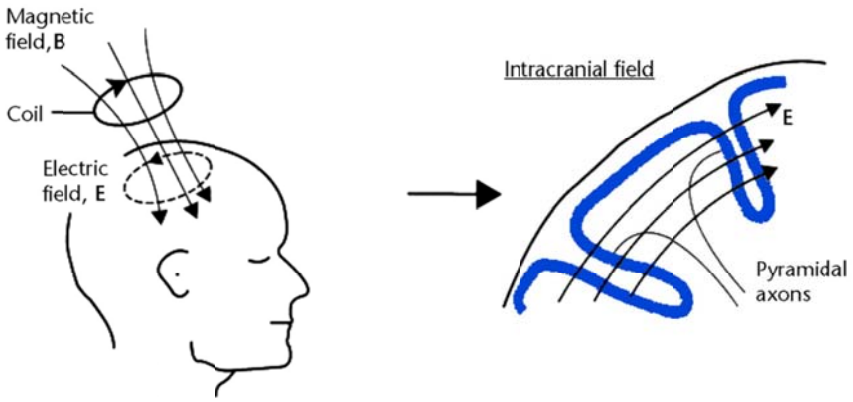

FIG. 2.9 Transcranial magnetic stimulation. The magnetic field crossing the skull and brainy tissue induces an opposite magnetic field which induces an electric field in the cortex that is reversed in opposite orientation to that of the coil. Taken from Physical Therapy (vol. 87, p.725), AJ Butler & SL Wolf, 2007.

In the particular case where EMF is influenced by a current flowing through a coil, the above equation can be rewritten into the following form:

$$EMF = -L\frac{dI}{dt}$$

Here, the relationship narrows into a change in current intensity, although the concept remains identical as the one identified in the previous equation. A higher change in current intensity results in a greater EMF and consequently greater induced current (in the opposite direction). One way to increase its value is by increasing the current's rate of change. The change in current over time describes the rate at which the capacitor storing electric potential is discharged. The introduction of a fast solid-state switch (thyristor) can speed up the capacitor's discharge rate. Another way of manipulating the EMF value is to toggle the inductance L of the stimulating coil. The inductance largely depends on the coil's properties, such as its permeability, its radius and its number of turns (windings).

The system's circuit launches a time-varying current discharge, which induces a magnetic field that flows through the skull and induces a current to flow in the opposite direction within a ring-like frame in the tissues of the brain. This induced current is responsible for stimulating the nerve fibers, depolarizing the cell membranes in what results in the firing and propagation of action potentials along the descending pathways of the nervous system. When the stimulated cells are excited in the motor cortex, resulting motor evoked

potentials (MEP) can be observed in EMG recordings. This serves as a powerful basis for studying the impact of the central nervous system on motor actions.

2.5.3 TMS Components

There are two basic physical components of a TMS system; a winding circular coil of wire attached to a circuit that powers the stimulation. A power source is essential in providing the necessary voltage for the circuit to operate, though it does not participate directly in the current's discharge when the stimulation is enabled. For this purpose, a capacitor with a large capacitance is used to store the electric potential provided by the power source; when the stimulation is launched, the switch (thyristor trigger) closes, creating a circuit powered by the charged capacitor. The latter immediately unleashes a high intensity transient current which reaches the coil with a delay of approximately 150-200 μsec (Rothwell, 2002). A simplified version of TMS circuitry is shown in Figure 2.10.

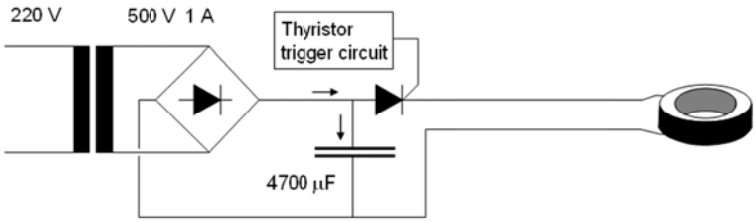

FIG. 2.10 Simplified TMS source circuitry feeding a single coil. It is the fast capacitor discharge that allows a changing magnetic field to be created. Taken from Malmivuo & Plonsey, 1995, p.376.

2.5.4 Current orientation and coil design

The principle of electromagnetic induction creates, as mentioned earlier, a magnetic field that originates at the center point of the coil and whose trajectory is perpendicular to the electric field flowing in the coil. The strength of the magnetic field, however, diminishes rapidly with distance, so that at 2cm below the focal point of the coil, it is considerably smaller than at its point of origin, with some studies citing the decay to be proportional to the cube of the distance (Epstein, 1990). With such considerations, the stimulation is unlikely to activate structures beyond the cerebral cortex or the subcortical white matter.

The change in the magnetic field induces a "back" EMF which counters the change and induces a momentary electric field in the underlying brain tissues in a parallel trajectory to the

electric field in the wire, but in an opposite orientation. Although the TMS coil can be positioned anywhere on the scalp, we will only be focusing on the M1 area to target neurons projecting to a specific area of the body. The current flowing through the brain cells is a mere fraction of the one flowing through the wire, but is strong enough to elicit MEPs that can be observed.

The orientation of the induced current in the brain can be chosen. If the current travels in a loop-like fashion around the brain, then one may decide whether the current should be pointed in anteroposterior (AP) or in posteroanterior direction (PA). Reversing the current orientation can easily be accomplished by pivoting the TMS coil by an angle of 180°. A study contemplated this issue whilst outlining the differences between monophasic and biphasic pulse forms found that a monophasic pulse had a greater effect when the current flowed in the posteroanterior direction (Kammer, 2001). Thus, PA direction may be more efficient in depolarizing cell membranes, allowing possibly the use of lower intensities of stimulation.

In what refers to the coil design, many interesting options can significantly impact the stimulation of a desired region of the brain. A figure-of-8 coil is less powerful than a simple circular coil since the current is divided between the two coils. But as each coil produces a perpendicular magnetic field and the 2 fields merge together at their intersection into a more focal point beneath the skull, this setup creates a current flowing in a much more precise location of the cortex than a simple coil. Since the area of M1 is quite small and the boundaries between the representations of body parts are distanced on the order of a few mm, a focal figure-of-8 coil is more likely to target the desired motor area. A double-cone coil uses the same principle as the figure-of-8, with the exception that both cylinders are meshed at an angle varying between 90° and 100°. The positioning of the coils not only creates a better fit for the contour of the skull, its geometry permits the induction of current in slightly deeper parts of the motor cortex, such as the area corresponding to the leg (Terao, 2002).

2.5.5 TMS in functional recovery

TMS transiently disrupts activity in focal brain regions allowing one to assess function on a precise time scale. TMS can be employed in motor control studies to evaluate cortical excitability in individuals with motor disorders (Hallett, 2000). It can be a much-needed evaluative tool as well as a predictor for stroke recovery (Pennisi, 1999). Moreover, a study

using TMS on post-stroke patients versus a control group of healthy subjects revealed that a longer than norm silent period following MEP onset was indicative and even predictive of an increased spasticity risk (Cruz, 1998).

TMS's role as a mapping tool of the motor cortex is however somewhat debated as some studies have shown that motor regions in M1 are not as discreted as those depicted in the somatosensory cortex. Individual corticospinal neurons can project to several different muscles of the body, a reality that makes the mapping of M1 via TMS all the more difficult. TMS mapping may, on the whole, provide a general notion of an approximate motor representation sketch. Through the observation of MEPs, the best points for the activation of certain muscles can be represented.

Two factors make the mapping of a particular muscle difficult. First, the targeted area in the cortex corresponds to a projection of neurons which innervate multiple muscles. By aiming the center of the TMS coil onto that projection, one can locate the ideal spot in the cortex to elicit MEPs in the target muscle. However, one cannot ascribe a cortical area as representing any one muscle with a high degree of certainty. Also, the appearance of MEPs may possibly depend on the strength of the stimulus and not necessarily on its precise location. With a strong stimulus, the spread of the electric flux gets larger and could excite other areas beyond the intended point, which may elicit MEPs but cannot reveal anything about the precise location that produces them.

Notwithstanding those restrictions, TMS has the potential to predict functional recovery in patients having suffered a stroke. In the acute phase following stroke, the inability to elicit MEPs in the affected hand muscles (corresponding to the contralateral lesion in the brain) may correlate with poor functional outcome. The presence of MEPs, on the other hand, is a marker of favorable outcome. Latencies in MEP responses also play a key role: the prolonged times witnessed in the acute phase slowly progress towards shorter latencies as the patient improves functionality following physiotherapy (Rapisarda, 1996).

2.6 Research hypothesis

Since corticospinal influences play a key role in all voluntary movements, our hypothesis is that spasticity following stroke is associated to changes in corticospinal influences on those voluntary movements. We used the equilibrium-point framework in which

spasticity is considered the result of a disorder in the central control of voluntary movements and more specifically to a decrease in the range of the stretch reflex thresholds.

Thus, the objective of the project is to show that in individuals with spasticity, corticospinal influences are different from those modulating movement in healthy individuals and that such a difference is associated to changes in the threshold control of the stretch reflex.

If our hypothesis is confirmed, spasticity could be assessed with a neurophysiologic measure and would provide clinicians with a tool to track whether a treatment is leading to a patient's partial or full recover from spasticity.

3. METHODOLOGY

3.1 Subjects

Experiments were conducted in the Motor Control Laboratory of the Institut de Réadaptation Gingras-Lindsay-de-Montréal (IRGLM) with 2 aged-matched groups of subjects. The first group consisted of patients having suffered a stroke no sooner than 3 months ago, as it is deemed the minimal length of time for stroke chronic stage to set in (Swayne, 2008). Any degree of spasticity present in the muscle around the elbow joint was accepted as long as it did not interfere with a minimal active range of motion around the elbow joint. Neither handedness nor affected side mattered for selection. The second group consisted of healthy subjects, with no prior incidence of stroke or spasticity. Six post-stroke subjects were recruited via the IRGLM and the Jewish Rehabilitation Hospital network, while seven control subjects were directly contacted to participate in the experiments.

All post-stroke subjects underwent a rigorous clinical evaluation prior to the day of the experiment. A physical assessment was carried out to measure the functional ability of the affected arm using the Fugl-Meyer test, degree of pain through the Visual Analog Scale (VAS), and increased muscle tone to passive stretch (MAS). Tables 3.1 & 3.2 summarize the inclusion and exclusion criteria respectively.

TABLE 3.1 Inclusion criteria for the recruitment of post-stroke patients with spasticity in the upper limb.

Criteria	Description
Muscle tone	Spasticity in elbow flexors and/or extensors. Composite Spasticity Score of 5/16 or more.
Chedoke arm scale	2 to 5
Age	40 to 75 years
Range of motion	Joint contracture ≤ 10º
Type of lesions	Ischemic or hemorrhagic
Required movements	Subjects must be able to comfortably rest the arm on a horizontal arm support at elbow level and perform movement in either flexion or extension or both
Language spoken	Subjects must understand either French, English, Spanish or Russian

TABLE 3.2 Exclusion criteria for the recruitment of post-stroke patients with spasticity in the upper limb. VAS = visual analog pain scale.

Criteria	Description
Vision	Left or right visual neglect
Number of strokes	1 (but can be more if patient is not weak)
Neurological conditions	Epilepsy, family history of seizures
Medical devices	Cardiac pacemaker, cochlear or other implants
Medication	Psychoactive drugs, or any other compound contra-indicated for TMS procedure

The Montreal Cognitive Assessment (MoCA) was also included to ensure the individual's level of spoken or written word understanding of the project's objectives (a score of 21/30 was considered a minimum requirement). A list of prescription medications taken by the subject was noted and verified to ensure none posed any contraindications for the use of TMS, such as psychoactive, antispasmodic or antiepileptic drugs. Candidate recruits in both groups were excluded if any had a personal or family history of seizures (e.g. epilepsy), possessed any metallic implants in the body (including a pacemaker but excluding dental implants), or in the case of women, if they were pregnant.

An informed consent form, approved by the Institutional Ethics Committee (CRIR) and in accordance with the 1964 Declaration of Helsinki, was either read out loud or handed to the candidates. If they accepted to participate, they were asked to describe in very broad terms the experimental protocol as well as the project's aim before signing the legal document.

3.2 Apparatus

Subjects sat comfortably on a reclining dental chair, their backs reasonably upright, at angles between 100 and 115° against the back support and the legs extending straight out into the horizontal plane. A manipulandum mounted on a table was adjusted on the side of the arm tested. In the case of post-stroke subjects, the manipulandum was placed on the hemiplegic side. In the case of control subjects, it was positioned next to their dominant arm. The manipulandum is a slender slab of composite material which is approximately as long as the length of a human forearm, to allow the forearm to fully rest on it. It pivots around a point in such a way that a subject is able to fully flex or extend the elbow joint in a horizontal plane (Figure 3.1). In such a position, the shoulder is at a horizontal abduction of roughly 45° while the hand and forearm are in semi-supine position. When the elbow joint is at rest, its neutral

position usually makes an angle of 100°, with some variability among subjects. Velcro straps were used to fasten the forearm to the manipulandum to limit all other degrees of freedom. A torque motor (Parker iBE342G model) was connected to the axis of the manipulandum.

FIG. 3.1 Subject positioning during experiment. Arm rests on horizontal manipulandum pivoting around the axle of the motor.

3.3 Experimental setup

Four arm muscles were chosen for the purposes of the analysis, two flexors (biceps brachii (BB), brachioradialis (BR)) and two extensors (triceps lateralis (TL), triceps medialis (TM)). The skin was cleansed with alcohol and quickly dried. The bellies of all four muscles were isolated, via a series of muscle contractions, and marked with a surgical pen. Two disposable Ag-AgCl surface electrodes (10 mm^2 area of sensor) were affixed around the marked bellies of each muscle and a ninth electrode was used as reference signal on a bony prominence near the elbow joint (lateral epicondyle). Once installed, electrodes were connected to a portable hub which communicates wirelessly with the EMG recording equipment (Figure 3.2).

3.4 EMG acquisition

Raw EMG signals recorded by the electrodes were amplified (x2000) within the Data relay and displayed on 2 oscilloscopes for quality control purposes. The Data relay output

signals were also linked to a data acquisition card for sampling and storing data on a computer; this processing was accomplished through an application interface (LabVIEW of National Instruments, USA) allowing the experimenter to fix parameters such as torque motor force, trial duration and the 2kHz sampling frequency. In a window, the angular movement of the elbow joint was presented as a visual feedback to the subject in order, when asked, to correct or enhance the motion of flexion or extension.

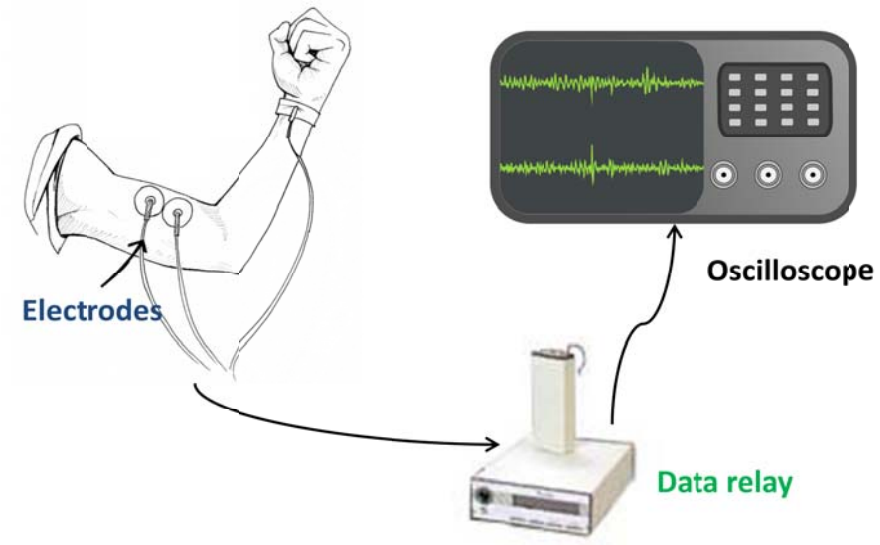

FIG. 3.2 A simplified schematic depicting EMG acquisition. The electrodes ferry data to a hub (Telemyo of Noraxon, USA) which redirects them for viewing on an oscilloscope. Arm drawing taken from: http://backyardbrains.com/experiments/emgspikerbox.

3.5 TMS

The device used to power the butterfly-shaped TMS coil was a Masgstim 200 (UK) mono-phasic single-pulse stimulator. The coil's wings disposed at 110° from each other have an outer radius of 7 cm (Figure 3.3). The shape of the coil made it an ideal fit for its placement over a human skull. The coil was supported by a gantry to facilitate its handling while reducing pressure applied on the head.

FIG. 3.3 Double-coned coil used throughout the experiments. The shape made it an ideal fit onto the subject's head and made the positioning of it easier to maintain throughout the experiment.

3.5.1 Hot spot

A “hot spot” is defined as the point where an MEP can be elicited under the least intensity of stimulation possible. To identify that location on the motor cortex corresponding to the arm muscles' cortical projections, a measurement tape was placed on the nasion (the intersection of the frontal and nasal bones) and extended along and around the middle of the skull up to the inion (the prominent projection of the occipital bone). The half point mark of the distance was calculated and marked on the scalp. The tape was then transferred onto the coronal plane, by extending it from the middle of the left ear to the middle of the right ear. By calculating half the distance, one would ensure of obtaining a properly aligned point along the mid-sagittal plane. The intersection of both markings corresponds to the vertex (Cz point). From this point, 2 cm were measured in the rostral direction along the mid-sagittal line. From this new landmark, 5-6 cm was measured in the lateral direction of the scalp in the contralateral direction to the arm tested. This last position represented the hot spot.

3.5.2 Coil positioning

As mentioned earlier, studies have shown that the stimulation was more effective when the induced current flowed in a poster-anterior (PA) direction (Mills, 1992; Kammer, 2001). The double-cone coil was then positioned in such a way that the current in the middle wire

was flowing in the opposite direction, namely the antero-posterior direction, so as to produce an induced current in the PA direction. The same orientation was applied to all patients, regardless of the onset time of stroke or of spasticity severity.

3.5.3 Motor Threshold

To confirm the hot spot location, we used a standard intensity of stimulation which was ~30% of the maximal intensity deliverable by the TMS source. The coil was moved within a small distance of the marked point until the resulting EMGs displayed visible MEPs with each stimulus. The intensity of TMS stimulation was steadily decreased until MEPs were barely perceptible onscreen. The motor threshold was found once MEP amplitudes of more than 50 μV in at least 3 out of 5 sequential trials, consistent with what previous studies performed (Raptis, 2010; Sangani, 2011). Resting motor threshold intensities in post-stroke subjects are listed in Table 3.3. When the hot spot was finally optimized, the TMS coil was immobilized while markings were made around its contour on the subject's head in case the coil's position had to be modified during the experiment.

TABLE 3.3 Demographic and clinical data for hemiparetic subjects. S = subject, M = male, F = female, E = extensors, FX = flexors. Spasticity score based on the Composite Spasticity Index.

S	Age	Sex	Site of lesion	Years since stroke	Motor score (66)	Spasticity (FX) score (16)	Spasticity (E) score (16)	TMS Motor threshold (%)
1	59	F	Left	1.8	16	9	13	54
2	58	M	Left	1.5	15	10	15	68
3	46	M	Right	0.5	56	7	5	52
4	51	M	Right	1.5	42	4	5	46
5	47	M	Left	0.6	18	11	10	47
6	68	F	Right	7.3	16	10	10	41

In most cases, the arm was maintained in a fully relaxed neutral position throughout these proceedings. In other cases, when the MEPs were difficult to observe, the subject was either asked to apply a minimal pressure in the flexors (when searching for MEPs in flexors). If neither neutral position nor minimal contraction worked to elicit MEPs, the subject was asked to actively establish flexion and extension positions. Once the intensity of stimulation corresponding to motor threshold (MT) was found, an intensity of 1.2 MT was chosen for the

duration of the experiment. This supra-threshold stimulus is chosen for the purpose of eliciting MEPs that clearly exceeded background EMG levels (Sangani, 2011).

3.6 Experimental procedures

All trials of the experiment were based on repeated movements of the arm resting on the manipulandum as it is hinged around the elbow joint. For the first part of the experiment, subjects were instructed to completely relax the muscles of their arm while the experimenter moved the manipulandum to perform a full range of motion twice (e.g. from a fully extended position of the elbow to a fully flexed and back to fully extended; F→E→F). The nature of the movement being passive, the objective of the task was to observe at which biomechanical angles of the joint there appeared a significant increase in EMG activity. The same movements were repeated once more, but this time in voluntary mode, with the full participation of the subject. The full experimental protocol is represented in Figure 3.4.

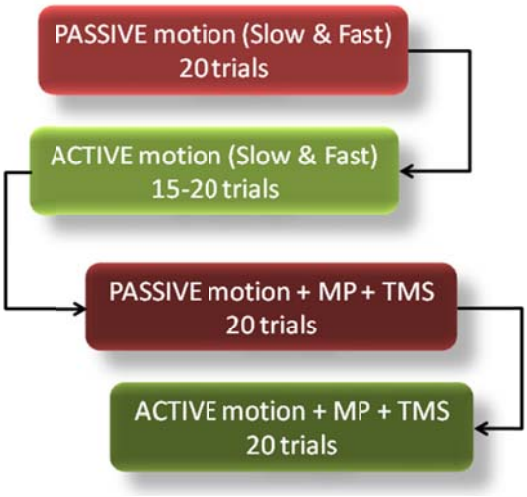

FIG. 3.4 Diagram representing the experimental protocol in a chronological order from top to bottom. MP = motor pulses.

In the second part of the experiment, trials consisted in a simple passively-administered full range of motion, starting either in the flexion or in the extension position (20 trials, starting order switched every two trials) while 2 TMS pulses were applied at each trial: one at the initial position and one at the end position of the movement. The difference in MEPs at the two positions (flexion, extension) of the elbow joint depends not only on corticospinal influences but also on the difference in motoneuronal excitability at those positions. To

equalize the motoneuronal excitability at these positions, a silent period was induced around the time window where MEPs were likely to appear. This was accomplished by introducing brief motor perturbations (P= 0.5 Nm, as used in previous studies) 18 ms prior the application of the TMS pulse in order to create a brief muscle shortening. Muscle shortening induces a pause in the discharge of muscle spindle afferents, thus creating a silent period in the EMG activity, which reduces facilitation of the motoneurons.

The resulting MEPs from the TMS pulses would thus reflect the state of corticospinal excitability (Raptis, 2010; Sangani, 2011). The choice of the 18 ms delay between the motor perturbations and the TMS pulse was based on previous empirical findings (Ilmane, 2012). It is difficult to ascertain that the accuracy of the set delay is best or if it should be subject to change according to each individual's response to motor perturbations. The latter option could have been a better choice but would have prolonged the experimental session. Subjects were asked not to anticipate nor intervene in response to these perturbations; a few test trials early in the experiment were used to train the subject to relax the arm in static positions. To test the exact same conditions but under volitional movement, another set of trials were performed with the active participation of the subject.

In 5 of the 7 healthy subjects, a technique of EMG equalization involving force compensation was used as an extension of the active movement. For those subjects, a motor torque assisted the arm to move in the desired direction in such a way that EMG levels were minimal. To make sure that EMG equalization was obtained at each established position, the root-mean-squared (RMS) values of the EMG responses were calculated over a 200 ms time span prior to the onset of TMS. Only trials where EMG levels did not differ by more than 15% of the RMS value were retained.

3.7 Data and statistical analysis

Data stored with the custom-designed acquisition program were converted in the .MAT format (MATLAB readable) and band-pass filtered (35-350 Hz). The MEPs were detected from those signals and classified into flexion and extension positions for each muscle group. This was carried out separately for the passive motion trials and the voluntary ones. In order to display MEPs of each subject on a histogram, MEP amplitudes were normalized relative to the maximal MEP amplitude found within each subject's responses. Averages (±s.d.) of

MEPs in flexion were compared with those in extension. To insure that the studied variables were normally distributed, the Shapiro-Wilk test was done with the SPSS software. For normal distributions, a two-paired dependent-variable Student t-test was run to determine statistical significance in MEP average differences. The null hypothesis assumes that a significant difference exists between MEP averages at flexion and extension. For non-normal distributions, the non-parametric Wilcoxon test was used to determine significance. A significance level of $p<0.05$ was chosen in all tests.

4. RESULTS

4.1 Healthy subjects

4.1.1 Passive motion

Figure 4.1 shows typical EMG signals obtained in response to a passive movement where a healthy subject was asked to fully relax the muscles of the arm while the experimenter rotated the manipulandum with the arm on it around the elbow axis. The directions of motion varied from F→E→F or E→F→E (see Methods). The resulting low levels of EMG amplitude and the fairly uniform nature of the signal throughout the duration of the trial clearly indicates the subject's ability to fully relax flexor muscles. The subject was also successful in relaxing extensor muscles during stretching (motion E→F) but intermittently activated them during shortening (probably due to a tendency to assist the passive movement).

This brief activation lingered in subsequent trials, possibly indicating an inability to completely relax muscles. Such was the case for all healthy subjects.

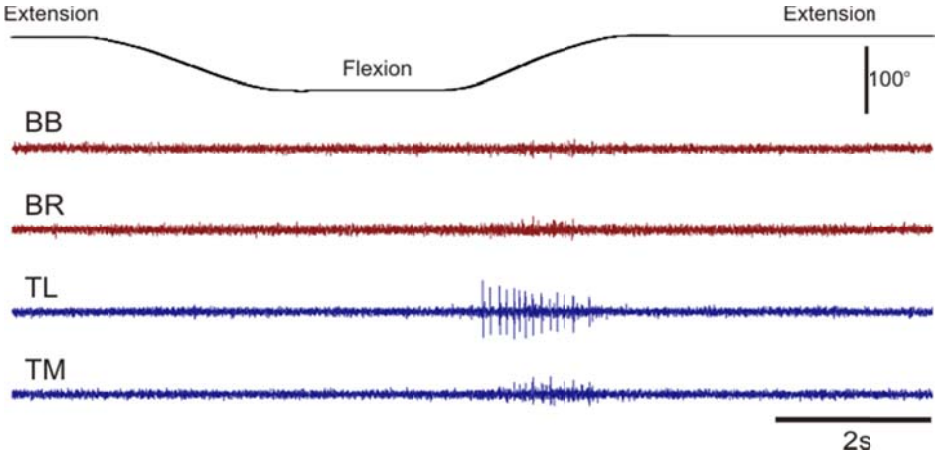

FIG. 4.1 EMG signals taken for a single trial during passive motion of the arm around the elbow joint in a healthy subject (H4). Angular motion is depicted by the upper curve. Flexor muscles (BB, BR) were silent. Extensor muscles (TL, TM) were silent during passive stretching (motion from extension to flexion position, but a small transient EMG activity appeared in extensor muscles during shortening (motion from flexion to extension position). BB = biceps brachii; BR = brachioradialis; TL = triceps lateralis; TM = triceps medialis.

4.1.2 Passive motion with TMS and motor perturbations

To elicit MEPs that reflect the corticospinal tract's contribution, TMS was used in conjunction with shortening pulses produced by the torque motor. By shortening a muscle at both positions before TMS activation, motoneuronal excitability was equalized and changes in MEPs at these positions basically reflected changes in the corticospinal influences. TMS was applied twice in every passive motion trial, which allowed MEPs in flexion and extension positions to be recorded. The sequence of passive movements varied between F→E and E→F. Only muscles shortened by motor perturbation were analyzed in each trial, so flexor and extensor MEPs were analyzed, depending on whether the perturbation shortened flexors or extensors. A flexor response in a typical trial is shown in Figure 4.2. The motor perturbations in the flexion direction can be plainly seen by the indentations on the movement curve. In blue, is shown the TMS signal. To assess the MEPs, we have magnified the time windows around which TMS occurs. The resulting MEPs, seen at the bottom of the graph, clearly exceed the baseline signal. MEP amplitudes in flexion and extension slightly differ but in no significant manner.

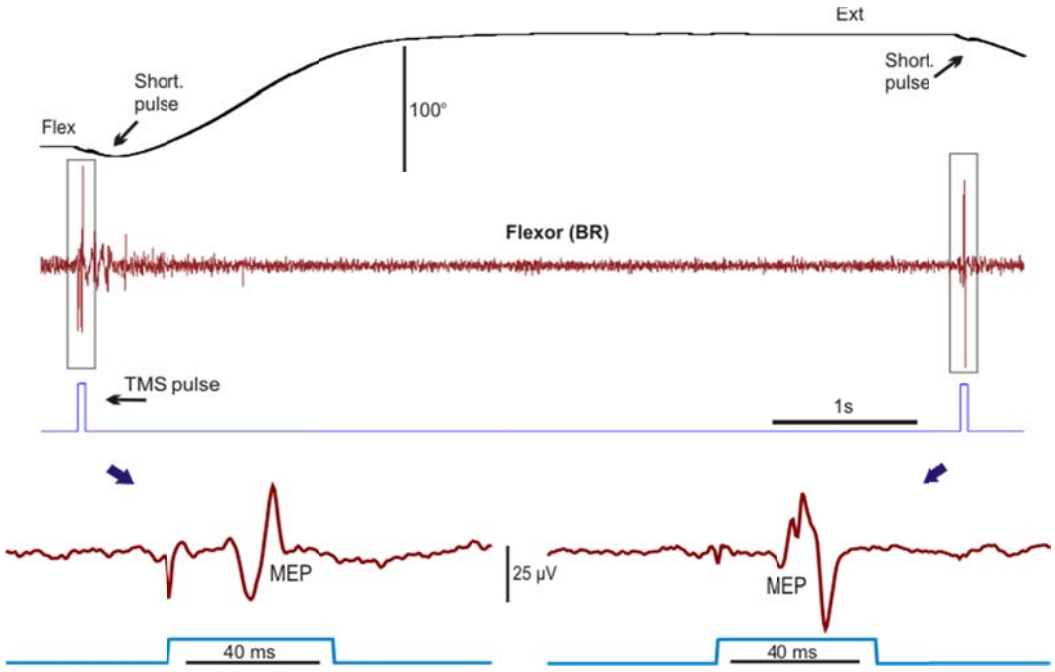

FIG. 4.2 Typical flexor (BR) EMG responses to TMS before and after passive motion from a flexion to an extension position of the elbow joint, in healthy subject H7. Small indentations in the motion curve (upper curve) depict muscle shortening pulses. The light blue line represents TMS signal. In the bottom row, segments of MEP signals associated with each of the 2 TMS pulses are zoomed in. MEP amplitudes are similar indicating that corticospinal influences remain unchanged at both positions.

4.1.3 MEP averages in passive movements

Averages for the 7 control subjects were obtained for the BB muscle. MEP amplitudes were normalized prior to averaging as described in Methods. In Figure 4.3, we present MEP averages found in flexor BB across all subjects and Table 4.1 summarizes the statistical significance of BB MEPs for each subject.

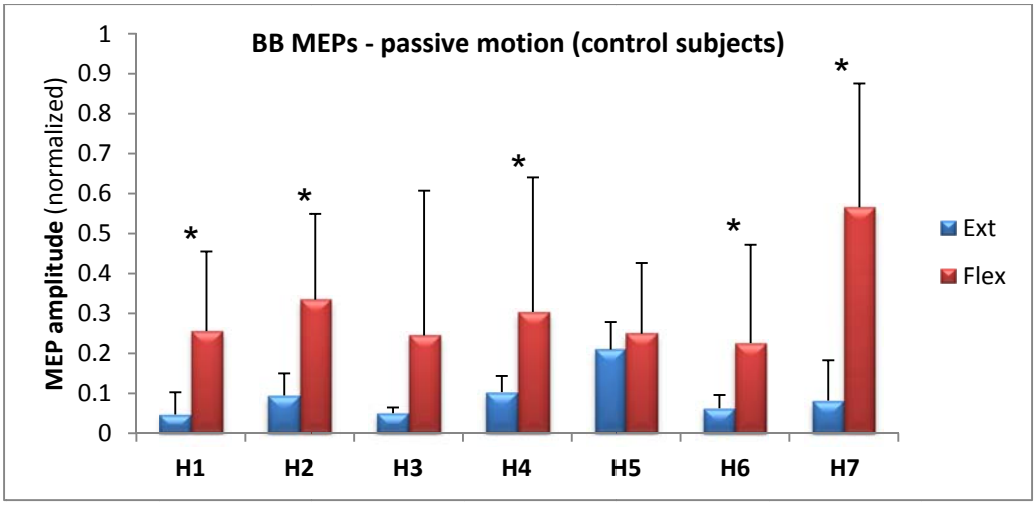

FIG. 4.3 MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement of the 7 control subjects. Asterisks denote statistically significant differences in MEPs at both positions.

TABLE 4.1 P-values of MEPs in BB, in passive movement. In 5 of 7 control subjects, MEPs in BB were higher at flexion (reciprocal pattern) while no differences were perceived in the other 2.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BB MEPs*
H1	No	Wilcoxon	0.009	Flex > Ext
H2	No	Wilcoxon	0.050	Flex > Ext
H3	No	Wilcoxon	0.128	None
H4	No	Wilcoxon	0.038	Flex > Ext
H5	No	Wilcoxon	0.953	None
H6	No	Wilcoxon	0.038	Flex > Ext
H7	No	Wilcoxon	0.008	Flex > Ext

In Figure 4.4, we present MEP averages found in flexor BR across all subjects and Table 4.2 summarizes the statistical significance of BR MEPs for each subject. In Figure 4.5, we present MEP averages found in flexor TL across all subjects and Table 4.3 summarizes the statistical significance of TL MEPs for each subject.

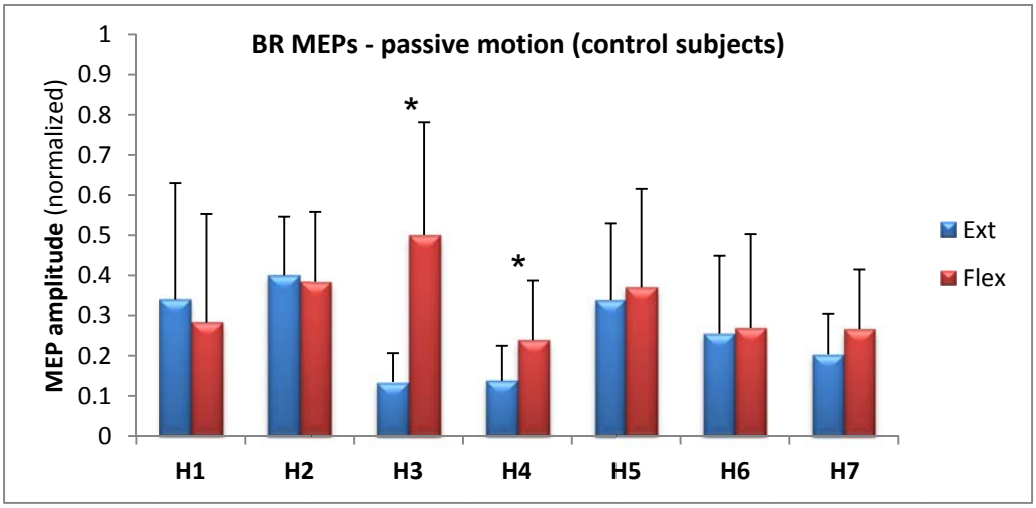

FIG. 4.4 BR MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.2 P-value of MEPs in BR, in passive movement. In 2 of 7 control subjects, MEPs in BR were higher at flexion (reciprocal pattern) while no differences were perceived in the other 5.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BR MEPs*
H1	No	Wilcoxon	0.646	None
H2	Yes	Student t-test	0.782	None
H3	Yes	Student t-test	0.014	Flex > Ext
H4	No	Wilcoxon	0.021	Flex > Ext
H5	No	Wilcoxon	0.953	None
H6	Yes	Student t-test	0.861	None
H7	No	Wilcoxon	0.314	None

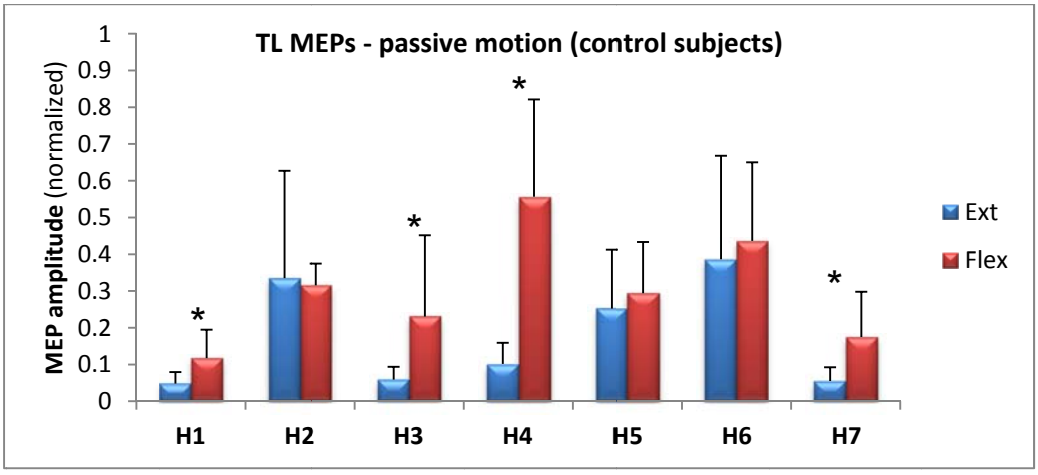

FIG. 4.5 TL MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.3 P-values of MEPs in TL, in passive movement. In 4 of 7 control subjects, MEPs in TL were higher at flexion (inverted pattern) while no differences were perceived in the other 3.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TL MEPs*
H1	No	Wilcoxon	0.013	Flex > Ext
H2	No	Wilcoxon	0.799	None
H3	No	Wilcoxon	0.038	Flex > Ext
H4	No	Wilcoxon	0.008	Flex > Ext
H5	No	Wilcoxon	0.515	None
H6	No	Wilcoxon	0.173	None
H7	Yes	Student t-test	0.023	Flex > Ext

In Figure 4.6, we present MEP averages found in flexor TM across all subjects while Table 4.4 summarizes the statistical significance of MEP differences for each subject.

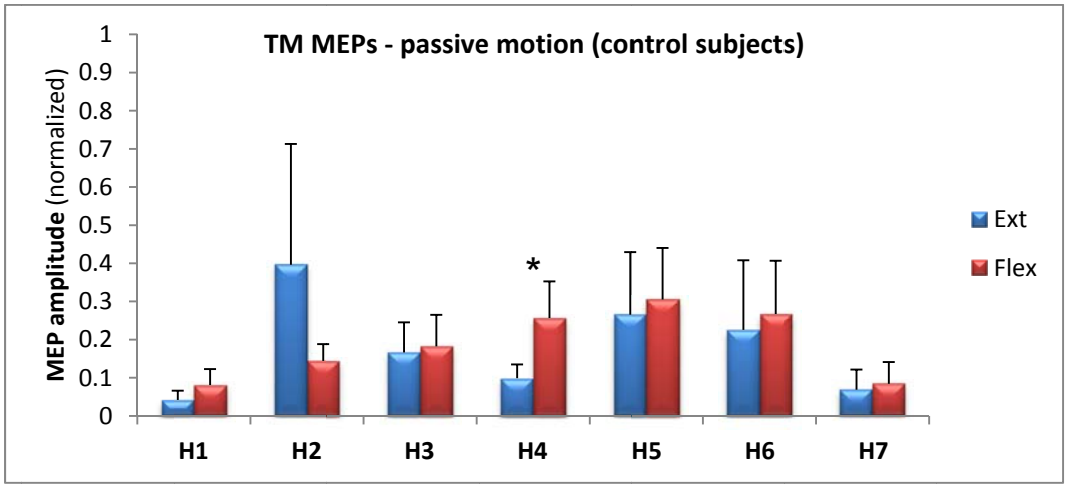

FIG. 4.6 TM MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.4 P-values of MEPs in TM, in passive movement. In 1 of 7 control subjects, MEPs in TM were higher at flexion (inverted pattern) while no differences were perceived in the other 6.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TM MEPs*
H1	No	Wilcoxon	0.074	None
H2	No	Wilcoxon	0.059	None
H3	No	Wilcoxon	0.767	None
H4	Yes	Student t-test	0.003	Flex > Ext
H5	No	Wilcoxon	0.441	None
H6	No	Wilcoxon	0.173	None
H7	Yes	Student t-test	0.512	None

The latencies corresponding to the time difference between the start of TMS and MEP onset were averaged for every subject. This was done across all muscles, as latencies of each separate muscle were generally similar among one another. Table 4.5 displays the average MEP latencies per subject.

TABLE 4.5 Average (±s.d.) MEP latencies during passive movement for each control subject. All muscles were included in the average.

Subject	**H1**	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**
MEP Latency *(ms)*	20.7±3.2	19.8±2.5	22.3±4.0	21.7±4.2	22.0±3.8	23.7±4.3	20.2±2.4

4.1.4 Voluntary motion

In voluntary movement trials, the subject was asked to perform F→E→F and E→F→E sequences. For a healthy subject, results of a typical trial are depicted in Fig. 4.7. We observe a reciprocal pattern of activation, where flexor activity increases only for the duration of the movement towards flexion while extensor activity increases during the extension phase. Although there were trials where co-contraction occurred (a phenomenon in which both flexors and extensors activate simultaneously, as seen in the figure during elbow flexion, when flexor muscles activation was combined with tonic activation of extensor, TL), a reciprocal pattern was seen in the all 7 healthy subjects.

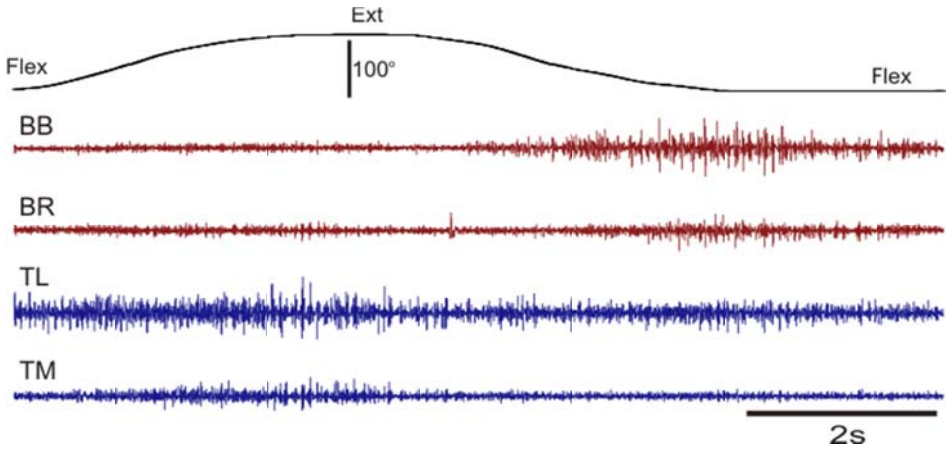

FIG. 4.7 Active elbow flexion and extension in a representative healthy subject (H4). Reciprocal pattern of muscle activation: extensors (TL, TM) are active during extension while flexors remain silent; flexors (BB, BR) are active during flexion while one of the extensors (TL) remains tonically active (coactivation).

4.1.5 Active motion with TMS and motor perturbations

In trials with voluntary movements TMS stimulation was applied twice per trial, to assess MEP amplitude at both established positions. Figure 4.8 shows two separate typical trials of a healthy subject showing the BB flexor and TM extensor responses. The time windows around the TMS pulses were expanded for a better illustration of the results. A clear difference can be observed between the MEP amplitudes at both positions, with the one at flexion being considerably greater for BB. On the other hand, the MEP is higher at extension for TM. These results are in line with the reciprocal pattern of activation in volitional movements seen earlier.

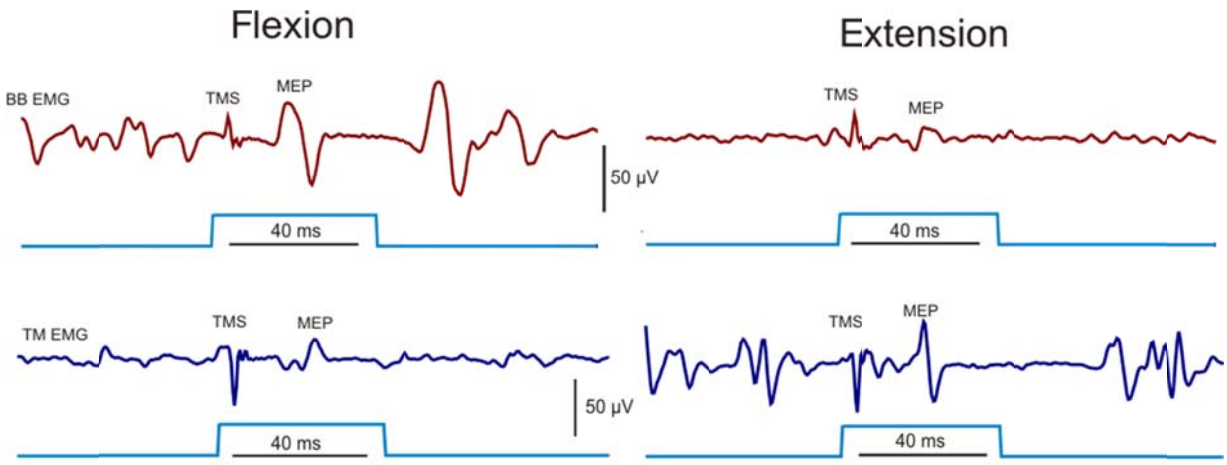

FIG. 4.8 Healthy subject (H1) EMG responses of the BB flexor (red) and the TM extensor (dark blue) to TMS before and after active motion from an elbow flexion to an extension position, in two separate trials. The light blue line represents TMS signal. The MEP amplitude is significantly higher at flexion than at extension elbow position for the BB. The opposite pattern is seen for TM. Both responses combine to produce a reciprocal pattern of corticospinal influences.

4.1.6 MEP averages in voluntary movements

As for passive movements, MEP averages found in flexor BB across the 7 healthy subjects are shown in Fig. 4.9. A quick glance of the histogram below reveals that MEPs in BB are consistently higher at the flexion position during voluntary movements. Table 4.6 summarizes the statistical significance of greater MEPs at flexion for each subject.

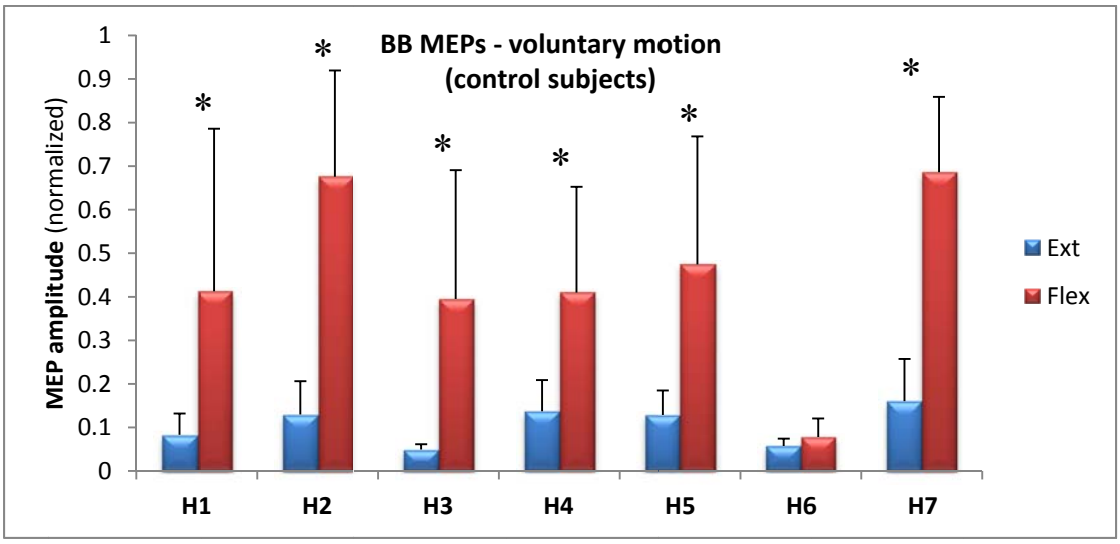

FIG. 4.9 BB MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.6 P-values of MEPs in TM, in voluntary movement. In 6 of 7 control subjects, MEPs in BB were higher at flexion (reciprocal pattern).

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BB MEPs*
H1	Yes	Student t-test	0.026	Flex > Ext
H2	Yes	Student t-test	<0.001	Flex > Ext
H3	Yes	Student t-test	0.014	Flex > Ext
H4	Yes	Student t-test	0.006	Flex > Ext
H5	No	Wilcoxon	0.009	Flex > Ext
H6	Yes	Student t-test	0.110	None
H7	Yes	Student t-test	<0.001	Flex > Ext

The table above confirms statistical significance in 6 out of 7 subjects that the MEPs in BB are higher at the flexion position (reciprocal pattern). The case of BB shows a strong tendency towards a reciprocal pattern of excitability. In Figure 4.10, we present MEP averages found in flexor BR across all subjects. No consistent pattern can be inspected by looking at the comparison between BR MEPs at flexion and extension. Table 4.7 summarizes the statistically significant findings.

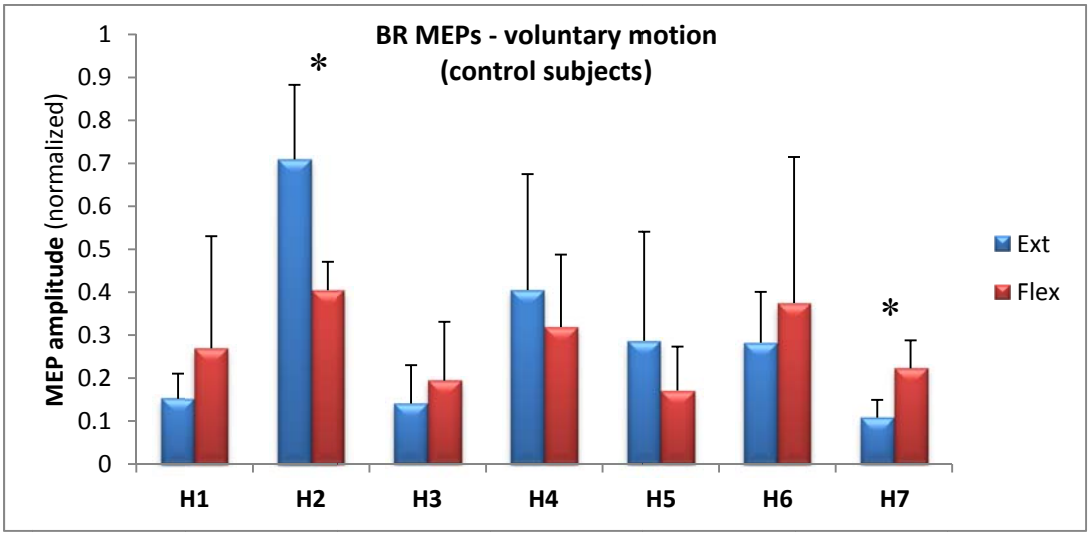

FIG. 4.10 MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.7 P-values of MEPs in BR, in voluntary movement. In 1 of 7 control subjects, MEPs in BR were higher at flexion (reciprocal pattern) while 1 of 7 subjects had higher MEPs at extension (inverted pattern). The inverted pattern was highlighted in boldface in the outcome column.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BR MEPs*
H1	Yes	Student t-test	0.175	None
H2	Yes	Student t-test	<0.001	**Ext > Flex**
H3	Yes	Student t-test	0.217	None
H4	Yes	Student t-test	0.119	None
H5	No	Wilcoxon	0.445	None
H6	No	Wilcoxon	0.878	None
H7	Yes	Student t-test	<0.001	Flex > Ext

The data above show that only 1 of 7 subjects had a higher BR MEPs at flexion (reciprocal pattern), while 1 of 7 had higher BR MEPs at extension (inverted pattern). No statistically significant outcomes could be established for the other 5 subjects. In Figure 4.11 we present MEP averages in extensor TL across all subjects. A look at the histogram below does not clearly reveal particular patterns for MEP differences at both positions. Table 4.8 outlines statistically significant outcomes for TL MEPs.

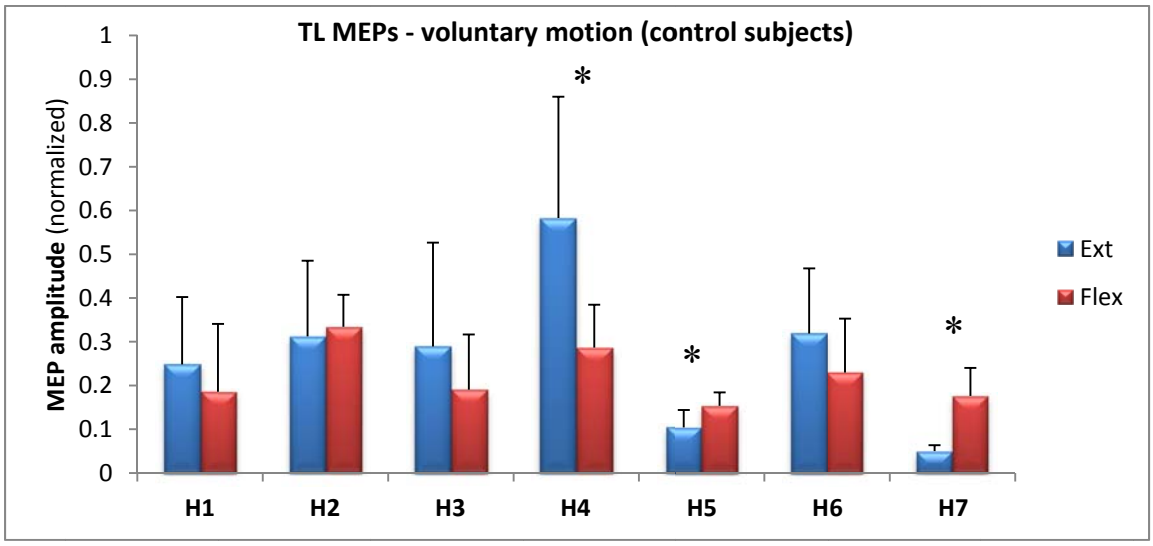

FIG. 4.11 TL MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.8 P-values of MEPs in TL, in voluntary movement. In 1 of 7 control subjects, MEPs in TL were higher at extension (reciprocal pattern) while 2 of 7 subjects had higher MEPs at flexion (inverted pattern). The inverted pattern was highlighted in boldface in the outcome column.

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TL MEPs*
H1	No	Wilcoxon	0.203	None
H2	Yes	Student t-test	0.706	None
H3	No	Wilcoxon	0.575	None
H4	Yes	Student t-test	0.026	Ext > Flex
H5	Yes	Student t-test	0.018	**Flex > Ext**
H6	Yes	Student t-test	0.182	None
H7	Yes	Student t-test	<0.001	**Flex > Ext**

In the case of TL, no patterns were consistently reproduced across subjects. Only 1 of 7 had higher MEPs at extension (reciprocal pattern) while 2 of 7 had higher MEPs at flexion (inverted pattern). Figure 4.12 depicts MEP averages for TM across all subjects. A more distinct pattern can be inspected from the histogram below. MEP averages at extension seem to be higher in most cases. Table 4.9 summarizes the statistically significant findings.

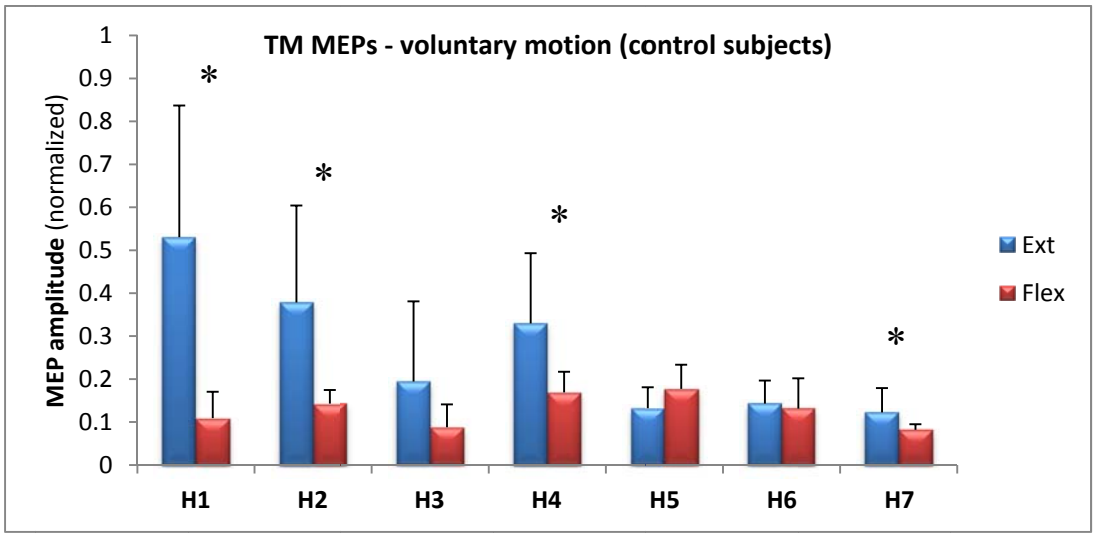

FIG. 4.12 TM MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 7 control subjects. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.9 P-values of MEPs in TM, in voluntary movement. In 4 of 7 control subjects, MEPs in TM were higher at extension (reciprocal pattern).

Subject	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TM MEPs*
H1	Yes	Student t-test	0.003	Ext > Flex
H2	Yes	Student t-test	0.010	Ext > Flex
H3	No	Wilcoxon	0.241	None
H4	No	Wilcoxon	0.015	Ext > Flex
H5	Yes	Student t-test	0.057	None
H6	Yes	Student t-test	0.0761	None
H7	Yes	Student t-test	0.040	Ext > Flex

Results in Table 4.9 indicate that in TM, MEPs were higher at extension in 4 out of 7 subjects, or a majority of the sample. As in the case of BB, a reciprocal pattern of corticospinal facilitation in TM is present in many subjects.

In Table 4.10, the number of cases of facilitation patterns observed in each muscle for all subjects is presented. BB exhibited a reciprocal pattern in most of the cases while in TM, reciprocal patterns were found more often than in the *No difference* situation. BR and TL on the other hand, offered little insight as to how corticospinal influences mediated voluntary movement in those muscles.

TABLE 4.10 Number of instances of corticospinal facilitation patterns seen in each muscle across all 7 healthy subjects.

Pattern	BB	BR	TL	TM
Reciprocal	6	1	1	4
Inverted	0	1	2	0
No difference	1	5	4	3

The latencies corresponding to the time difference between the start of TMS and MEP onset were calculated and averaged for each subject (Table 4.11). There was no need to compute latency averages for each muscle individually as they were nearly identical in range, within subject.

TABLE 4.11 Average (±s.d.) MEP latencies for each control subject during voluntary movement. All muscles were included in the average.

Subject	H1	H2	H3	H4	H5	H6	H7
***MEP Latency** (ms)*	19.5±3.1	19.7±2.5	20.3±3.1	20.0±2.6	23.1±3.7	22.2±4.0	19.1±1.9

4.1.7 Tonic EMG equalization (torque compensation)

The purpose of EMG equalization is to establish whether there are differences in MEPs when tonic EMG levels are equivalent at both established positions of the elbow joint. Only the last 5 healthy subjects were tested as the technique was employed late in the experimental stage. In 3 out of the 5 subjects, the BR muscle presented a reciprocal pattern of facilitation in trials where EMG levels were equal at every position. In 1 out of 5 subjects, TM also had a reciprocal pattern of facilitation. Overall, far too few trials were retained; many trials were discarded on the basis of unequal EMG levels at established positions. Too few results were collected to be of much relevance at this point.

4.2 Post-stroke patients with spasticity

4.2.1 Passive motion

In passively moving the arm around the elbow joint, the patients were instructed that no assistance was desired. Movements once again followed the F→E→F or E→F→E patterns and were carried out at a moderate angular speed (~30°/s). Passive movement where spasticity is present normally elicits a higher muscular activity when a muscle is stretched beyond a certain threshold. Figure 4.13 shows the EMG responses to passive motion for 2 patients. Although location and severity of spasticity in the arm varied substantially, a clear burst of EMG activity was usually visible in either the flexors or extensors.

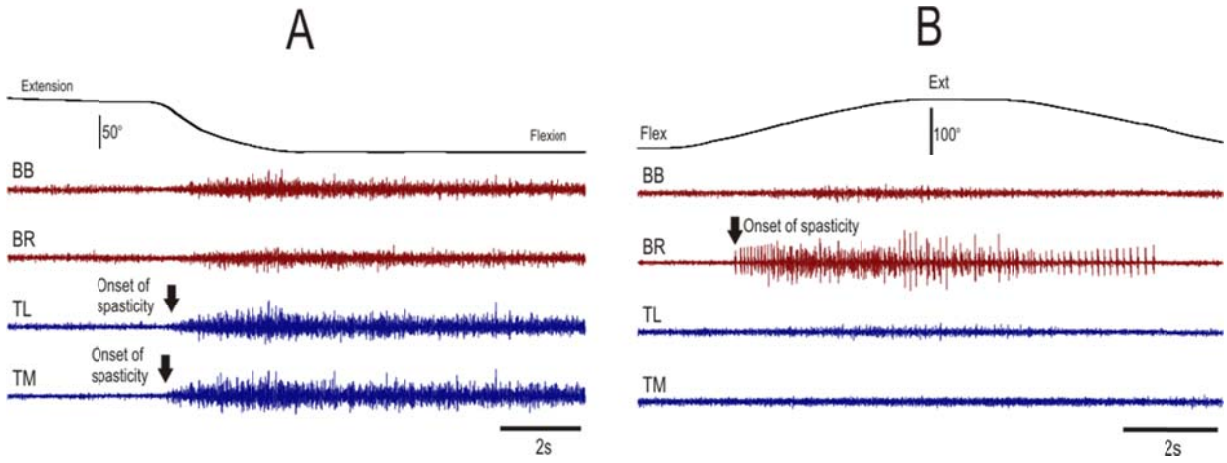

FIG. 4.13 EMG responses during passive motion of the arm in post-stroke patients (A) The motion curve (black) indicates an E→F movement for patient S1 as the extensors stretch (blue), a higher EMG activity appears (TL & TM). This was labeled as the onset of spasticity. (B) For patient S5, movement is in the F→E direction. As flexors stretched, the BR response greatly increased; this was marked as the onset of spasticity. Spasticity was less visible in BB.

The EMG responses on the left display a pattern of coactivation, the activity in flexors increases in step with that of extensors. As movement towards flexion is performed on the subject, the extensors' activity grows stronger as a result of spasticity's resistance to stretch. The simultaneous activity in flexors is not due to spasticity, but rather to an inability to relax flexors when extensors are clenched. The joint angle corresponding to the onset of extensor activity is the marker for the minimal threshold angle. Beyond this point, as the elbow angle closes towards a full flexion, the extensors enter their spasticity zone. In the EMG responses depicted on the right panel, spasticity in flexor BR can be clearly seen. BR activity occurs

when the muscle elongates beyond the indicated threshold. Extensors do not activate simultaneously, showing that in this case, the patient is capable of relaxing extensors in spite of flexor activity.

4.2.2 Assessing spasticity zones

To determine spasticity zones we detected for any considerable increase in EMG activity while muscles were passively stretched. Spasticity was evaluated based on EMG threshold, indicating the joint angle (R_+ in flexors and R_- in extensors) at which patients began producing active resistance despite the instruction to fully relax muscles. 5 of 6 post-stroke patients exhibited visible signs of spasticity through EMG inspection. Patients were deemed to have spasticity based on a clinical evaluation by the research team's physiotherapist. Spasticity severity was not a criterion for selection. This explains the little presence of spasticity in patients S3 and S4. Figure 4.14 summarizes the patients' spasticity zones.

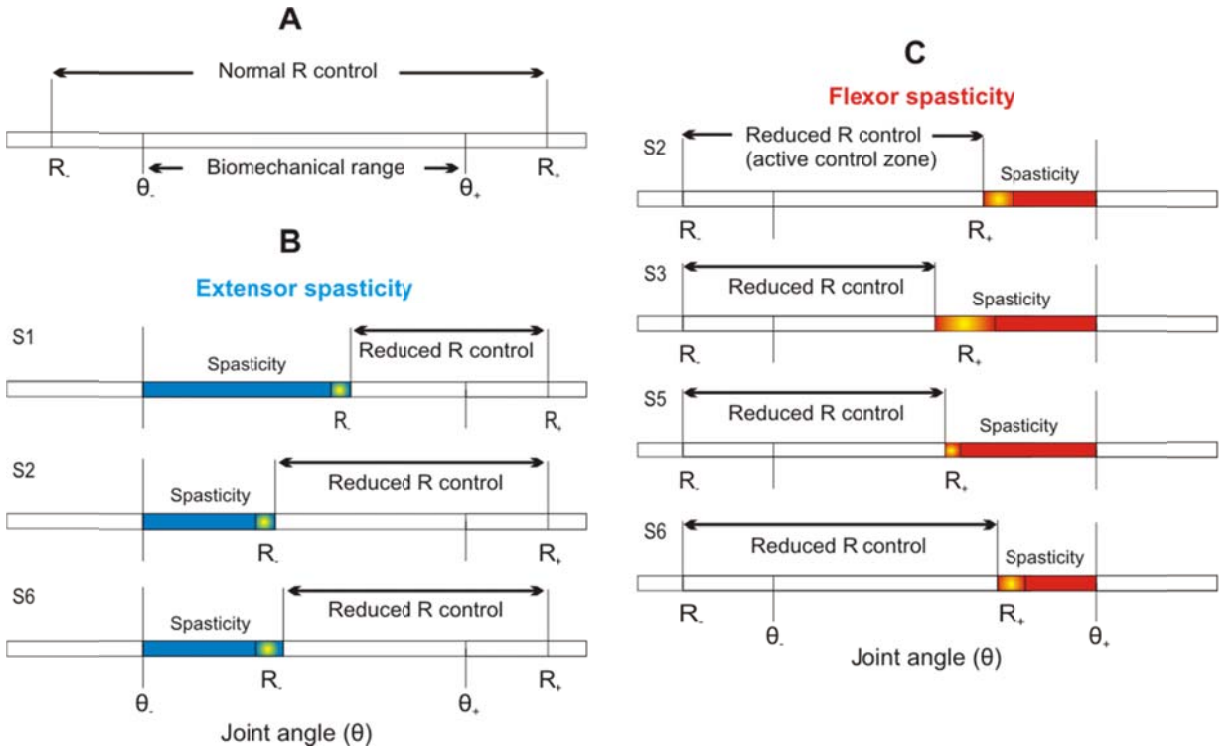

FIG. 4.14 Spasticity zones within the angular range of the elbow joint. Reduced R control corresponds to the narrower R- to R+ range of threshold regulation in patients with spasticity. (A) Threshold range of regulation in a healthy person. No spasticity zones present: range R- to R+ is wider than the biomechanical range (θ-, θ+). (B) Spasticity zones (in blue) found in at least in one of two extensors (TL, TM) in 3 post-stroke patients. The lower limit R- is located within the biomechanical range of the joint. The area in yellow represents average threshold angle ± 1 s.d. (C) Spasticity zones (in red) found in the flexors of 4 post-stroke subjects. The upper limit R+ is located within joint angle range. The area in yellow represents average (± s.d.) threshold angle.

4.2.3 Passive motion with TMS and motor perturbations

A sample of MEP responses collected during a passive movement trial is depicted in Figure 4.15. The resulting MEP amplitudes do not reflect average MEP amplitudes for the same subject. The trial is not representative of a particular MEP pattern.

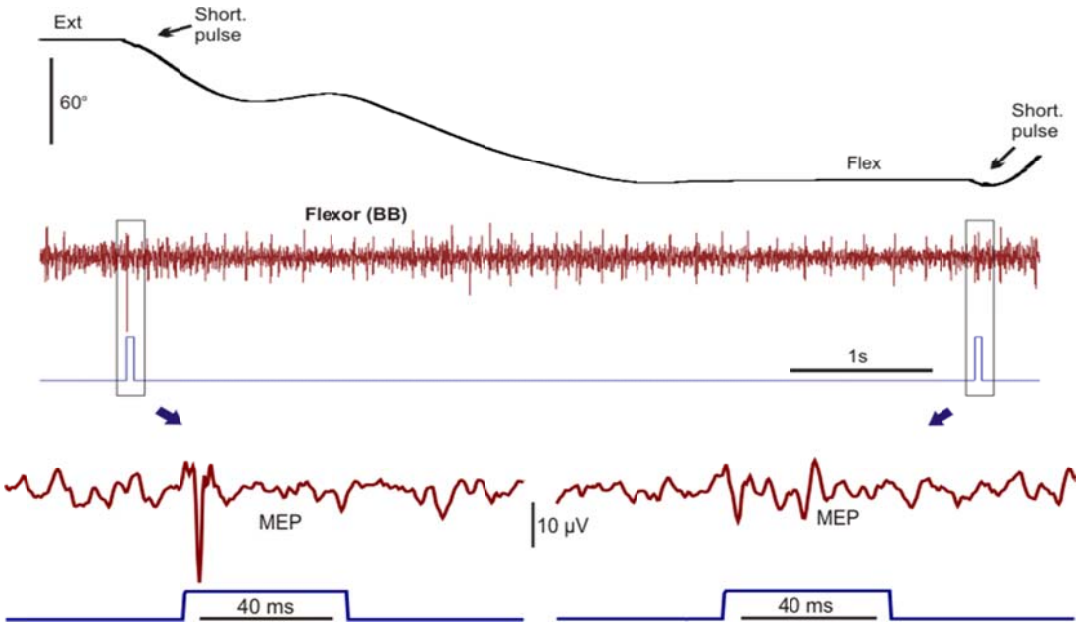

FIG. 4.15 Post-stroke patient S5. Flexor (BB) EMG response to TMS before and after passive motion from a extension to a flexion position of the elbow joint. Small indentations in the motion curve (upper curve) depict muscle shortening pulses. The light blue line represents TMS signal. The segments of signal pertaining to TMS pulses were zoomed in. The MEP amplitude at extension is barely perceptible while the one at flexion is somewhat greater.

4.2.4 MEP averages in passive movements

MEP averages were computed for all 6 post-stroke patients and were then grouped by muscle. In the figures that follow, we plotted the comparison of MEPs at each established position in passive movement trials into concise histograms. The bars in red denote MEP averages in the flexed position of the elbow, while in blue are displayed MEP averages at extension. MEP amplitudes were normalized prior to averaging, as described in the methodology section. In Figure 4.16, we present MEP averages found in flexor BB across all patients and Table 4.12 summarizes the statistically significant outcomes in MEP differences.

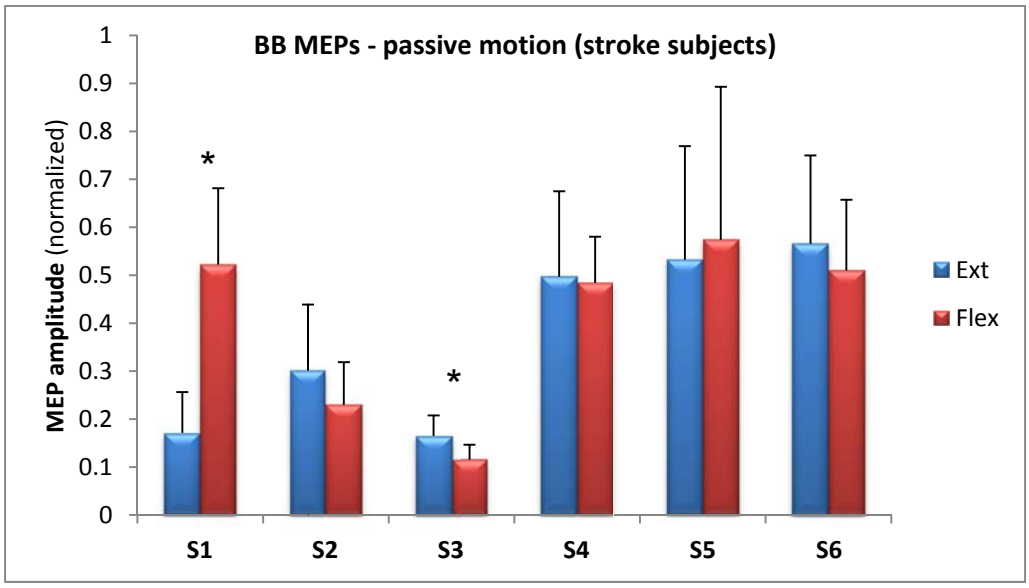

FIG. 4.16 BB MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.12 P-values for MEPs in BB, in passive movement. In 1 of 6 post-stroke patients, MEPs in BB were higher at flexion (reciprocal pattern) while in 1 of 6 MEPs in BB were higher at extension (inverted pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BB MEPs*
S1 (LT)	Yes	Student t-test	0.002	Flex > Ext
S2 (SN)	Yes	Student t-test	0.126	None
S3 (JM)	Yes	Student t-test	0.041	Ext > Flex
S4 (ML)	Yes	Student t-test	0.814	None
S5 (AM)	Yes	Student t-test	0.672	None
S6 (MC)	No	Wilcoxon	0.169	None

In Figure 4.17, we present MEP averages found in flexor BR across all patients while Table 4.13 summarizes the statistically significant outcomes in MEP differences.

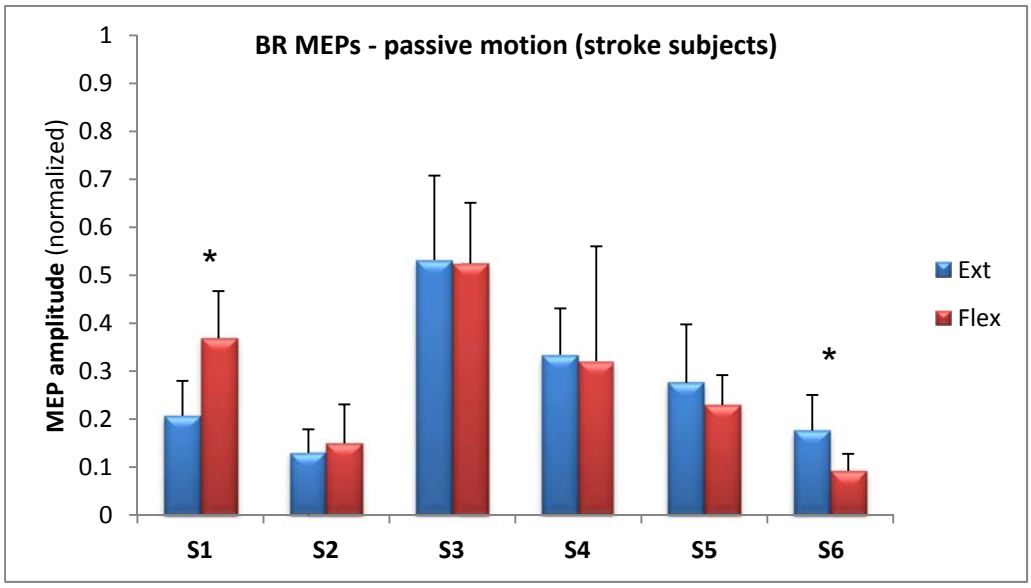

FIG. 4.17 BR MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.13 P-values for MEPs in BR in passive movement. In 1 of 6 post-stroke patients, MEPs in BR were higher at flexion (reciprocal pattern) while in 1 of 6 MEPs in BR were higher at extension (inverted pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BR MEPs*
S1 (LT)	Yes	Student t-test	0.012	Flex > Ext
S2 (SN)	No	Wilcoxon	0.445	None
S3 (JM)	Yes	Student t-test	0.895	None
S4 (ML)	Yes	Student t-test	0.850	None
S5 (AM)	Yes	Student t-test	0.142	None
S6 (MC)	Yes	Student t-test	0.002	Ext > Flex

In Figure 4.18, we present MEP averages found in flexor TL across all patients while Table 4.14 summarizes the statistically significant outcomes in MEP differences.

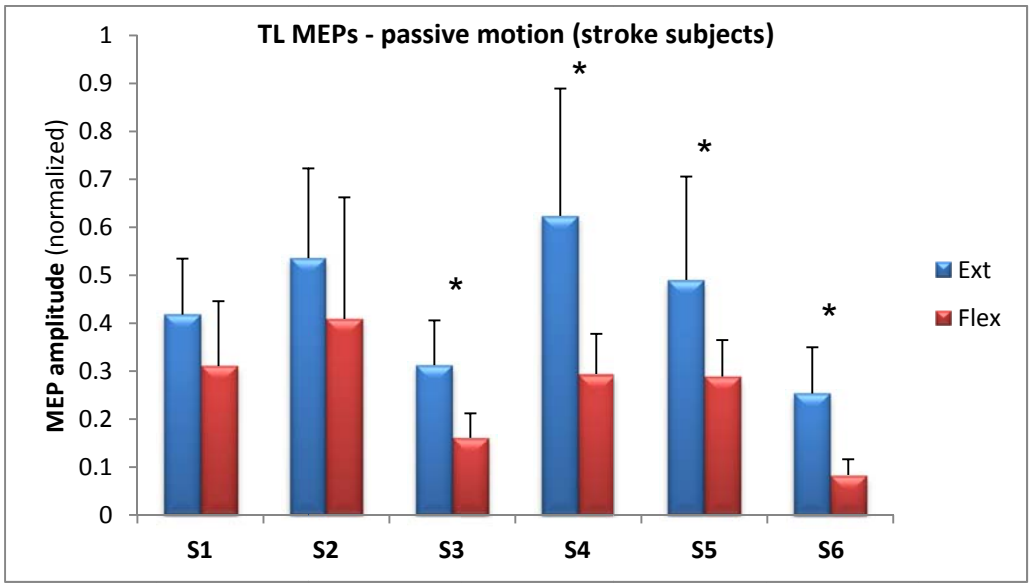

FIG. 4.18 TL MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.14 P-values for MEPs in TL in passive movement. In 4 of 6 post-stroke patients, MEPs in TL were higher at extension (reciprocal pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TL MEPs*
S1 (LT)	Yes	Student t-test	0.129	None
S2 (SN)	Yes	Student t-test	0.102	None
S3 (JM)	Yes	Student t-test	0.001	Ext > Flex
S4 (ML)	Yes	Student t-test	0.015	Ext > Flex
S5 (AM)	Yes	Student t-test	0.016	Ext > Flex
S6 (MC)	Yes	Student t-test	0.001	Ext > Flex

In Figure 4.19, we present MEP averages found in flexor TM across all patients while Table 4.15 summarizes the statistically significant outcomes in MEP differences.

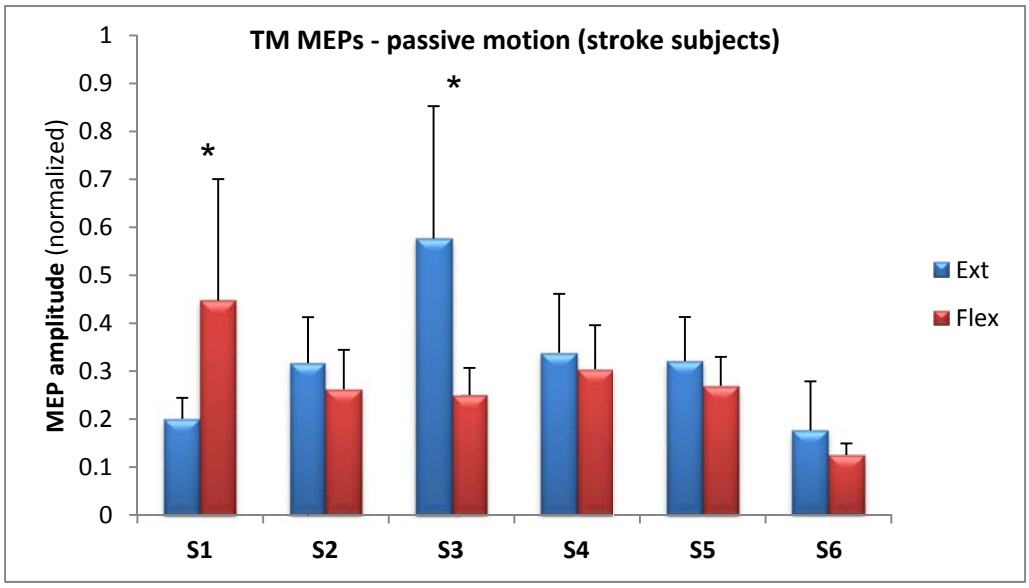

FIG. 4.19 TM MEP averages (+s.d.) at flexion (red) and extension (blue) during passive movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.15 P-values for MEPs in TM in passive movement. In 1 of 6 post-stroke patients, MEPs in TM were higher at flexion (reciprocal pattern) while in 1 of 6 MEPs in TM were higher at extension (inverted pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TM MEPs*
S1 (LT)	Yes	Student t-test	0.016	Flex > Ext
S2 (SN)	No	Wilcoxon	0.093	None
S3 (JM)	Yes	Student t-test	0.006	Ext > Flex
S4 (ML)	Yes	Student t-test	0.648	None
S5 (AM)	Yes	Student t-test	0.266	None
S6 (MC)	Yes	Student t-test	0.165	None

The latencies between the start of TMS and MEP onset were calculated and averaged for each patient. Table 4.16 displays the average MEP latencies for all patients.

TABLE 4.16 Average (±s.d.) MEP latencies for each post-stroke patient during passive movement. All muscles were included in the average.

Patient	**S1 (LT)**	**S2 (SN)**	**S3 (JM)**	**S4 (ML)**	**S5 (AM)**	**S6 (MC)**
***MEP Latency** (ms)*	29.3±6.6	31.0±5.5	32.7±4.2	25.1±5.3	25.2±5.2	23.8±4.3

4.2.5 Voluntary movement

Patients were asked next to actively move the arm, in spite of the difficulties imposed by spasticity. Figure 4.20 presents the EMGs in one subject with considerable spasticity in both flexors and extensors.

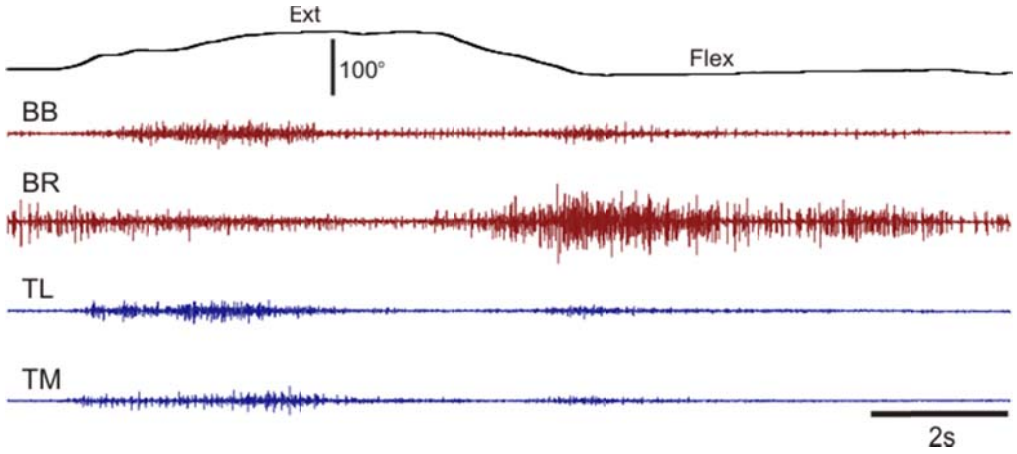

FIG. 4.20 EMGs during voluntary movement in a post-stroke patient (S5). The motion curve (black) depicts the F→E→F direction. At extension, spasticity is inspected in flexors (BB & BR) although all muscles are active; this is the coactivation pattern. At flexion, there is some spasticity in extensors and a high activity in flexors; this forms a coactivation pattern as well.

As the elbow joint extends, both flexors enter the spasticity zone and become very active. The extensors counter this resistance, leading to a coactivation pattern. The same applies, although to a lesser extent in flexion, where spasticity in the extensors seems less marked. In this case, flexors (especially BR) gain a significant increase in EMG activity in response to extensor spasticity, producing once more a coactivation pattern. The increase in BR activity could also be a compensatory mechanism to assist weakness in BB (as seen in the clinical evaluation of this patient). This coactivation pattern is in stark contrast to the one observed in healthy subjects, where a reciprocal pattern of activation was seen.

4.2.6 Active motion with TMS and motor perturbations

Figure 4.21 depicts MEP responses in 2 separate trials during voluntary movement.

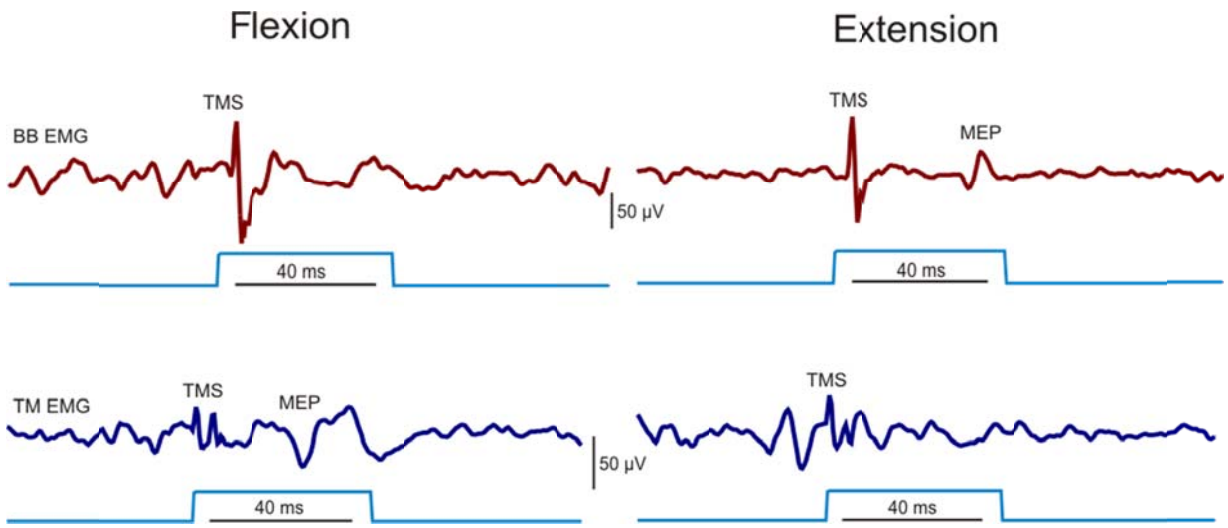

FIG. 4.21 Patient (S1) EMG responses of the BB flexor (red) and the TM extensor (dark blue) to TMS before and after active motion from an elbow flexion to an extension position, in two separate trials. The light blue line represents TMS signal. In the case of BB, the MEP is clearly seen at the extension position although it is barely visible at flexion. In the case of TM, the MEP at flexion is clearly greater than the one at extension (barely visible). This patient's TM extensor enters its spasticity zone while the elbow is flexed.

The TM extensor MEP at flexion is higher in amplitude than at extension, as portrayed by Figure 4.21. This is a clear sign of spasticity in the extensor. The results show that corticospinal influences cannot inhibit the facilitation of extensors (antagonist) when the muscle is in its spasticity zone. No inferences can be made about the MEP amplitudes of the BB flexor as no perceptible difference in amplitude can be observed.

4.2.7 MEP averages in voluntary movements

The same calculations were made as described in the previous section, this time in the case of voluntary movement. In Figure 4.22, we present MEP averages found in flexor BB across all patients. The histogram below displays MEP patterns in BB. Differences at both established positions can be clearly observed in S1, where MEPs are higher at flexion (S2 suffers from too much variability). Table 4.17 summarizes the statistically significant outcomes in MEP differences.

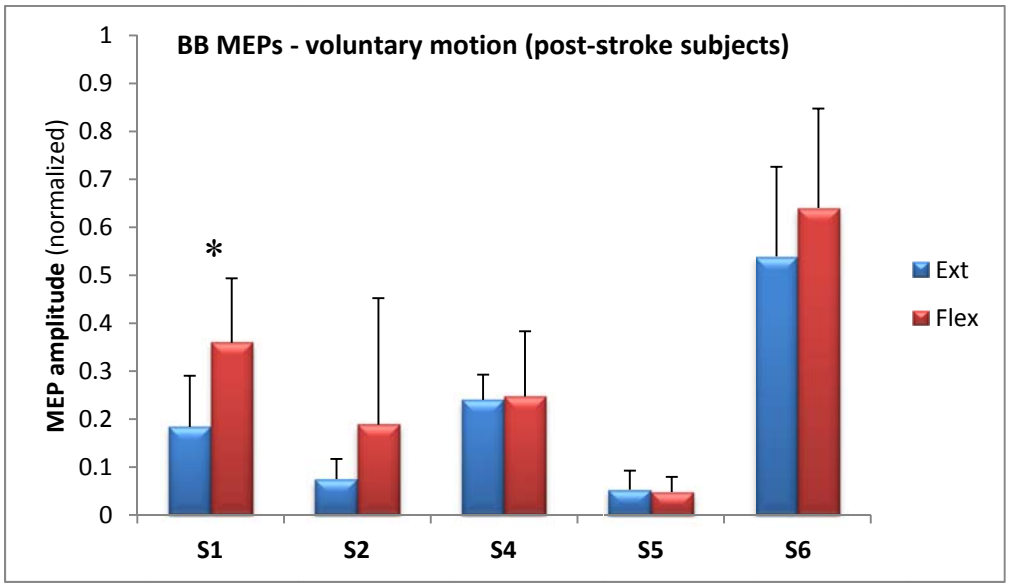

FIG. 4.22 BB MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 5 post-stroke patients (patient S3's data was discarded due to poor EMG acquisition). Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.17 P-values for MEPs in BB in voluntary movement. In 1 of 5 post-stroke patients (patient S3's data was discarded), MEPs in BB were higher at flexion (reciprocal pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BB MEPs*
S1 (LT)	No	Wilcoxon	0.013	Flex > Ext
S2 (SN)	No	Wilcoxon	0.117	none
S4 (ML)	No	Wilcoxon	0.959	none
S5 (AM)	Yes	Student t-test	0.776	none
S6 (MC)	Yes	Student t-test	0.091	none

The tabled data confirms that a reciprocal pattern of activation in BB MEPs only occurs in one patient (S1). We note that these results contrast with those observed in healthy subjects, notably that a majority (6 of 7) had a reciprocal pattern of corticospinal facilitation (higher MEPs at flexion). Figure 4.23 displays MEP averages for flexor BR across all patients. A quick glance reveals that in possibly 3 cases (S4 being too variable for statistical significance), BR MEPs are higher at flexion. Table 4.18 summarizes those findings.

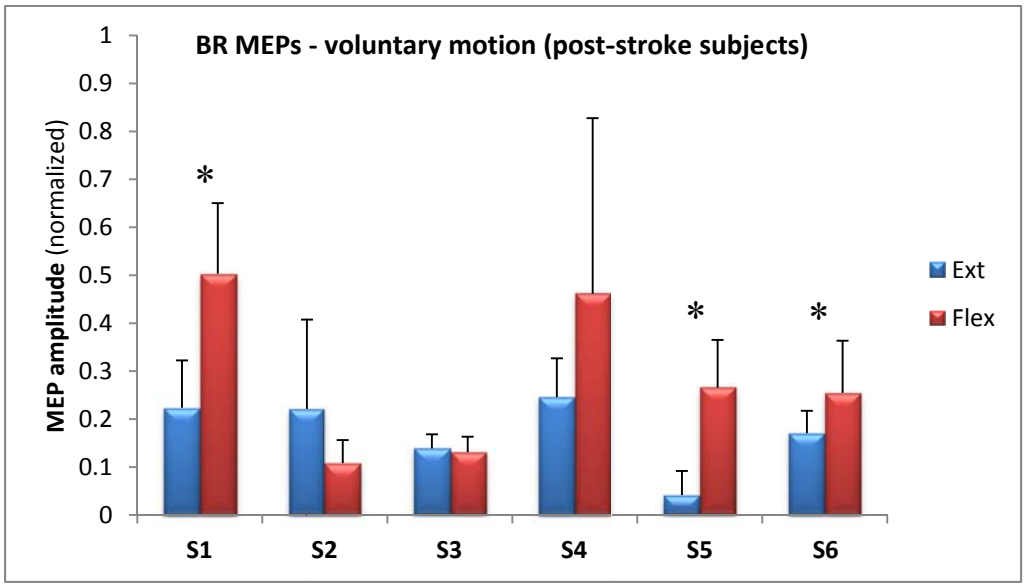

FIG. 4.23 BR MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.18 P-values for MEPs in BR in voluntary movement. In 3 of 6 post-stroke patients, MEPs in BR were higher at flexion (reciprocal pattern).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of BR MEPs*
S1 (LT)	No	Wilcoxon	0.005	Flex > Ext
S2 (SN)	No	Wilcoxon	0.117	none
S3 (JM)	Yes	Student t-test	0.377	none
S4 (ML)	No	Wilcoxon	0.285	none
S5 (AM)	No	Wilcoxon	0.005	Flex > Ext
S6 (MC)	No	Wilcoxon	0.022	Flex > Ext

The table above confirms that 3 out of 6 subjects have higher MEPs at flexion (while no differences were observed in the others). It is interesting to note that this reciprocal pattern of facilitation occurred more frequently than in the case of healthy subjects. Figure 4.24 shows MEP averages for extensor TL across all patients. Although no concordance of MEP patterns can be observed in the histogram below, some differences can be keenly observed. Table 4.19 outlines the statistically significant outcomes.

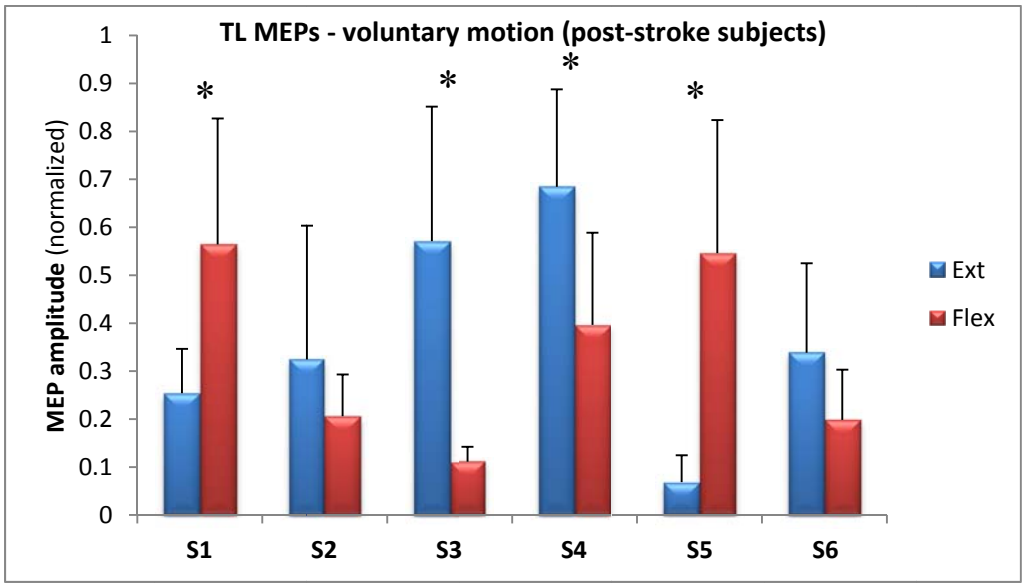

FIG. 4.24 TL MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.19 P-values for MEPs in TL in voluntary movement. In 2 out of 6 patients, MEPs in TL were higher at extension (reciprocal pattern). In 2 out of 6 patients, MEPs were higher at flexion (inverted pattern, shown in boldface).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TL MEPs*
S1 (LT)	No	Wilcoxon	0.005	**Flex > Ext**
S2 (SN)	No	Wilcoxon	0.347	None
S3 (JM)	Yes	Student t-test	0.001	Ext > Flex
S4 (ML)	Yes	Student t-test	0.030	Ext > Flex
S5 (AM)	Yes	Student t-test	0.001	**Flex > Ext**
S6 (MC)	Yes	Student t-test	0.062	None

The results in the table above confirm MEP differences at both positions in 4 out 6 patients. In 2 patients (S3 & S4), MEPs were higher at extension, inferring a reciprocal pattern of corticospinal facilitation. In the other 2 patients (S1 & S5), MEPs were higher at flexion, indicating corticospinal facilitation at flexion, when TL was in the spasticity zone. Figure 4.25 illustrates MEP averages in extensor TM across all patients. Differences can be seen in at least 3 instances from the histogram below. Table 4.20 confirms those findings.

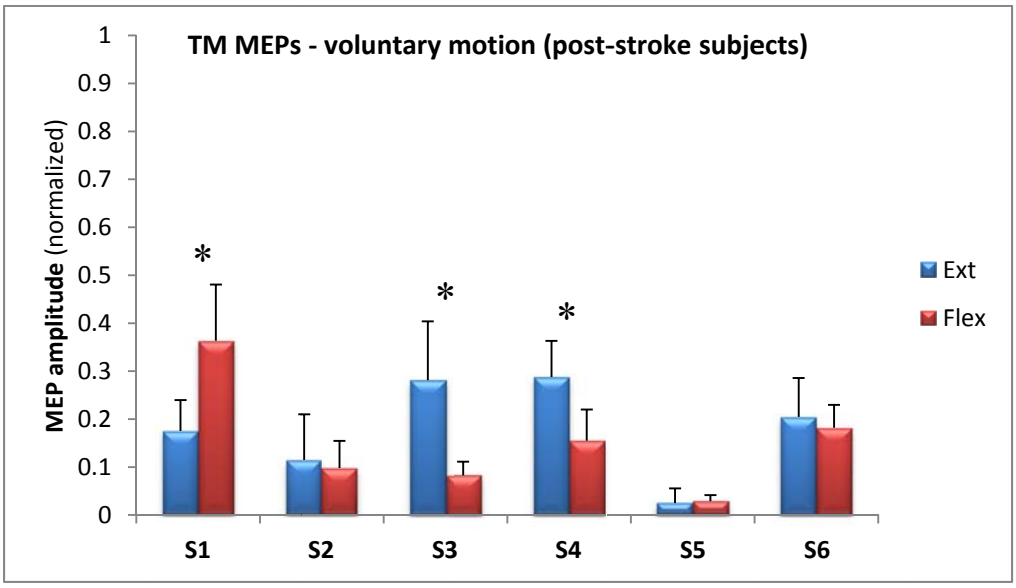

FIG. 4.25 TM MEP averages (+s.d.) at flexion (red) and extension (blue) during voluntary movement in 6 post-stroke patients. Asterisks denote $p<0.05$ significant differences in MEPs at both positions.

TABLE 4.20 P-values for MEPs in TM in voluntary movement. In 2 out of 6 patients, MEPs in TM were higher at extension (reciprocal pattern). In 1 out of 6 patients, MEPs were higher at flexion (inverted pattern, shown in boldface).

Patients (initials)	*Normal dist. of MEPs (flex & ext)?*	*Statistical test used*	*p-value*	*Statistically significant outcome of TM MEPs*
S1 (LT)	Yes	Student t-test	0.001	**Flex > Ext**
S2 (SN)	No	Wilcoxon	0.875	none
S3 (JM)	Yes	Student t-test	0.001	Ext > Flex
S4 (ML)	Yes	Student t-test	0.001	Ext > Flex
S5 (AM)	No	Wilcoxon	0.333	none
S6 (MC)	Yes	Student t-test	0.253	none

The results above confirm that 2 out of 6 patients had TM MEPs higher at extension (reciprocal pattern of corticospinal facilitation) versus one patient who had higher MEPs at flexion (inverted pattern).

4.2.8 Individual analysis of MEPs during voluntary movement

MEP latencies, expressed as individual averages, were computed and are presented in Table 4.21. The average latencies in post-stroke patients were decidedly greater compared with those of healthy subjects.

TABLE 4.21 Average (±s.d.) MEP latencies for each post-stroke patient during voluntary movement. All muscles were included in the average.

Patient	**S1 (LT)**	**S2 (SN)**	**S3 (JM)**	**S4 (ML)**	**S5 (AM)**	**S6 (MC)**
MEP Latency *(ms)*	33.3±5.8	31.5±6.4	31.8±4.8	23.9±6.3	27.5±5.1	28.9±6.1

Results for patient S1 (LT) show that flexor (BB & BR) MEPs are higher at flexion while extensor (TL & TM) MEPs are also higher at flexion. Since extensors λ- is exceeded when the elbow joint in fully flexed, extensors are in their spasticity zone and their MEPs reflect corticospinal facilitation at that position. Flexor MEPs are higher at flexion since more effort is needed to counter the resistance of the spastic extensors. Together these results produce a co-facilitation pattern of corticospinal influences.

Patient S2 (SN) exhibited no statistically significant differences throughout all muscles. No patterns of corticospinal influences can be inferred.

Patient S3 (JM) had extensor (TL & TM) MEPs that were higher at extension while no differences in flexor MEPs were observed. This reflects a reciprocal pattern of corticospinal influences, similar in some ways to what was observed in healthy subjects (with the difference that at least one flexor had a reciprocal pattern of MEPs). The strong similarity to the control case is comprehensible, as very mild spasticity had been clinically detected in this patient.

A similar pattern of activation arises in patient S4 (ML). Once more, extensor (TL & TM) MEPs were higher at extension while no differences were seen in flexor MEPs. The reciprocal pattern reflecting the case of control subjects is once again, explained by the fact the patient was assessed a low clinical spasticity score.

Patient S5 (AM) had extensor (TL) MEPs higher at flexion while flexor (BR) MEPs were higher at flexion. The other muscles displayed no MEP differences. However, the results point to a co-facilitation pattern of corticospinal influences, similar to those of patient S1. These results are validated by the fact both patients were assessed high spasticity scores in the extensors.

Patient S6 only displayed higher MEPs at flexion for BR, while no statistically significant differences were observed elsewhere. No clear pattern of corticospinal influences can be inferred. Table 4.22 attempts to classify all post-stroke patients according patterns of corticospinal influences.

TABLE 4.22 Classification of patients' MEP responses into patterns of corticospinal influences. We note the similarities between S1 and S5; between S3 and S4. S2 and S6 have no particular pattern.

Pattern / Patient	1 (LT)	2 (SN)	3 (JM)	4 (ML)	5 (AM)	6 (MC)
Coactivation	✓				✓	
Reciprocal			✓	✓		
No clear pattern		✓				✓

4.3 Overview of major findings

Healthy subjects produced little to no EMG responses in the arm muscles during passive movements throughout the whole range of motion of the elbow joint. At flexion and extension positions established passively by the experimenter, no significant differences in MEP amplitudes were recorded, with the exception of MEPs in BB (in 5 of 7 subjects) and TL (in 4 of 7 subjects) which were stronger in both cases at the flexion position. There seems to be a reciprocal pattern of activation in both BB and TL. In voluntary movement, subjects produced a reciprocal pattern of activation, marked by increased agonist EMG levels while antagonist EMG levels remained minimal. At actively established positions, MEP responses in BB were greater at flexion in 6 of 7 subjects whereas those in TM were greater at extension in 4 of 7 subjects.

In contrast, ***post-stroke patients*** with spasticity produced an increased EMG response in the arm muscles during passive movements in certain angular ranges of the elbow joint. These angular ranges are spasticity zones, in which muscle activity and resistance to stretching was present despite the instruction to fully relax muscles. 4 of 6 patients had spasticity flexor muscles, 3 of 6 had spasticity in extensor muscles and 2 of 6 had spasticity in both. At elbow positions established passively, differences in MEP responses varied across post-stroke patients. In patient S1 (LT), MEPs were higher at flexion in BB and BR. These results correspond to the coactivation pattern observed in active movement. In patient S3 (JM), MEPs were higher at extension in TL and TM. These results were linked to a reciprocal pattern in active movement.

The presence of a spasticity zone in a muscle might be accompanied by coactivation of the antagonist muscle. Each patient had a distinct pattern of spasticity, which made

classification challenging. Coactivation, however, was hardly avoidable in active movement in post-stroke subjects since the presence of spasticity causes higher activity in agonists to overcome the resistance to movement. A coactivation pattern could be seen in 4 of 6 patients (all 4 having moderate to severe spasticity, according to the clinical scale).

At elbow positions established actively, MEPs significantly differed at flexion and extension positions. Reciprocal patterns, such as the ones seen in healthy subjects, were observed in two patients (S3& S4) with mild spasticity. These patterns, seen in both extensors (TL and TM), seem to corroborate with the near-absent spasticity in the extensors of both patients. No differences however, were observed in flexor MEPs, unlike the case of healthy subjects, where an overwhelming majority had a reciprocal pattern in the BB flexor. A coactivation pattern was observed in two other patients (S1 & S5), characterized by higher MEPs at flexion in flexor and extensor muscles. MEP responses for patients S2 and S6 did not show any clear patterns.

We notice that the coactivation pattern seen in some post-stroke patients is absent in healthy subjects, who had a reciprocal pattern in at least one flexor and one extensor muscle (4 of 7 subjects). There were few significant MEP differences across post-stroke patients. In flexor muscles, MEPs were higher at flexion only in patients with a coactivation pattern (2 of 6). In extensors, MEPs were higher at flexion in patients with as coactivation pattern (2 of 6) and higher at extension in patients with a reciprocal pattern (2 of 6). The absence of reciprocal patterns across post-stroke patients, notably in the case of BB, is already in itself an indicator that corticospinal influences are producing different patterns than those expected in healthy individuals.

5. DISCUSSION

5.1 Hypothesis confirmation

According to the main hypothesis, corticospinal influences are responsible for the establishment of the range of regulation of the stretch reflex threshold, thereby setting the angular range of a joint where muscles can activate or relax depending on the task demands. The limitation in the range of stretch reflex threshold regulation is responsible for spasticity. Deficits in corticospinal influences in post-stroke patients are likely responsible for the decrease in the range of reflex threshold control. This accounts for the spatial zones associated to spasticity that were observed in 5 of 6 post-stroke patients.

The results clearly show that in healthy subjects, corticospinal influences associated with active changes in the arm position followed a reciprocal pattern for flexor (BB) and extensor (TM) motoneurons. They are consistent with findings based on the wrist joint (Raptis, 2010). Although nothing could be deduced from the study of the BR and TL muscles, the results do not contradict the expected reciprocal pattern; insufficient statistical significance was mostly responsible for the lack of MEP differences between both actively established positions. In the case of post-stroke subjects, no group tendency could be seen as results varied from one individual to the next and therefore characterized separately according to the presence of coactivation and/or reciprocal patterns.

Corticospinal influences are the key contributor to position resetting in voluntary movement. It is not known to what extent other descending pathways also influence voluntary movement. When TMS targets the M1 area, corticospinal neurons are directly affected by the stimulation. The stimulated neurons may then send collaterals to neurons in other descending systems such as the rubrospinal or reticulospinal tracts (Keyzer, 1989), which can combine together to influence the threshold position resetting (Raptis et al. 2010).

It has been confirmed previously that the reciprocal Ia inhibitory pathway is involved in ensuring that antagonist muscles remain relaxed when agonist muscles are activated during voluntary movement (Nielsen, 2007). The development of spasticity after stroke would account for reduced spinal inhibitory mechanisms. We made our best attempts to equalize

motoneuronal excitability through the muscle shortening technique in order to isolate the corticospinal contribution during voluntary movement. Despite this, we cannot exclude the possibility that spinal interneurons may also contribute in the establishment of reciprocal inhibition in healthy persons or to a reduced inhibition in patients with spasticity.

The reciprocal patterns of activation found in healthy and post-stroke subjects show that corticospinal influences differ at different voluntarily established elbow positions. This difference in MEPs at flexion and extension can occur whether EMG levels are equivalent or not at both positions. In contrast, internal model representations of motor control strongly suggest that EMG levels reflect corticospinal influences (Bhushan, 1999). That is, if EMG levels are null, descending influences should be low, and vice versa, if EMG levels are high, it is as a direct result of an increase in descending influences. EP theory proposes that corticospinal influences do not impact EMG activity directly in voluntary control of movement, but rather, the EMG activity emerges depending on threshold position resetting and the current kinematic and kinetic events on the periphery. Using EMG compensation as a technique to equalize EMG levels at the flexion and extension positions of the wrist joint, Raptis et al. (2010) found clear differences in corticospinal influences at different wrist positions established actively. The reciprocal patterns observed in that study clearly showed that EMG levels did not correlate with corticospinal influences.

The internal model approach does not satisfactorily explain why corticospinal influences differ when EMG activity levels at two positions are equal. This shows that the internal model approach is incorrect in its statement that displacement towards a new position necessarily involves direct computation of movement kinematics and EMG activity. Although our study did not employ EMG equalization, use of the muscle shortening technique eliminated the effect of motoneuronal excitability from the resulting MEPs, which was sufficient to isolate the corticospinal component of MEPs.

As far as the MEPs in passive movement are concerned, we already mentioned that healthy subjects exhibit reciprocal patterns of activation in the case of the BB muscle. Some MEP differences were observed in TL, but an inverted pattern was observed. In the case of post-stroke patients, it was noted that patient S1 had MEP patterns that matched those in voluntary movement and similarly, S3 had similar patterns seen in voluntary movement as well. Passive movements imply a relaxed state of muscles. Descending systems act to de-

facilitate or inhibit the agonist and antagonist pair of the joint (Lemon, 2008). Given the MEP patterns observed in both groups of subjects, we may be led to believe that corticospinal influences may strongly modulate passive movement. However, the differences perceived in MEPs at differently established positions may reflect the influences of other descending systems.

5.2 Impact of movement direction on MEPs

We investigated the possibility that direction of arm motion during voluntary movement between flexion and extension positions could potentially change MEP results at both positions. We separately classified flexor MEP amplitudes at both positions when movement was initiated at extension and ended at flexion (E→F) or when motion progressed in the opposite direction (F→E). In healthy subjects, movement direction essentially did not cause any change in the outcome of the MEPs at either position in any of the muscles. In this sense, TMS responses reflected corticospinal influences at specific positions rather than the history of movement trajectory (Raptis, 2010).

In one post-stroke patient (S2) with considerable spasticity in both flexors and extensors, we compared flexor MEPs in the E→F versus F→E directions. In the E→F case, MEPs in flexors were much higher at flexion than at extension, indicating either a reciprocal pattern or one of co-facilitation. In the F→E case, MEPs in flexors were found to be higher at extension, a result that is concordant with spasticity in the flexors. This pattern shows once again that spasticity forces this subject to overcome resistance to active motion, resulting in a prevailing coactivation pattern of corticospinal influences. By separating recorded MEPs by direction of motion, we may actually perceive the presence of coactivation or reciprocal patterns of corticospinal influences, as is the case of patient S2. Movement direction may thus influence the resulting MEP patterns as seen in this case. Under this perspective, S2 exhibits patterns of corticospinal co-facilitation that resemble those seen in patients S1 and S5.

5.3 Limitations of the study

Our study compiled a mere 6 post-stroke patients and 7 control subjects. The small number of subjects, particularly in the post-stroke cases, does not permit a generalization of

the observed results. A minimum number of 10 post-stroke patients would have been more satisfactory, although it is possible that the inter-variability between post-stroke subjects would have made it too difficult to generalize results, even if the number of subjects were higher. In many instances, high variability between trials in each subject made it difficult to achieve statistically significant MEP differences at flexion and extension positions. Had there been less variability, more reciprocal patterns would have been confirmed in the muscles studied across healthy subjects. Also, the use of motor perturbations limited the study of MEPs to either flexors or extensors at any one time, depending on whether the perturbation went in the flexion or extension direction. This allowed only 50% of the number of trials to culminate into the computation of MEP averages at both positions. This reduces outright the statistical power of the calculated variables (MEP amplitudes, latencies). Remedying this problem may be approached by increasing the number of trials, to the detriment of the experimental protocol.

The amount of torque applied for each motor perturbation is another element that could alter the results. The same force of 0.5 Nm was used for all motor pulses, in both extension and flexion directions, across all subjects to maintain consistency. Values ranging between 0.1 to 0.3 Nm were potent enough to elicit a silent period in the EMG responses in the muscles of the wrist joint (Sangani, 2011). In the case of the elbow joint, a higher value was needed to create a substantial perturbation. In hindsight, we cannot be sure that the chosen value of 0.5 Nm was optimal for eliciting a silent period in the EMGs of every subject. Perhaps the only way to produce a silent period would be to test several force levels until the desired result is accomplished in each subject. This customized fine-tuning, while helpful in eliciting MEP within a background of minimal motoneuronal excitability, could considerably lengthen the experiment's duration.

The use of compensatory forces in both directions of movement, acting as assistance to flexion and extension of the arm, would enable EMGs to remain in low levels of activity throughout the trial. The mechanical setup in our lab was unfortunately improperly suited to ensure EMG equivalence during the time frames TMS was applied, creating far too few trials in which EMG levels were equal at both positions. A correction in the equipment's setup could solve this issue. This would ultimately permit the capture of MEPs across all 4 muscles

at each TMS pulse, optimizing the experiment's effectiveness. However, the method would complement, not replace, the muscle shortening technique.

Conclusion

Corticospinal influences are at the foundation of voluntary movements in humans. By facilitating or inhibiting descending pathways, voluntary movement can be accomplished by adjusting the necessary muscle forces required for the limb to perform a task. The Equilibrium Point theory proposes a model based on stretch reflex threshold resetting to explain why muscle activation or relaxation can occur at any angular range of the joint. Healthy subjects have the ability to regulate the threshold through a range R that encompasses the full biomechanical range of the joint. The reciprocal patterns that were consistent in at least two of the recorded muscles (BB and TM) across all healthy subjects confirms that corticospinal influences act to inhibit or facilitate muscle activity as per the voluntary wish of the individual as a movement is initiated. In 3 of 6 post-stroke patients, a pattern of coactivation emerged. Spasticity is typically characterized by this pattern. It occurs because the R range of antagonist muscles is narrower than that of a healthy individual. The CNS cannot exercise an inhibiting influence beyond a threshold that lies *within* the biomechanical range of the joint. The facilitating influence that occurs instead causes a heightened muscular activity in this zone, regardless of the individual's desire to activate or relax a given muscle.

Spasticity hampers body movement and interferes with activities of daily living. Currently, rehabilitation permits limited recovery in most patients through physiotherapy and drug treatment. The lack of more effective treatments derives from a lack of understanding of the causes of spasticity. The present work attempted to explain this phenomenon by studying its neurological origin. The conclusions of our study show that patterns of corticospinal influences are altered in patients with spasticity. These different patterns are causal to the generation of spasticity, which can later worsen through changes in physical properties of muscle and other tissues of the joint. The contention that spasticity results from altered corticospinal influences provides a new perspective through which one could assess and attempt to treat spasticity.

Assessing EMG responses to passive movement can provide a first-hand extent of spasticity in a given muscle. Integrating TMS in the clinical realm would allow the study of patterns of corticospinal influences in patients with spasticity. A novel tool, repetitive TMS

(rTMS), is now considered as a potential therapeutic alternative in the recovery of some movement disorders. By applying low frequency trains of pulses on the unaffected hemisphere of a stroke patient, it was found that reactions times and dexterity of the affected hand had improved (Mansur, 2005).

Notwithstanding the potential benefits rTMS holds for the future, if the integration of TMS proves financially unfeasible for now, a low-cost alternative would consist in simple EMG recording equipment. This would allow the clinician to closely monitor the patient's threshold angles of activation on a daily basis, to verify whether physiotherapy and other interventions are helping reduce the range of the spasticity zone. Such a measure would be critical in the decision to pursue actual treatment if there is improvement, or to adopt another treatment if no recovery is noticed.

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