Examination of Two Novel Therapies for Enhancing Motor Ability in Chronic Stroke Patients Using Behavioural Measurements and Transcranial Magnetic Stimulation

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- Abstract -

Rehabilitation techniques are currently the major therapeutic approach for helping stroke patients recover from hemiparesis, yet the neurophysiological mechanisms underlying their effectiveness are poorly understood. In the present investigation, chronic stroke patients were chosen at least one year after stroke and received either Mirror Therapy (Altschuler et al., 1999) or Constraint-Induced (CI) Movement Therapy (Taub et al., 1993). Motor improvements were examined in parallel with transcranial magnetic stimulation (TMS) and electromyography (EMG). TMS was combined with EMG to record *recruitment curves* and *silent periods* induced by direct stimulation of the motor cortex before and after treatment. The data revealed that motor ability gained with CI Therapy was particularly impressive, and that neurophysiological patterns of recovery may differ with respect to pathology. Data obtained in two patients with capsular lesions acquired in adulthood suggest the involvement of ipsilateral pathways in recovery mechanisms. By contrast, data from a patient with perinatal lesions in the thalamus and the red nucleus area suggest involvement of contralateral pathways in recovery mechanisms.

- Résumé -

Les techniques de réhabilitation sont couramment l'approche thérapeutique principale pour aider les patients atteints d'accident cérébrovasculaire (ACV) à récupérer de leur hémiparésie, pourtant les mécanismes neurophysiologiques sous-jacents sont mal compris. Dans la présente étude, des patients ayant subi un ACV depuis au moins un an ont été choisis et ont reçu soit la thérapie du miroir (Altschuler et al., 1999) ou la thérapie de mouvement incité par contention (Taub et al., 1993). Leurs améliorations motrices mesurées ont été examinées en parallèle avec la stimulation magnétique transcrânienne (SMT) et l'électromyographie (EMG). La SMT a été combiné avec l'EMG pour enregistrer les *courbes de recrutement* et les *périodes de silence* induites par la stimulation directe du cortex moteur avant et après traitement. Les données révèlent que les améliorations motrices gagnées à la suite de la thérapie de mouvement incité par contention ont été particulièrement impressionnantes, et que les mécanismes de récupération diffèrent selon la pathologie. Les données provenant de patients avec des lésions capsulaires acquis a l'âge adulte, suggèrent une participation des voies ipsilatérales. Au contraire, les données d'un patient avec des lésions périnatales dans le thalamus et la région du noyau rouge suggèrent une prépondérance des voies contralatérales.

- Acknowledgements -

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- Abbreviations -

95-CI	95% Confidence Intervals
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AOU	Amount of Use
AOUT	Amount of Use Test
CBF	Cerebral Blood Flow
CNS	Central Nervous System
CI Therapy	Constraint-Induced Movement Therapy
EMG	Electromyography
FA	Functional Ability
FDI	First Dorsal Interosseous
IQ	Intelligence Quotient
TMS	Transcranial Magnetic Stimulation
MAL	Motor Activity Log
MEG	Magnetoencephologography
MEP	Motor Evoked Potential
MR	Magnetic Resonance
PET	Positron Emission Tomography
M1	Primary Motor Cortex
r	Pearson's Correlation Coefficient
RC	Reliability Coefficient

TPA	Tissue Plasminogen Activator
QOM	Quality of Movement
WAIS-R	Weschler Adult Intelligence Scale-Revised
Wolfe	Wolfe Motor Function Test

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Food and Drug Administration in 1996 and has proven to be effective (Peraira et al., 2001). Unfortunately, TPA must be administered within a three-hour time window to maximize its efficacy. Often stroke victims are not admitted to a hospital expeditiously, and therefore the majority do not benefit from TPA and are afflicted with significant stroke injury, which is manifest over the remaining life span.

In the monkey, a good model for the study of stroke, the effects are well documented (e.g. Liu and Rouiller, 1999). Although deficits persist for three to four months, significant recovery of manual dexterity takes place without therapeutic intervention. Spontaneous recovery is also observed in humans but is thought to plateau by six months. Such recovery is thought to involve acute neurophysiological processes that lead to recovery of the functionality of affected tissue in the penumbra, a region in and around the site of injury (Nudo, 1999). Current physical rehabilitation regimens aim to take advantage of these adaptive processes within the months immediately following trauma in order to maximize outcome using behavioural therapy. Residual motor deficits are conventionally considered more or less permanent one year following a stroke because the possibility that damaged tissue in the penumbra can regain function is diminished (Parker et al., 1996). In certain cases, however, enhancement in motor abilities can persist for years, and must therefore involve other processes (Nudo, 1999).

Current behavioural measurements provide little information on the neurophysiological patterns of recovery. For example, behavioural measurements that examine recovery at the disability level (i.e. activities of daily living) fail to address the effects of compensatory movements and may record improvement regardless of whether there is amelioration in stroke deficits (Nakayama et al., 1994). Although certain behavioural measurements such as the Fugl-Meyer assessment scale (Fugl-Meyer et al., 1975) attempt to delineate more precisely impairments specific to different muscle groups, precision is limited to what the trained therapist can observe. With current advances in electrophysiological and imaging techniques, new possibilities are emerging for measuring functional recovery that provide not only greater precision of measurements, but also a basis for understanding neurophysiological patterns of recovery. Mechanisms of recovery are poorly understood, and finding a central nervous system (CNS) correlate of motor improvement might enhance the search for a more effective treatment strategies.

One electrophysiological technique that has received much attention of late is transcranial magnetic stimulation (TMS). During TMS, a brief current is passed through a coil, which is placed on the scalp, that induces a rapid rise of magnetic field, and this field can in turn induce a current in underlying brain tissue. TMS is a powerful tool for assessing CNS function because it allows reversible modulation of cortical activity. Some of its applications include the study of cognition (Walsh and Cowey, 1998), the treatment of depression (Post et al., 1999), and the examination of motor physiology (Chen, 2000). Mapping of the primary motor cortex (M1) is a widely used TMS method for examining motor plasticity. It involves stimulating different positions over the skull and noting those positions where motor evoked potentials (MEP) are induced in a muscle, as recorded by electromyography (EMG); thus a motor cortical representation can be delineated (Wassermann et al., 1992). However, the interpretations that can be drawn are limited by the technique, and in this regard, TMS mapping has limited spatial resolution. Furthermore many mapping studies rarely report EMG data in parallel with derived motor cortical maps. EMG has excellent temporal resolution, and when combined with TMS can provide valuable data on motor pathways arising from primary motor cortex (M1) all the way to the contralateral muscle it activates.

Lesions in the CNS that create movement impairment most often compromise motor pathways activating muscles. One method that might be used to study both the integrity of the motor system and the putative effects of rehabilitative procedures is to monitor changes in the relationship between increasing intensities of TMS and measurements of induced muscle activity recorded by EMG, before and after a given rehabilitation therapy. The relationship of MEPs as a function of increasing TMS intensity corresponds to the *recruitment curve*, and this represents the extent to which the pool of alpha motor neurons is activated with increasing TMS intensities (Cohen et al., 1998). By comparing differences in *recruitment curves* between sessions, it is possible to extrapolate whether there are changes in corticospinal excitability. On the other hand, the *silent period* is a neurophysiological phenomenon induced when TMS is applied to M1 during voluntary contraction of the muscle of interest, and is characterized by suppression in EMG activity driven by local inhibitory interneurons in M1 as well as inhibitory mechanisms in the spinal cord (Hallett, 1996).

Recently, two novel rehabilitation techniques have been employed to drive enhanced motor ability following stroke: 1) Mirror Therapy (Altschuler et al., 1999), and 2) Constraint-Induced (CI) Movement Therapy (Taub et al., 1993). In Mirror Therapy, patients use a mirror that hides their weak arm and provides in its place a seeing the reflection of the movement of their good arm (Figure 1). In this way, an illusion was created such that the weak arm appeared to the patient as a fully functional arm. The authors postulated that enhanced performance is in part due to the recruitment of premotor areas, known to be active during the observation of arm movements (Rizzolatti et al., 1996a,b).

The experimental design used by Altshuler and colleagues (1999) was not ideal because it failed to establish whether the mirror was responsible for observed motor enhancements. In Altschuler and colleagues's (1999) study, a double-crossover design was used in which all patients completed exercises at home and they were either randomly assigned to spend the first four weeks using either a mirror or a transparent plastic sheet, and then crossed-over to the other treatment for the next four weeks. Although this design compares the mirror treatment to a treatment that does not use a mirror, it fails to control for the effects of repetitive training. A research design that consists of separate groups that either used or did not use a mirror, and groups that either used or did not use their stroke-affected arm would better define the effects of repetitive training. The mirror may have had a greater effect over the transparent sheet simply because patients were encouraged to train more.

In CI Therapy (Taub et al., 1993), patients are encouraged to use their affected arm in activities of daily living (ADL) by restraining the use of the good arm, and in addition undergoing shaping exercises geared towards improving function of the affected arm. Shaping refers to the substantial practice of a given movement that is approached in small steps of progressively increasing difficulty. The theoretical basis

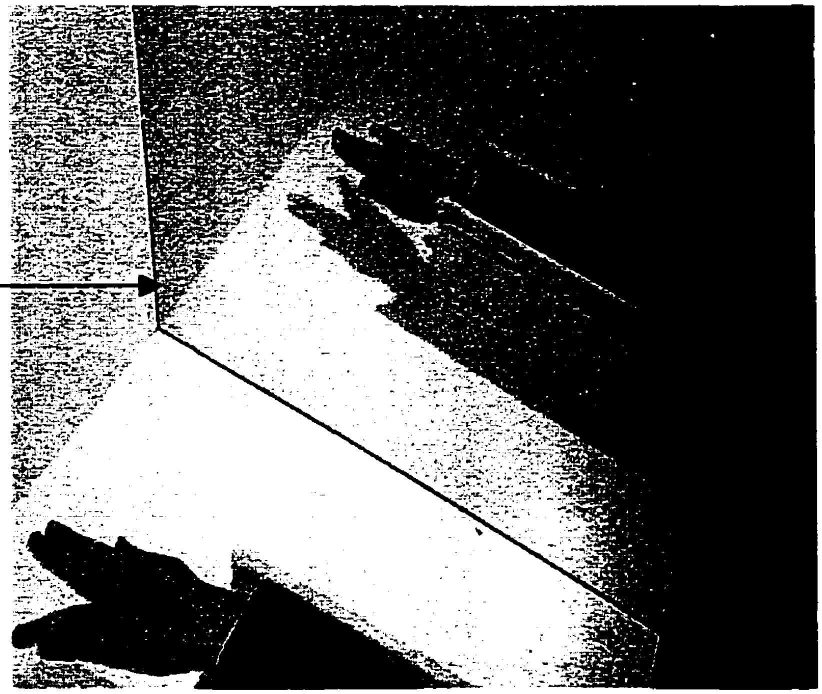


Figure 1. Mirror Therapy: a mirror is placed at the body mid-line between the patient's two arms. The weak arm is behind the mirror and the good arm is in front of the mirror. The patient is then asked to move both arms while looking in the mirror. The illusion of the weak arm being as functional as the good arm is thus created.

underlying the effectiveness of CI Therapy arises from research in the monkey. It has been clearly demonstrated that unilateral dorsal rhizotomy abolishes all sensory feedback on one side, and that following such an operation, monkeys are unable to regain purposive movements in the deafferented limb (Lassek, 1953). However, when such animals are required to wear a restraint on their good limb, they are subsequently able to develop purposive movements in the deafferented limb (Stein and Carpenter, 1965). Taub's (1980) theory of learned non-use seeks to explain these differences and states that when an animal tries to use its deafferented limb, it quickly discovers that it cannot. Continuous attempts to use the limb lead to on-going frustration coupled with failure and the animal is therefore quickly conditioned to avoid using it. As a result, the animal never realizes that after a period of recovery the limb regains potential usefulness. In contrast, deafferented monkeys wearing restraints on their good limb must continue to attempt use of the deafferented limb, and in time, are able to regain purposive movement.

The first attempt to examine the learned non-use phenomenon in humans was carried out by Wolfe and colleagues (1989). In their study, chronic stroke patients had their good arm constrained during waking hours for a period of two weeks. No specific exercises were combined with the constraint procedure and a battery of motor tasks was developed to assess the effectiveness of the intervention. Results showed significant improvement in the function of the weak arm, and the authors were confident that the results supported the existence of the learned non-use phenomenon in humans. They also believed that forced use (by constraining the good limb) could reverse the debilitating effects of hemiparesis. Encouraged by these initial results, Taub and colleagues (1993) developed CI therapy in which patients wore a restraint on their good arm to discourage its use and performed shaping exercises with their weak arm to improve its functional ability.

Present Investigation

1. *Recruitment curves* and *silent periods* have been employed to study impairments in various neurological diseases (Ridding and Rothwell, 1997; Ikoma et al., 1996; Valls-Solé et al., 1994). However, the present project is among the first to apply these measurements as a method for examining CNS change over time and in tandem with physical rehabilitation. The first aim of this project was to examine the reliability of *recruitment curves* and *silent periods* as valid measurements, and therefore a study was conducted in healthy subjects (N = 7) who did not receive any treatment in order to assess whether these neurophysiological measures were consistent across sessions.
2. The second aim employed Mirror Therapy in an attempt to drive motor ability improvement. This therapy is a new procedure and is not yet well understood; it remains unclear if the mirror is critical in driving improvement. Therefore, for the present project, it was deemed important to address the issue by conducting a study in healthy control subjects in order to differentiate between the effects of the mirror and of repetitive training in the learning of a simple manual task. If the weak arm's "amount of use" is critical for motor improvement, then this would imply that the mirror intervention has but a placebo effect. Nevertheless, it is known that observation of movement can enhance excitability of the motor system (Fadiga et al.,

1995, 1999; Strafella and Paus, 2000), and therefore, it might be possible that visual stimuli relentlessly presented over time could drive CNS plasticity by strengthening motor pathways. Based on this possibility, it was predicted that Mirror Therapy could significantly improve motor ability, and therefore an attempt was made to remediate the stroke-affected arm in one patient who had long standing lesions.

3. The third aim was to promote motor recovery in the affected arm of two chronic stroke patients, but this time using CI Therapy. This therapeutic intervention has been widely validated, and is recognised as efficacious (Miltner et al., 1999, Taub, 1993). It was predicted that CI Therapy would aid our patients improve motor function. In addition, the present study is among the first to extend the intervention to an adult patient who has been hemiparetic since early infancy.

4. The fourth aim was to take motor enhancements documented in chronic stroke patients and establish a link to electrophysiological measurements made before and after Mirror and CI Therapy. Electrophysiological data in the patients were compared to those of seven healthy subjects. In stroke patients, excitability of motor pathways to relevant muscles is often reduced and *silent periods* either shortened or prolonged (Ahonen et al., 1998). We predicted that in our patients, who have lesions causing motor impairment, similar neurophysiological phenomena would be observed but these would return towards normal levels consequent to therapy. It has been reported with the TMS mapping of M1 before and after CI Therapy (Liepert et al., 1998, 2000) that there is both a decrease in motor cortical representations in the unaffected hemisphere and an increase in motor cortical representations in the affected hemisphere. To explain their results, these authors suggested that observed changes

reflect use-dependent cortical reorganization: i.e., with therapy, the constrained arm was not used, and this then led to a decrease in motor cortical representations in the hemisphere operating that arm, and similarly, by forcing the use of the weak arm in performing ADL, motor cortical representations in the affected hemisphere were enlarged for that arm.

1- Validation of TMS / EMG Procedures

This section outlines the TMS / EMG methodology used to assess CNS plasticity, and is primarily focused on a validation study conducted in healthy subjects. Though TMS mapping is not a new procedure, its use in conjunction with *recruitment curves* and *silent periods* has only rarely been employed to examine possible CNS changes between TMS sessions. It was therefore considered important to examine the reliability of these latter measurements in healthy subjects that did not undergo any intervention between TMS sessions. Seven healthy volunteers underwent the TMS / EMG procedures two weeks apart. This group had a mean age of 27.4 ± 4.5 SD (one female and 6 males; one left-handed and 6 right-handed). Having established the efficacy of the method we also used 95% Confidence Intervals (95-CI) of their data in comparative analyses with like data taken from the chronic stroke patients. Although there is an age difference between the control subjects and the patients who participated in the studies, the comparisons nevertheless provide useful insight about TMS-induced responses in a healthy versus stroke population.

Method

Single pulses of TMS were carried out with a Magstim 200 magnetic stimulator connected to a bistim module (Magstim, UK), and delivered through a circular coil (9 cm external diameter) oriented so that the induced electric current flowed in a posterior-anterior direction beneath the coil. Induced muscle activity was recorded with Ag-AgCl surface electrodes fixed on the skin using a belly-tendon montage. EMG signal was amplified (gain: X 1 000 to 10 000 depending on the size of the response), filtered (10 Hz-10kHz bandpass), digitized at 2 kHz, displayed on the computer screen, and stored for off-line analysis using Matlab (MathWorks, Inc. USA).

EMG recordings of TMS-induced muscle activity were taken in the contralateral first dorsal interosseous (FDI) muscle both while the muscle was at rest and during voluntary contraction of 50% of maximal contraction. In a resting muscle, TMS induces a "resting" MEP (Figure 2); and in a tonically activated muscle, TMS induces both an "active" MEP and a *silent period* (Figure 3). The first step in the TMS / EMG procedure involved the determination of thresholds for resting and active MEPs for both FDI muscles. TMS pulses were delivered at multiple locations around the contralateral central sulcus in order to find the site of maximal response. Once the optimal site was established, the stimulation intensity was then decreased until 5 out of 10 MEPs had amplitudes higher than 50 microvolts (Rossini et al., 1994). Subjects sat with their elbows flexed at 90 degrees, and hands in a half-pronated position. When asked to contract the contralateral FDI muscle during the determination of active thresholds, subjects made voluntarily contractions at 50% of their maximum; they were aided in this task by observing a read-out on a hand dynamometer.

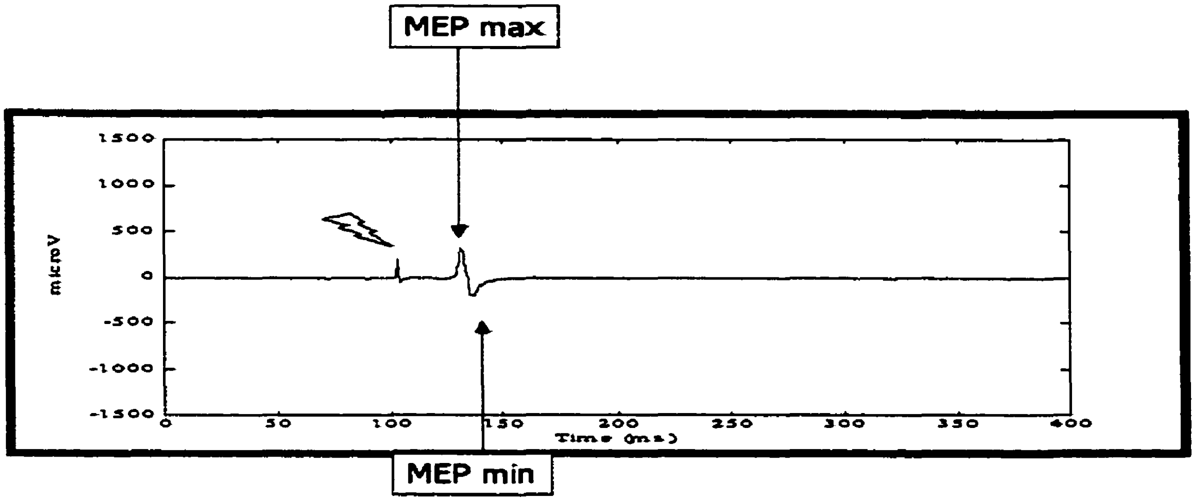


Figure 2. The above EMG recording shows a resting MEP: while TMS is delivered during muscle relaxation, an excitatory response (MEP) occurs in the muscle after TMS stimulation.

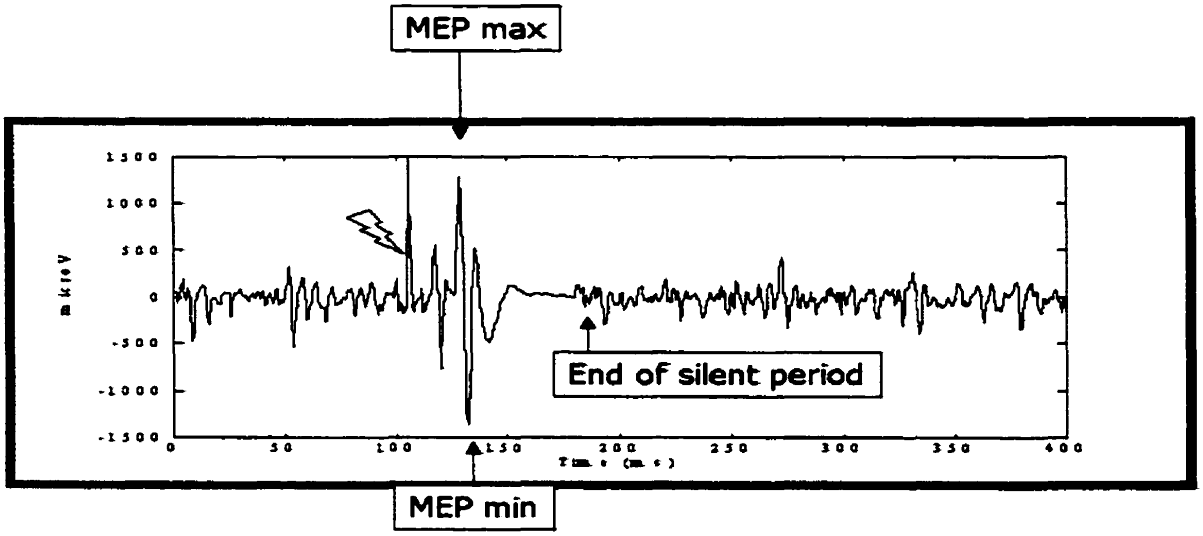


Figure 3. The above EMG recording shows an active MEP and a *silent period*: while TMS is delivered during voluntary muscle contraction, an excitatory response (MEP) and an inhibitory response (*silent period*) occurs in the muscle after TMS stimulation.

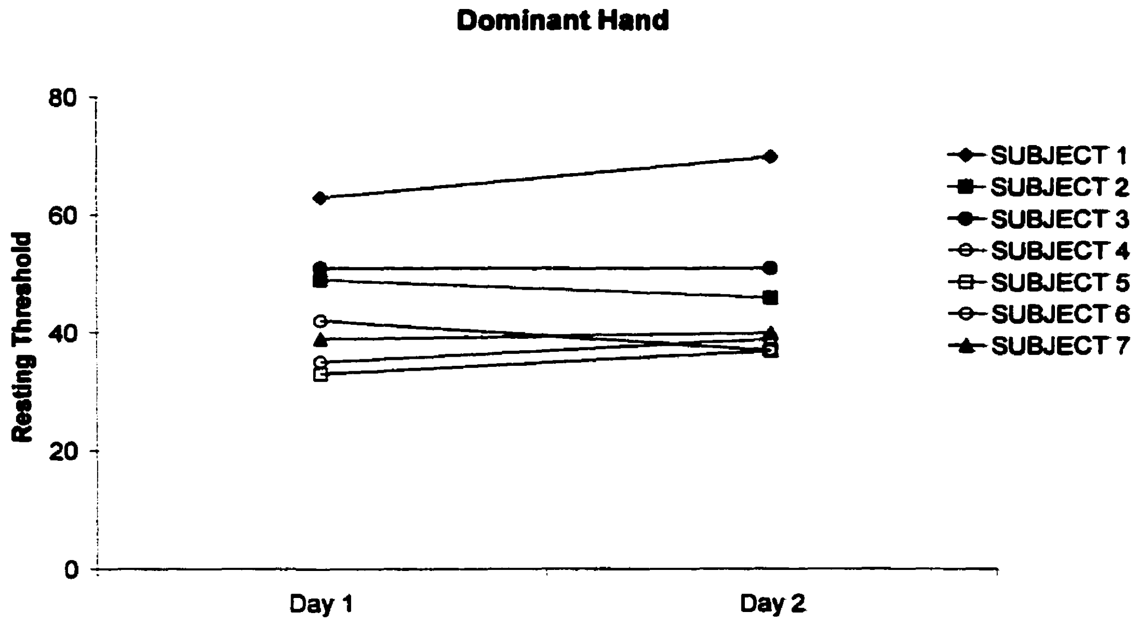
Two types of statistical analyses were conducted for evaluating the consistency of resting and active threshold values, resting and active MEP amplitudes, corrected active MEPs, and *silent period* durations between the two TMS sessions. The first analysis yielded the reliability coefficient (RC); this is a recognized method for evaluating consistency between two measurements (Bland and Altman, 1986). RC expresses reliability as two standard deviations of the distribution of differences between the two days as a percentage of the mean of all the measurements. The smaller the reliability coefficient, the more reliable the two measurements would be. In addition, the degree of similarity between the two sessions was also expressed as Pearson's correlation (two-tailed) coefficient between the two days. An important limitation with the latter method is that it examines fit to a regression line, but does not reveal scalar differences between the overall measurements.

Additional statistical analyses were conducted to examine the effects of baseline EMG contraction on active MEP amplitudes and *silent period* durations for each day at different TMS intensities. One-tailed Pearson correlation analysis was used to examine the relationship between active MEP amplitude and baseline EMG contraction, because it was previously reported that this relationship is positively dependent (Hess et al., 1987). Unlike the active MEP amplitude, Ho and colleagues (1998) demonstrated that there is no relationship between baseline EMG contraction and the *silent period* duration. Because no claim has yet been made with regards to their relationship, a two-tailed Pearson correlation analysis was used.

Results

The analyses conducted on the resting threshold values suggest that they were reliable between the two days (Figure 4). The reliability coefficient for the resting threshold values between days, on the dominant side, was 10.3% and the Pearson correlation coefficient was 0.94 ($p < 0.01$). For the non-dominant side, the reliability coefficient was 13.8% and the Pearson correlation coefficient was 0.89 ($p < 0.01$). Similar results were obtained for active threshold values (Figure 5). The reliability coefficient for active threshold values between days on the dominant side was 10.5% and the Pearson correlation coefficient was 0.83 ($p < 0.01$). For the non-dominant side, the reliability coefficient was 14.3% and the Pearson correlation coefficient was 0.89 ($p < 0.01$).

Results show that resting MEP amplitudes were less reliable than the threshold values (Figure 6). For the dominant side, the reliability coefficients (RC) and Pearson correlation coefficients (r) were as follows: RC = 138.8% and $r = 0.39$ at 5% TMS intensity above threshold; RC = 97.9% and $r = 0.10$ at 10% TMS intensity above threshold; RC = 143.7% and $r = 0.36$ at 15% TMS intensity above threshold; RC = 88.6% and $r = 0.85$ ($p < 0.01$) at 20% TMS intensity above threshold; and, RC = 34.9% and $r = 0.63$ at 25% TMS intensity above threshold. For the non-dominant side: RC = 59.5% and $r = 0.81$ ($p < 0.05$) at 5% TMS intensity above threshold; RC = 82.2% and $r = 0.16$ at 10% TMS intensity above threshold; RC = 102.3% and $r = 0.53$ at 15% TMS intensity above threshold; RC = 99.7% and $r = 0.04$ at 20% TMS intensity above threshold; and, RC = 80.7% and $r = 0.41$ at 25% TMS intensity above threshold.



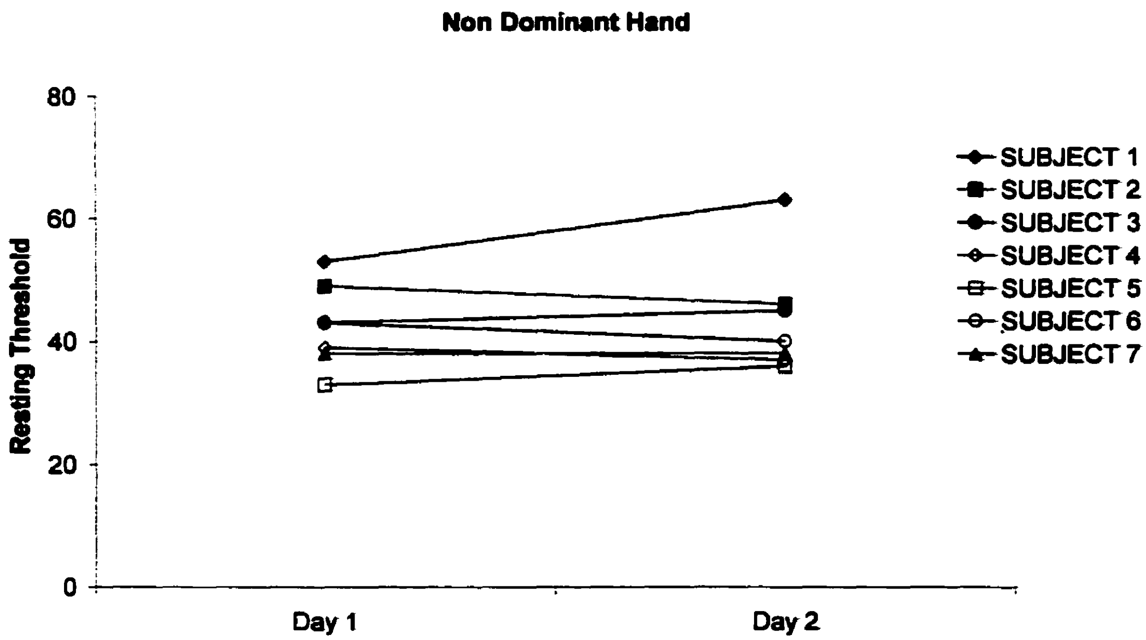
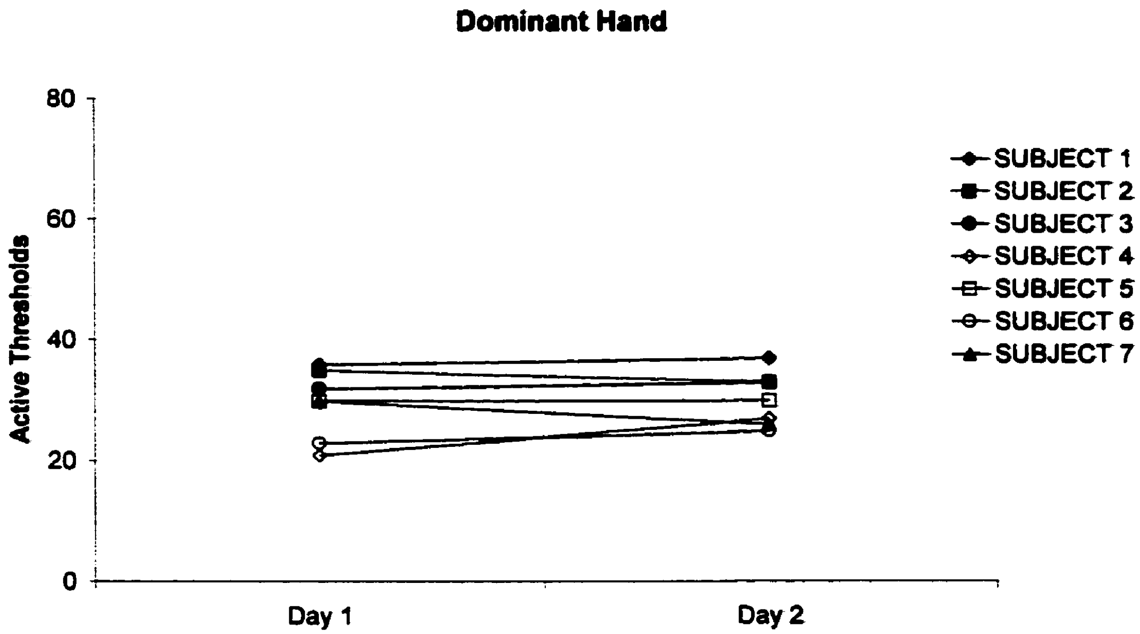


Figure 4.: Illustrates the reliability of resting threshold values for the dominant and non-dominant hand, each line represents a subject: the Y-axes represent threshold and the X-axes Day. The data between the two days were consistent.



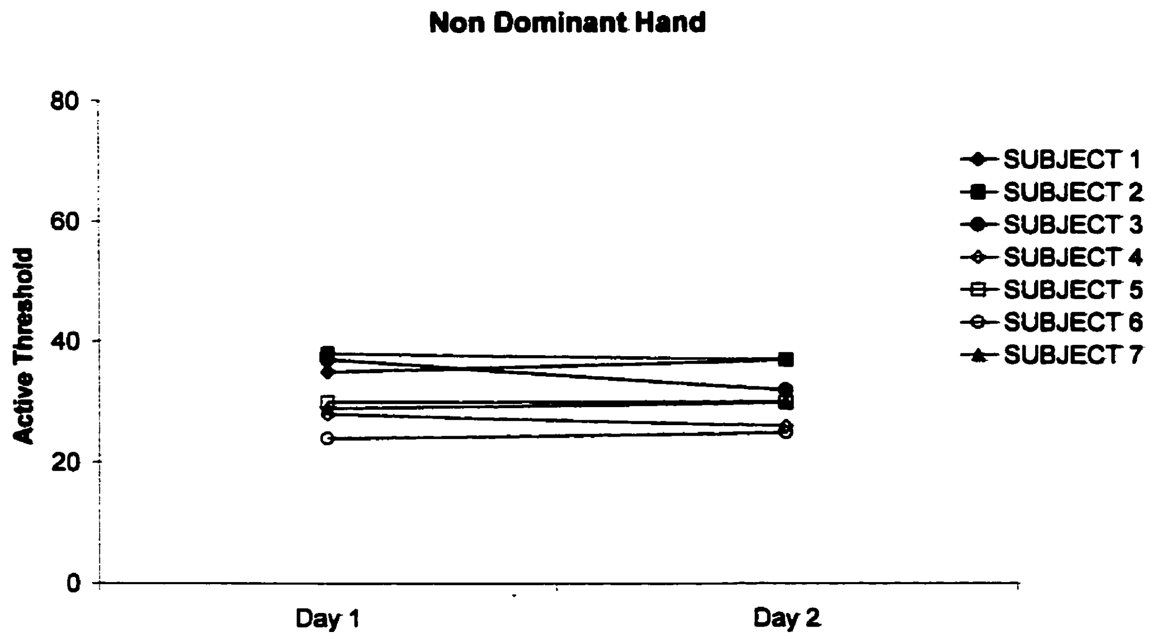


Figure 5. Illustrates the reliability of active threshold values for the dominant and non-dominant hand, each line represents a subject: the Y-axes represent threshold and the X-axes Day. The data between the two days were consistent.

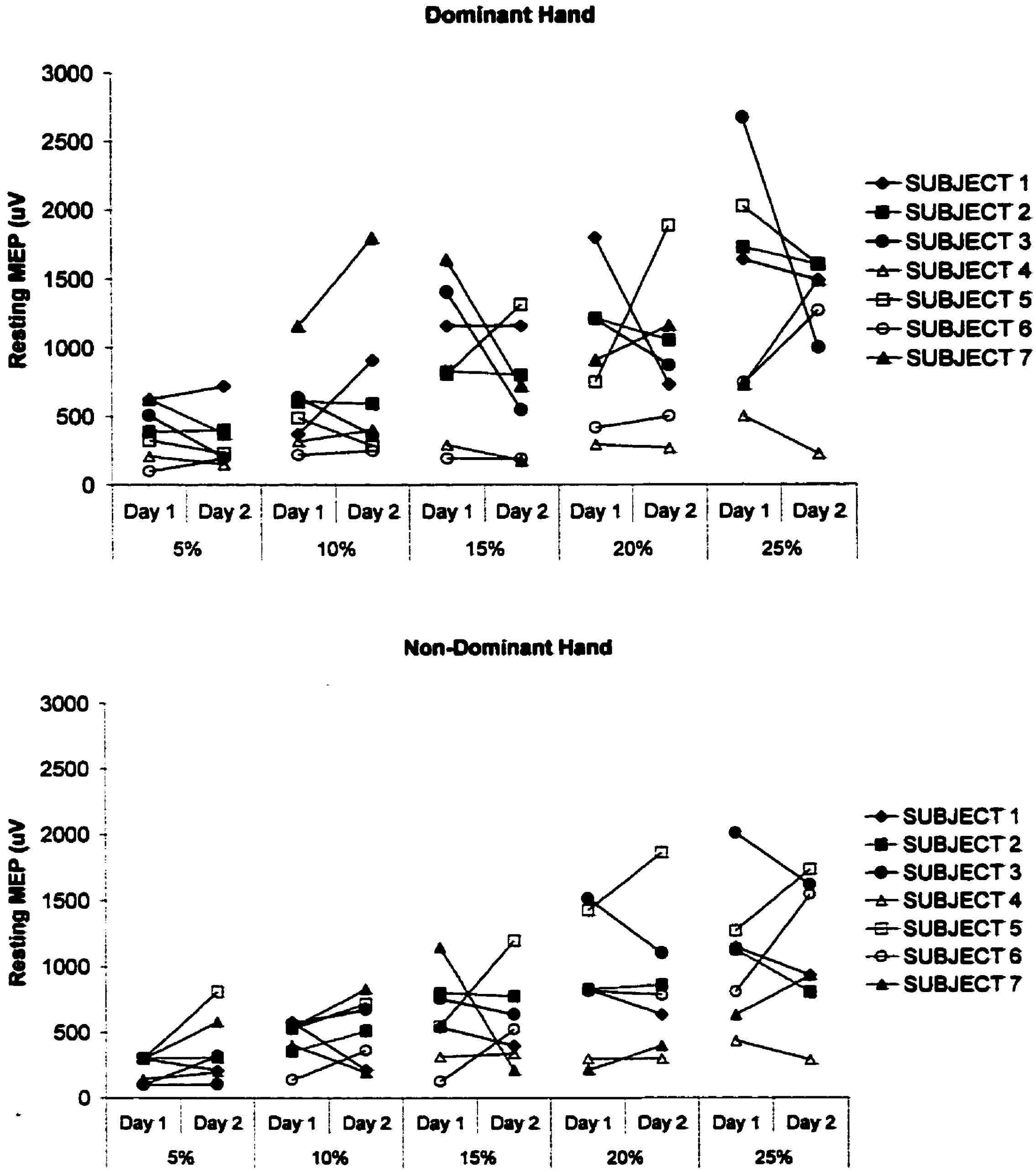
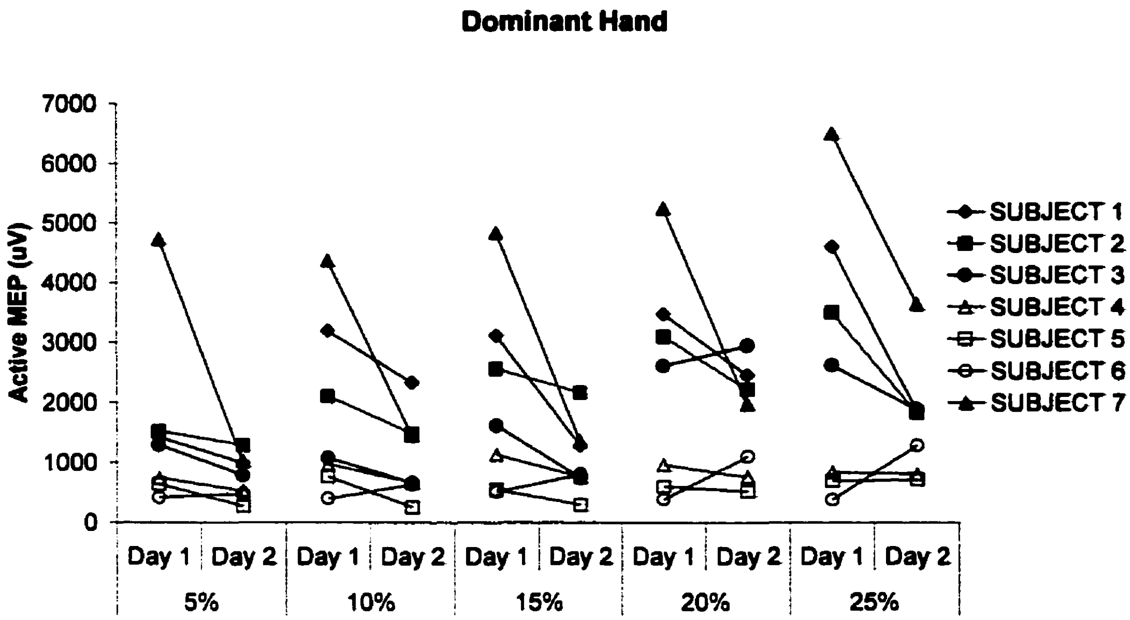


Figure 6. Illustrates the reliability of resting MEP amplitudes for the dominant and non-dominant hand, each line represents a subject: the Y-axes represent MEPs in microvolts and the X-axes represent the intensities of TMS applied between the two days. The data were inconsistent and reflect variability in resting MEPs.

Statistical analyses conducted on the active MEP amplitudes reveal that the measurements were also not as reliable between sessions (Figure 7). For the dominant side: RC = 87.5% and $r = 0.93$ ($p < 0.01$) at 5% TMS intensity above threshold; RC = 85.4% and $r = 0.67$ at 10% TMS intensity above threshold; RC = 56.4% and $r = 0.73$ ($p < 0.05$) at 15% TMS intensity above threshold; RC = 94.5% and $r = 0.63$ at 20% TMS intensity above threshold; and, RC = 68% and $r = 0.92$ ($p < 0.01$) at 25% TMS intensity above threshold. For the non-dominant side: RC = 222.9% and $r = 0.55$ at 5% TMS intensity above threshold; RC = 128.4% and $r = 0.78$ ($p < 0.05$) at 10% TMS intensity above threshold; RC = 154.2% and $r = 0.63$ at 15% TMS intensity above threshold; RC = 107.4% and $r = 0.70$ ($p < 0.05$) at 20% TMS intensity above threshold; and, RC = 105.9% and $r = 0.92$ ($p < 0.01$) at 25% TMS intensity above threshold.

Pearson correlation analyses of the data support previous claims that active MEP amplitudes are proportionally dependent on baseline EMG contraction (Hess et al., 1987). Correlations were taken between active MEP amplitudes and baseline EMG as well as between *silent period* durations and baseline EMG for every applied TMS intensity on both days (Table 1). In general, active MEPs amplitudes were significantly correlated with baseline EMG, or close to significant, whereas this trend was not apparent for *silent period* durations. Based on these analyses, it was deemed appropriate to express active MEPs as a ratio of baseline EMG contraction and not to correct *silent periods* in this manner.

The reliability of corrected active MEPs was much higher than that for the uncorrected active MEP amplitudes (Figure 8). For the dominant side: RC = 32.2%



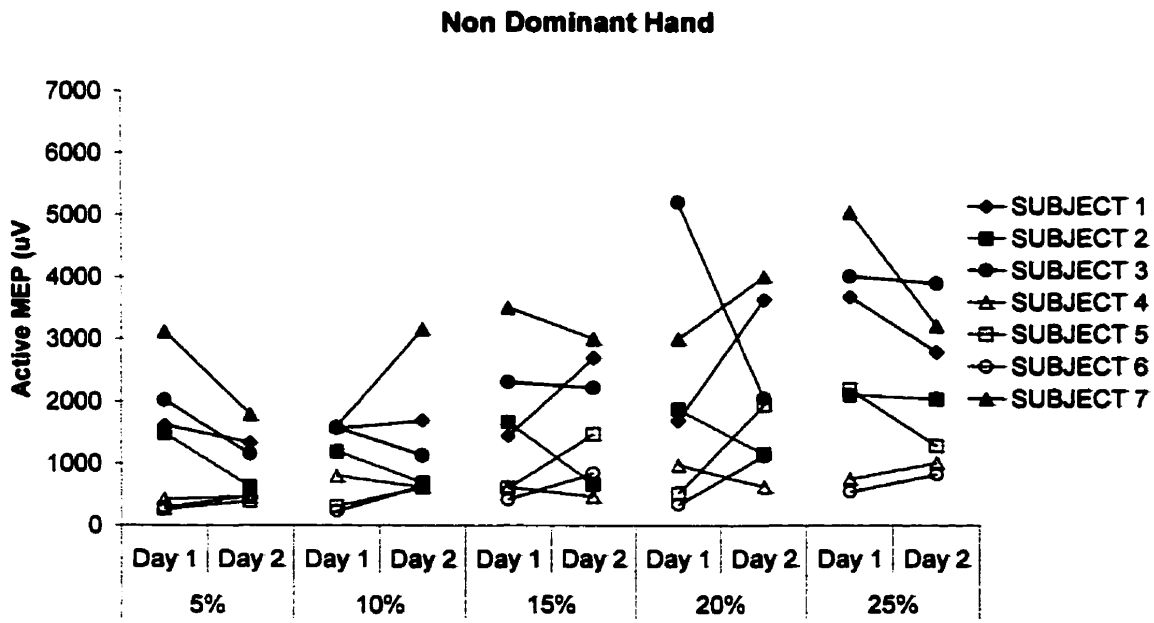


Figure 7. Illustrates the reliability of active MEP amplitudes for the dominant and non-dominant hands, each line represents a subject: The Y-axes represent MEPs in microvolts and the X-axes represent the intensities of TMS applied between the two days. The data were inconsistent and reflect the fact that active MEPs are variable. Further analyses show that MEP amplitudes are proportionally dependent on baseline EMG contraction levels.

Active MEP vs. Baseline EMG

one - tailed

	Dominant Hand	Non-Dominant Hand
Day 1 – 5%	**0.92	**0.96
Day 1 – 10%	**0.90	*0.76
Day 1 – 15%	*0.78	0.66
Day 1 – 20%	**0.93	0.46
Day 1 – 25%	0.68	*0.73
Day 2 – 5%	0.50	*0.78
Day 2 – 10%	**0.96	**0.92
Day 2 – 15 %	0.68	*0.76
Day 2 – 20%	0.49	**0.90
Day 2 – 25 %	0.54	0.49

Silent Period vs. Baseline EMG

two - tailed

	Dominant Hand	Non-Dominant Hand
Day 1 – 5%	0.03	0.04
Day 1 – 10%	-0.13	0.06
Day 1 – 15%	0.03	-0.04
Day 1 – 20%	0.03	0.31
Day 1 – 25%	0.01	0.14
Day 2 – 5%	0.43	-0.21
Day 2 – 10%	0.18	-0.16
Day 2 – 15 %	-0.16	-0.38
Day 2 – 20%	-0.56	-0.40
Day 2 – 25 %	-0.50	-0.54

Table 1. Pearson correlation analyses show that active MEP amplitudes were generally significantly correlated with baseline EMG, whereas this trend was not apparent for *silent period* durations (*$p < 0.05$, **$p < 0.01$). Separate analyses were conducted for each day at different intensities of TMS.

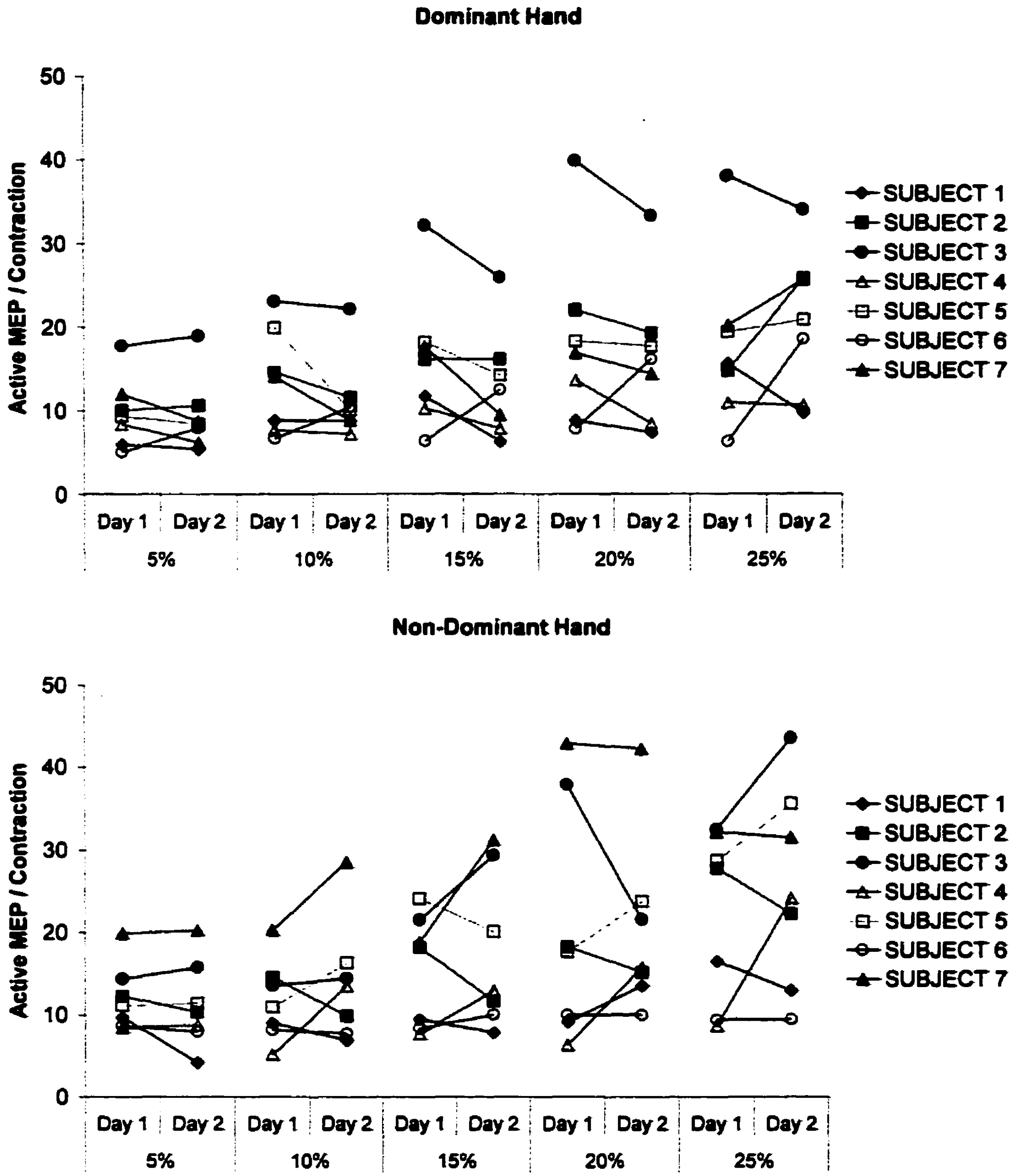


Figure 8. Illustrates the reliability of corrected active MEPs for the dominant and non-dominant hands, each line represents a different subject: the Y-axes represent the active MEPs expressed as a ratio to contraction and the X-axes represent the intensities of TMS applied between the two days. The transformed active MEP data shown here were more consistent than unmodified values.

and $r = 0.91$ ($p < 0.01$) at 5% TMS intensity above threshold; RC = 51.2% and $r = 0.72$ ($p < 0.05$) at 10% TMS intensity above threshold; RC = 46% and $r = 0.70$ ($p < 0.05$) at 15% TMS intensity above threshold; RC = 55.9% and $r = 0.82$ ($p < 0.05$) at 20% TMS intensity above threshold; and, RC = 46.6% and $r = 0.77$ ($p < 0.05$) at 25% TMS intensity above threshold. For the non-dominant side: RC = 23.8% and $r = 0.89$ ($p < 0.01$) at 5% TMS intensity above threshold; RC = 55.5% and $r = 0.73$ ($p < 0.05$) at 10% TMS intensity above threshold; RC = 37.4% and $r = 0.82$ ($p < 0.05$) at 15% TMS intensity above threshold; RC = 32.6% and $r = 0.90$ ($p < 0.01$) at 20% TMS intensity above threshold; and, RC = 46.4% and $r = 0.73$ ($p < 0.05$) at 25% TMS intensity above threshold.

The *silent period* durations were not corrected and were found to be reliable between the two sessions (Figure 9). For the dominant side: RC = 32.2% and $r = 0.91$ ($p < 0.01$) at 5% TMS intensity above threshold; RC = 51.2% and $r = 0.72$ ($p < 0.05$) at 10% TMS intensity above threshold; RC = 46% and $r = 0.70$ ($p < 0.05$) at 15% TMS intensity above threshold; RC = 55.9% and $r = 0.82$ ($p < 0.05$) at 20% TMS intensity above threshold; and, RC = 46.6% and $r = 0.77$ ($p < 0.05$) at 25% TMS intensity above threshold. For the non-dominant side: RC = 23.8% and $r = 0.89$ ($p < 0.01$) at 5% TMS intensity above threshold; RC = 55.5% and $r = 0.73$ ($p < 0.05$) at 10% TMS intensity above threshold; RC = 37.4% and $r = 0.82$ ($p < 0.05$) at 15% TMS intensity above threshold; RC = 32.6% and $r = 0.90$ ($p < 0.01$) at 20% TMS intensity above threshold; and, RC = 46.4% and $r = 0.73$ ($p < 0.05$) at 25% TMS intensity above threshold.

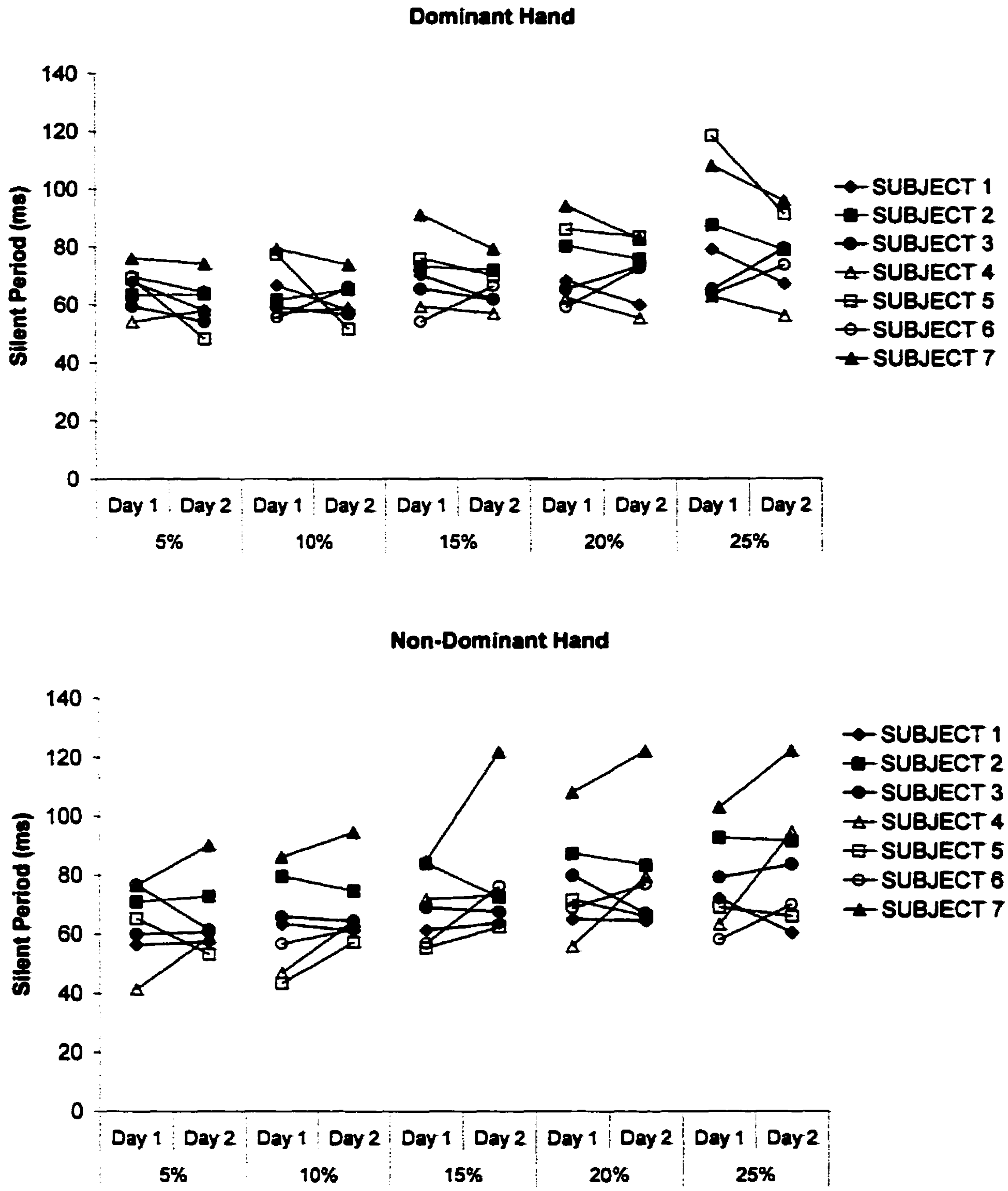


Figure 9. Illustrates the reliability of *silent period* durations expressed in milliseconds for the dominant and non-dominant hands, each line represents a different subject: the Y-axes represent the *silent period* in milliseconds and the X-axes represent the intensities of TMS applied between the two days. *Silent periods* between the two days were relatively consistent.

Overall, the results reveal that some measurements were more consistent between sessions than others. In this regard, both resting and active threshold values were consistent between sessions, *silent period* durations were relatively consistent between sessions, but with acceptable deviations. However, the resting and active MEP amplitudes were inconsistent. Active MEPs were relatively consistent between sessions when the values were corrected and expressed as a ratio to baseline EMG contraction, confirming that contraction levels facilitate the MEP response. Pearson correlations showed significant correlation between the two, confirming previous claims that levels of baseline EMG contraction facilitate active MEPs (Hess et al., 1987). The same analyses conducted on the *silent period* duration show that the measurement is not correlated with baseline EMG contraction and this finding is in keeping with that of Ho and colleagues (1998).

2- Assessing the Effects of the Mirror in Healthy Subjects

This study examined the effects of the mirror and that of repetitive training in the less adept hand of healthy subjects who have an asymmetry for a simple manual task. The study had the following advantages over Altschuler and colleagues's (1999) study: 1) we used a more structured and supervised regimen in which all subjects underwent the same training in the laboratory; 2) we used control conditions to differentiate the effects of the mirror from the effects of repetitive training in the less adept hand; and 3) a larger sample size was used so as to achieve greater statistical power.

Method

The task learnt, the so-called *Vulcan Salute*, is shown in Figure 10 and involves separating the third and fourth fingers while keeping other digits tightly together. Interestingly, most people are better at performing this task with their left hand, and only right-handed subjects who performed the task better on their left hand participated in the study. Because subjects can already do the task quite well with the left hand, the goal of the study was to improve right hand performance. In addition, all subjects were required to take a standard handedness questionnaire prior to the study (Crovitz and Zener, 1962). Subjects with a handedness index of ≤ 29 were considered right-handed (Milner, 1965), and were included in the study.

Thirty-two subjects participated (mean age = 24.6 ± 5.7 SD; 20 females and 12 males) and came to the laboratory and practiced the task for a fixed number of trials on five consecutive days. Subjects were randomly assigned to two mirror groups (n = 8 and 8) and two control groups (n = 8 and 8). All groups practiced the task for 15 Sets X 10 Repetitions X 5 Consecutive Days. Subjects kept their palm face down on a horizontal plane with the wrist straight whenever they performed the task in the laboratory, and refrained from practicing outside. The apparatus employed was a white box (120 X 59 X 79 cm) with an open front and top, and with a sagittal slit where a mirror or a control sheet of cardboard could be placed (Figure 1). Two white armrests, one for each arm, ensured that subjects were comfortable while performing the required hand movements.

Figure 10. The simple manual task involves abduction of the third and fourth fingers (fingers numbered 1 to 5) while keeping the second touching the third and the fourth touching the fifth.

The two mirror groups performed the task with the aid of a mirror, and watched the reflection of their left hand. The two control groups performed the task with a sheet of cardboard between their hands, and fixated their eyes on a marked spot in the cardboard. To discern the importance of repetitive training of the task, the mirror and control groups were further divided on the basis of the type of repetition performed during practice. Mirror Moving Both-Hands and Cardboard Moving Both-Hands practiced the required task with both hands. In contrast, Mirror Moving Left-Hand and Cardboard Moving Left-Hand practiced the required task with the left hand only.

Measurements were taken for the right hand only. The range of extension in the right hand was measured by recording the separation between the middle fingers on a piece of grid-paper, three times. Distances between each pair of marked points were measured with a standard ruler and a score was later calculated by taking the mean. These measurements were taken before training on each day and three days after the entire training period (Post-Test). We also measured speed by recording the number of times subjects could repeatedly perform the hand task in 15 seconds. These second measurements were taken before (Pre-Test) and three days after (Post-Test) the entire training period. Separate three-way analyses of variance (ANOVA) for both measurements served as statistical analyses with Condition (Mirror vs. Cardboard) and Type of Repetition (Moving Both-Hands vs. Moving Left-Hand) as between-subject factors and Days as a within-subject factor. Tukey's HSD tests were used for all post-hoc comparisons.

Results

The groups were matched in terms of age, handedness, and sex ratio. The Mirror Moving Both-Hands group had a mean age of 24 ± 1SD, a mean handedness index of 23.0 ± 0.4SD, and a female / male ratio of 5 / 3. The Cardboard Moving Both-Hands group had a mean age of 25 ± 2SD, a mean handedness index of 24.1 ± 1.8SD, and a female / male ratio of 6 / 2. The Mirror Moving Left-Hand group had a mean age of 24 ± 2SD, a mean handedness index of 23.4 ± 1.7SD, and a female / male ratio of 6 / 2. Finally, the Cardboard Moving Left-Hand group had a mean age of 25 ± 2SD, a mean handedness index of 23.6 ± 0.8SD, and a female / male ratio of 5 / 3.

In *Vulcan Salute* extension measurements, the analyses of daily measurements of range of extension in the right hand showed no three-way interaction between Condition, Days and Type of Repetition $F(5,140) = 0.47$, $p < 0.80$, no two-way interaction between Condition and Days $F(5, 140) = 0.00$, $p = 0.97$, and no main effect of Condition $F(1,28) = 0.13$, $p = 0.72$ (Figure 11). However, a significant two-way interaction between Days and Type of Repetition $F(5,140) = 3.58$, $p < 0.005$ (Figure 12) was manifest. Simple main effect tests show that groups Moving Both-Hands [$F(5,140) = 20.41$, $p < 0.01$] and Moving Left-Hand [$F(5,140) = 5.18$, $p < 0.01$] improved over Days. Simple main effect tests also revealed that Groups Moving Both-Hands and Moving Left-Hand were highly significantly different (all $p < 0.01$) on Day-2 [$F(1,168) = 8.38$], Day-3 [$F(1,68) = 5.36$], Day-4 F [$(1,168) = 9.21$], Day-5 [$F(1,168) = 7.67$], and Post-Test [$F(1,168) = 13.85$]. These latter results indicate differences between the two groups in the amount of improvement achieved on a given day compared to baseline: Groups Moving Both-Hands achieving better performance.

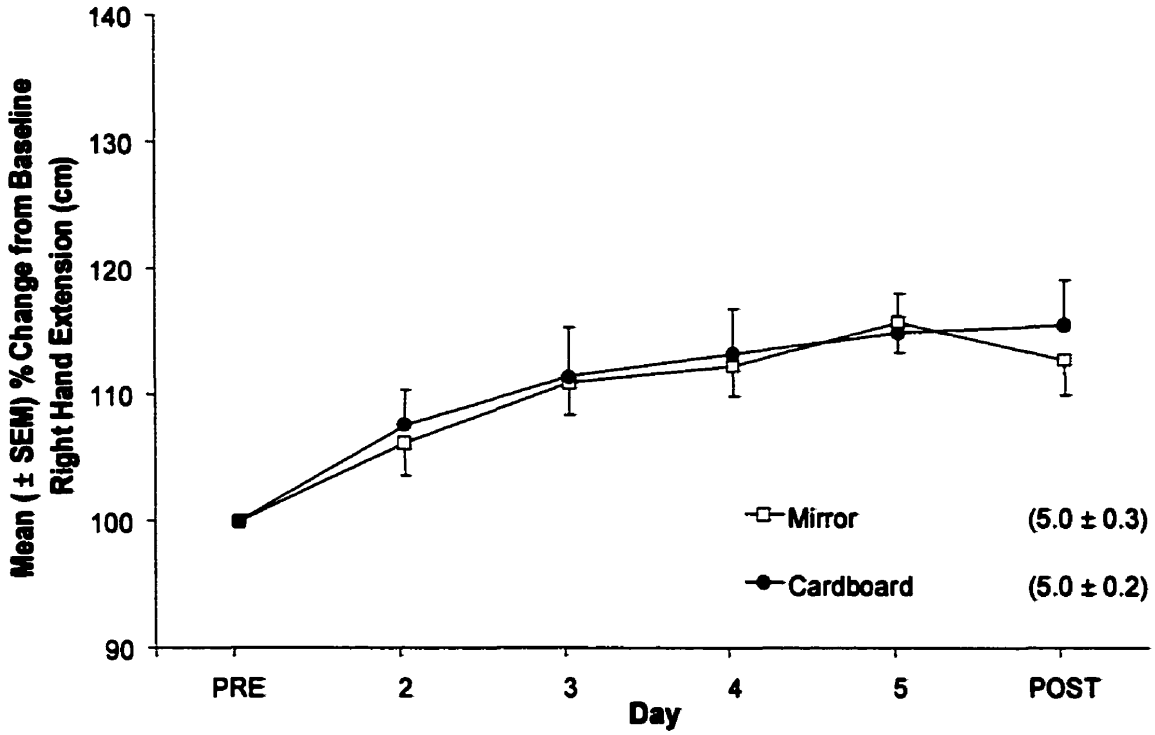


Figure 11. Mean % change from baseline in right hand extension for Groups Mirror and Cardboard. Values in parentheses in Figure legend represent mean baseline measurements (cm). No main effect of Mirror was observed.

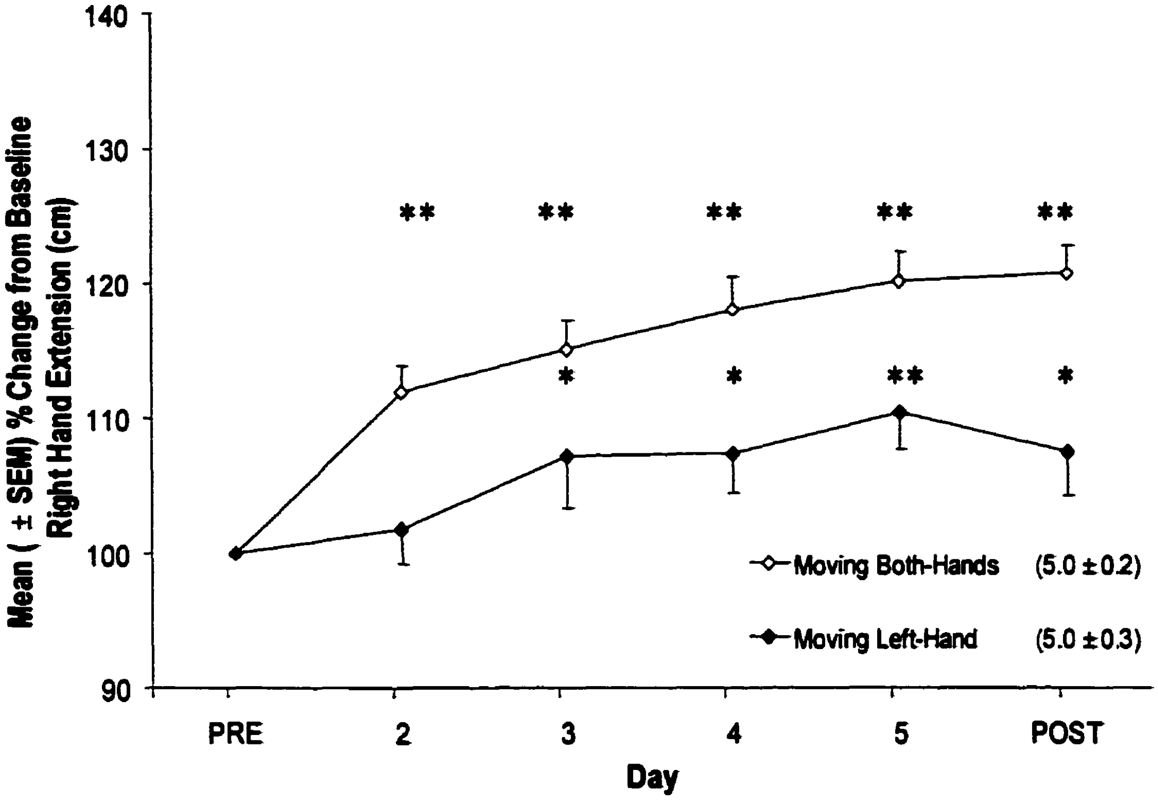


Figure 12. Mean % change from baseline in right hand extension for Groups Moving-Both-Hands and Moving Left-Hand. Values in parentheses in Figure legend represent mean baseline measurements (cm). Groups Moving Both-Hands and Moving Left-Hand were highly significantly different (all $p < 0.01$) on each day, except at baseline. Asterisks represent significant differences compared to baseline within a group; * $p < 0.05$, ** $p < 0.01$.

Using Tukey's HSD post-hoc comparison tests, we examined the significance of the pattern of observed improvements. Group Moving Both-Hands showed improvement on all days compared to baseline (all $p < 0.01$), and further improvement on Day-5 ($p < 0.05$) and Post-Test ($p < 0.01$) compared to Day-2. No further improvements were significant after Day-3, which suggests that maximal improvement was achieved by that day. By contrast, group Moving Left-Hand showed improvement on Day-3 ($p < 0.05$), Day-4 ($p < 0.05$), Day-5 ($p < 0.01$) and Post-Test ($p < 0.05$) compared to baseline, and no significant improvement was observed after Day-4, suggesting that maximal improvement was achieved by that day. These results show different rates of improvement for both groups.

In *Vulcan Salute* speed measurements, the analyses of speed measurements taken at Pre-Test and Post-Test showed that no three-way interaction was observed between Condition, Days and Type of Repetition $F(1,28) = 0.93$, $p = 0.34$. In addition, there was no significant interaction between Condition and Days $F(1,28) = 0.13$, $p = 0.72$ and no main effect of Condition $F(1,28) = 0.18$, $p = 0.67$ (Figure 13). These results suggest that there is no difference between the mirror and cardboard groups; however, a significant interaction between Days and Type of Repetition $F(1,28) = 10.35$, $p < 0.005$ was observed (Figure 14). Post-hoc tests revealed that group Moving Both-Hands had speed measurements of 2.24 repetitions per second at Pre-Test compared to 3.51 repetitions per second at Post-Test ($p < 0.01$). In addition, group Moving Left-Hand had speed measurements of 2.40 repetitions per second at Pre-Test compared to 3.12 repetitions per second at Post-Test ($p < 0.01$). This represents a 0.54 difference in repetitions per second between the two groups at Post-

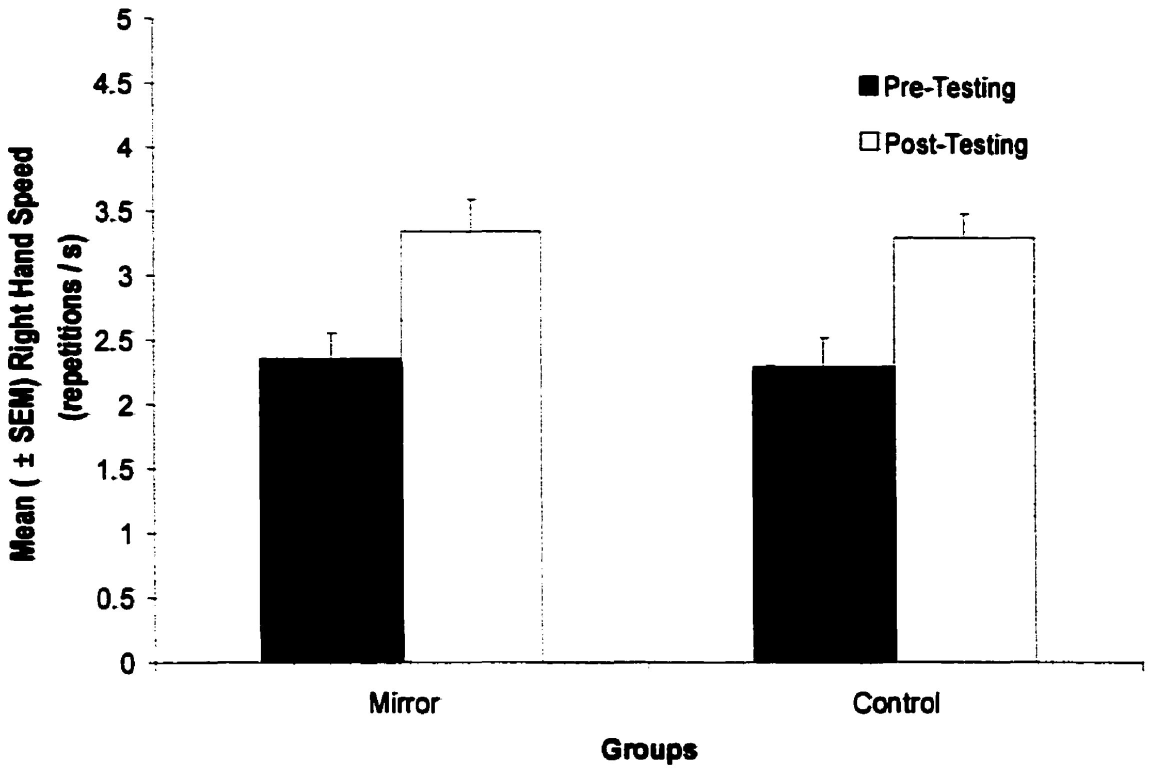


Figure 13. Mean right hand speed measurements at pre-testing and post-testing. No main effect of Condition F (1,28) = 0.18, p = 0.67.

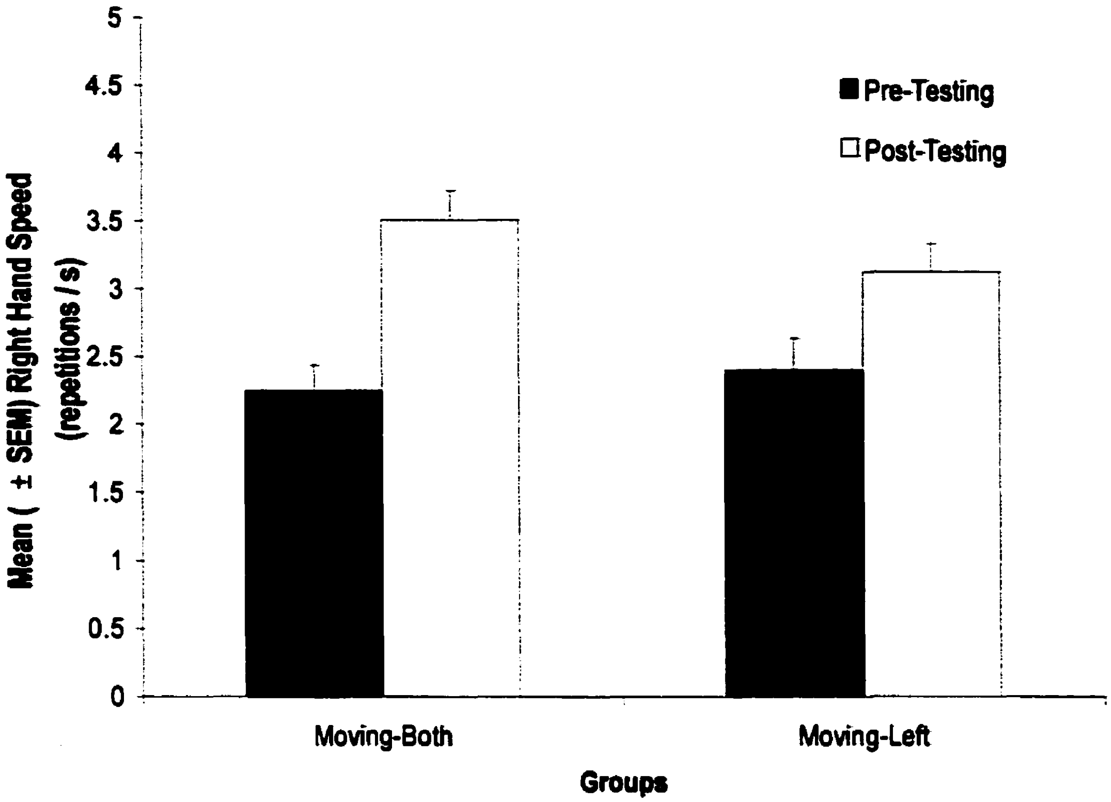


Figure 14. Mean right hand speed at pre-testing and post-testing. Significant interaction between Days and Type of Repetition, $F (1,28) = 10.35$, $p < 0.005$. Significant difference between pre-testing and post-testing for both groups (both $p < 0.01$). Significant difference between Groups Moving-Both and Moving-Left at post-testing ($p < 0.05$).

Test ($p < 0.05$), which indicates that group Moving Both-Hands were able to perform the task faster at Post-Test with their right hand compared to group Moving Left-Hand.

No effects of the mirror were demonstrated, and the results suggest that repetitive training by either hand contributes to improvement in the less adept hand. Greater improvement in the less adept hand is achieved when this hand performs simple repetition of the task, but some improvement is also achieved at a slower rate when the opposite hand exclusively performs simple repetition. This is known as the transfer effect (Allen, 1948; Cook, 1933; Ewert, 1926). Now that there is renewed interest in applying the mirror clinically, investigating this issue was important. Previous studies showing enhancements in motor ability with mirror training failed to separate the effects of the mirror from the effects of repetitive training.

3- Mirror Therapy and Neurophysiological Changes

Though we failed to demonstrate a positive effect of using a mirror to improve performance of a simple manual task in healthy volunteers, we decided to examine the effect of Mirror Therapy in a single patient affected by stroke based on the idea that a damaged CNS may respond differently. Mirror Therapy was used to drive motor improvement in the stroke-affected arm of this patient. Certain modifications were made to the original regimen employed by Altschuler and colleagues (1999) in order to guarantee compliance. In Altschuler and colleagues (1999) study, the patients were not supervised during their exercises and their regimen was not demanding.

Although the patients were asked to train with the mirror twice a day for fifteen minutes, this was done at home without supervision and therefore the study failed to ensure that training was in fact carried out. In the present study, the methodology used for examining Mirror Therapy was highly structured, and all exercises were carried out in the laboratory under supervision. After one week of intense training, behavioural motor improvements were observed, and TMS / EMG was applied to examine CNS changes.

The patient participating in this study was selected as follows. A neurologist screened for any medical condition, and determined whether the candidate was suitable for the study according to the following criteria. A candidate was considered suitable if they had suffered their stroke over one year ago, displayed hemiparesis without pronounced spasticity and / or excessive pain, and could extend their affected wrist against gravity. Following the medical examination, the patient completed a consent form, and was screened for any contraindications for engaging in magnetic resonance (MR) imaging and TMS / EMG examinations. Contraindications included cardiac pacemaker, aneurysm clip(s), heart and vascular clip(s), prosthetic valve(s), any other permanent metal in the body including prosthesis as well as a personal and / or family history of epilepsy. The candidate also had to be of at least low average intelligence as assessed by a neuropsychologist (Full Scale IQ rating > 75). Once the candidate passed the medical and neuropsychological examinations, a structural MR image (1 mm sagittal slices; T1-weighted, T2-weighted and Proton-Density images) determined the location and extent of the brain lesion: damage to M1 was exclusionary.

Patient JM

Patient JM was a right-handed 63 year-old retired secretary. Her magnetic resonance (MR) scan revealed general cortical atrophy and several lesions from strokes that occurred in 1998 (Figure 15). She had a right-sided hemiparesis probably related to a large lesion located in the left internal capsule. She also had a lesion in the posterior aspect of the left hemisphere including the parietal lobe. Her overall level of intelligence, as measured on the Weschler Adult Intelligence Scale-Revised (WAIS-R), was in the low average range with a Full-Scale Intelligence Quotient (IQ) of 88. There was no significant difference between her Verbal IQ (90) and her Performance IQ (86). The Weschler Memory Quotient of 86 suggests low average abilities consistent with her level of intelligence, however, further investigation of verbal and visuospatial memory suggested that JM experiences difficulties in the acquisition and retention of new material.

Method

Patient JM came to the laboratory on five consecutive days, and underwent Mirror Therapy for two hours each day. The apparatus used in the study was the same white box as the one used in the study with healthy subjects (Figure 1). Using the apparatus, the patient completed exercises by attempting to move both arms simultaneously and watching the reflection of the movements of the good arm in a mirror.

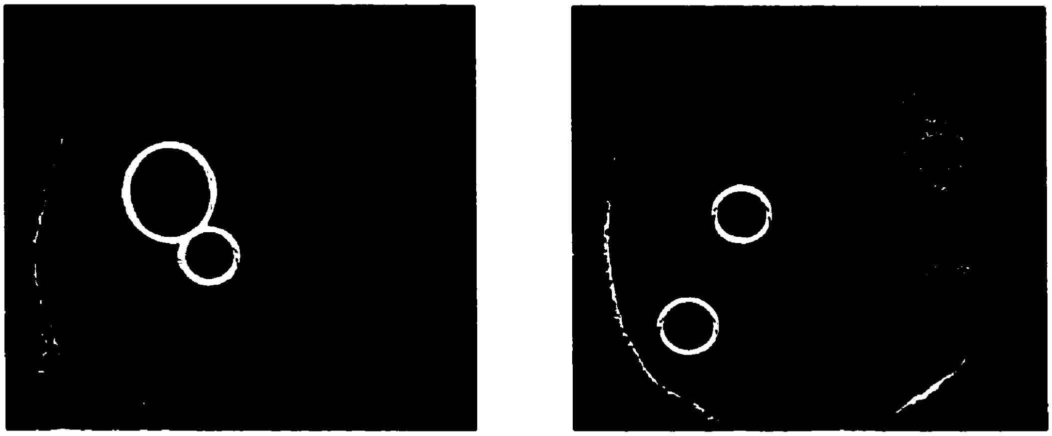


Figure 15. The above MR shows coronal and horizontal views in Patient JM. The images reveal cortical atrophy as well as lesions that include the left internal capsule, the left basal ganglia, and a large lesion in the left parietal lobe.

Each exercise was performed 70 times (7 sets X 10 repetitions) during each day of training. The regimen was geared towards making cardinal movements of the upper extremity. It began with two elbow exercises, the first of which involved sets of flexions and extensions and the second involved sets of pronations and supinations. These exercises were then followed by two wrist exercises that included sets of flexions and extensions and sets of ulnar and radial deviations. The regimen then moved to two thumb exercises that included sets of abductions and adductions and sets of flexions and extensions. Finally, the regimen ended with three finger exercises, including sets of abductions and adductions, sets of flexions and extensions of the metacarpals and sets of flexions and extensions of the phalanges. Appropriate breaks were given upon the patient's request, or whenever the experimenter deemed it necessary.

In order to document expected daily motor improvement, the Motor Activity Log (MAL) was given prior to every session and at the end of the study (Taub et al., 1993). This is a structured interview, and is designed to measure daily improvements in the usefulness of the weak arm in ADL. The patient was required to rate herself with the help of the examiner on how frequently she used her weak arm from a list of common everyday tasks that she normally performed outside the laboratory. In order to document whether enhanced performance was associated with changes in the CNS, TMS and EMG examinations were conducted before and after the intervention.

Results

Some motor enhancements were documented in Patient JM. Her amount of use (AOU) score on the MAL was 2.6 / 5 at the beginning of her training and 3.1 / 5 after her training. These scores correspond roughly to a medium amount of use of the affected arm at the beginning of therapy to some measurable increase in use after. Electrophysiological data revealed interesting trends. Both resting and active thresholds (expressed as a percentage of maximum stimulator output) decreased after the therapy but were still higher compared to the control data obtained in the seven healthy subjects (Figure 16). Resting thresholds prior to the therapy were 63% on the unaffected side and 65% on the affected side, and after therapy these thresholds decreased to 50% on the unaffected side and 52% on the affected side. Active thresholds prior to therapy were 40% on the unaffected side and 44% on the affected side, and likewise these thresholds decreased to 34% on the unaffected side and 36% on the affected side.

JM's resting *recruitment curves* were lower than control values suggesting reduced motor excitability, and interestingly, these values showed a substantial increase on the unaffected side following the therapy but no change on the affected side (Figure 17). JM's active *recruitment curves* were within the range of control values for both sides before therapy, and a substantial increase in motor excitability was also seen after therapy on her unaffected side (Figure 18). At the same time, JM's silent periods were substantially higher than the control values on both sides before therapy; these values decreased somewhat towards normal levels after the therapy (Figure 19).

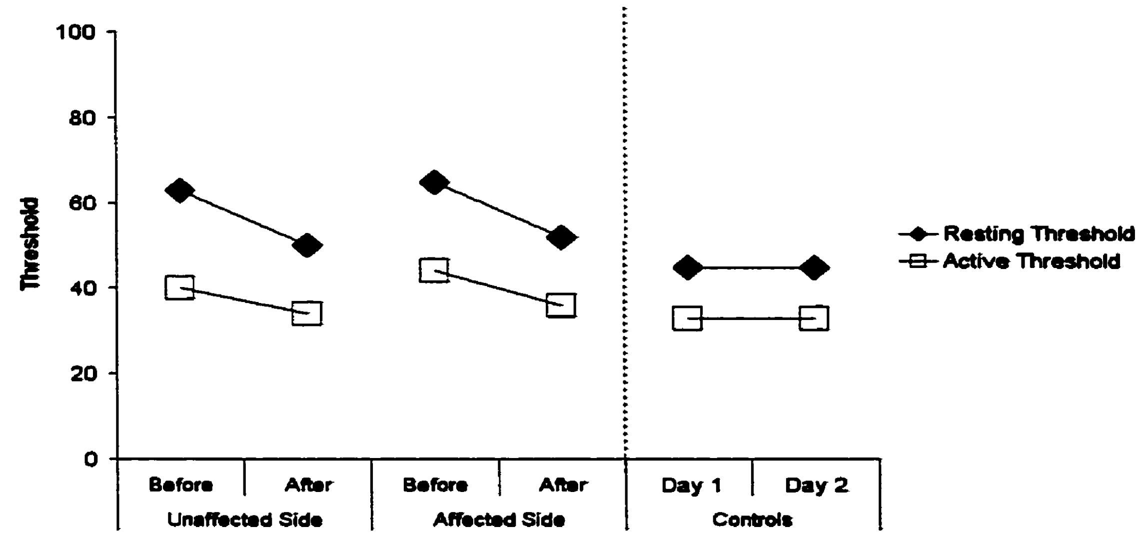


Figure 16. Illustrates resting (black diamonds) and active (white squares) threshold values in Patient JM: the Y-axis represents threshold values and the X-axis represents the unaffected and affected sides before and after treatment. Also shown are control data obtained in the seven healthy subjects. Resting and active thresholds decreased after therapy.

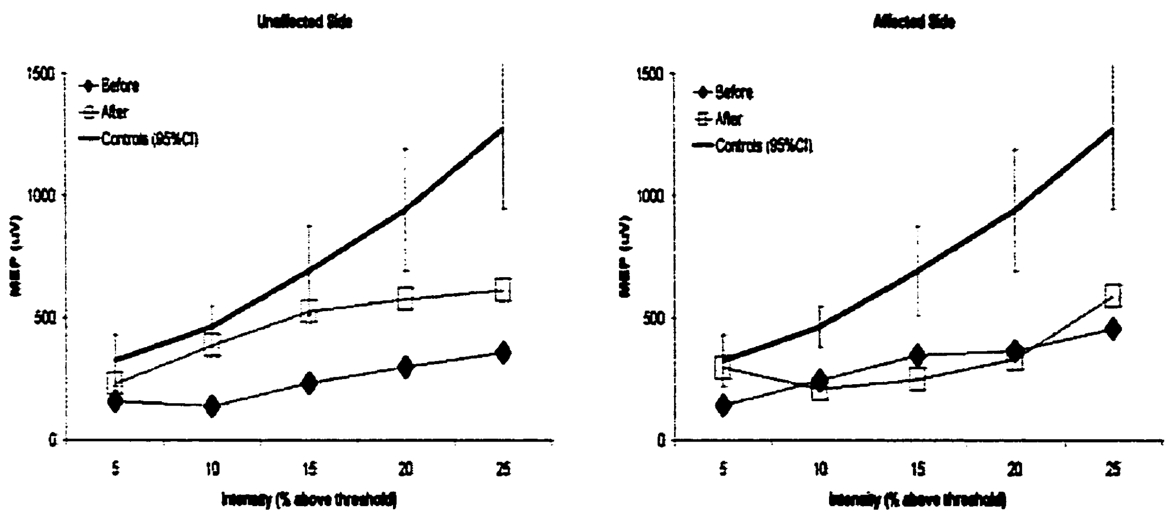


Figure 17. Illustrates the resting MEP amplitudes in Patient JM before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs in microvolts and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. An increase in *recruitment curves* after therapy was seen on the unaffected side.

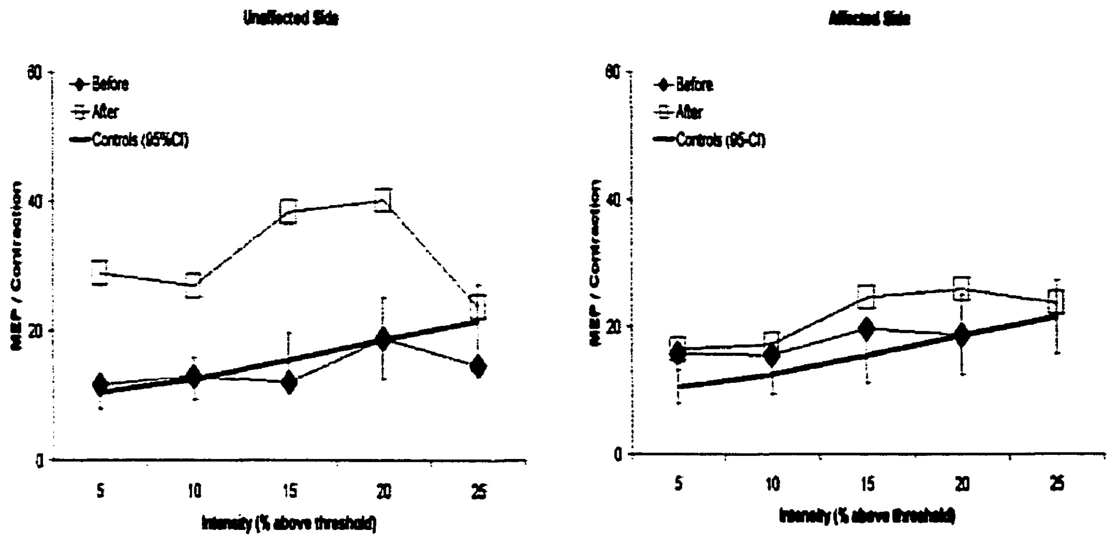


Figure 18. Illustrates corrected active MEPs in Patient JM before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs expressed as a ratio of MEP to EMG contraction and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. A large increase in *recruitment curves* was seen on the unaffected side.

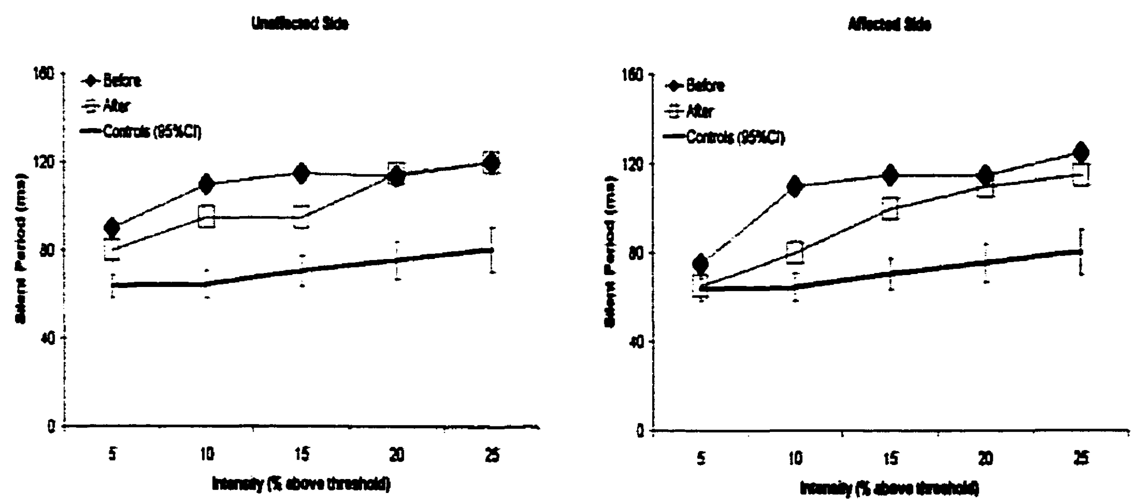


Figure 19. Illustrates *silent period* durations in Patient JM before (black diamonds) and after (white squares) treatment: the Y-axes represent the *silent period* in milliseconds and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. Decreases in the *silent period* were seen on both sides.

Comment

The MAL documented improvement in the usefulness of the stroke-affected arm, and this improvement parallels changes in electrophysiological measures. The higher threshold values in JM than those in control subjects may reflect an affected motor system that was less responsive to stimulation. Perhaps the decrease in thresholds after therapy reflects a more excitable motor system. There was little change in JM's *recruitment curves* before and after therapy for the affected side, suggesting that changes in the excitability of motor pathways to the affected FDI were minimal. Conversely, substantial increase in the excitability of the motor pathways to the unaffected FDI was observed in terms of enhancement of the *recruitment curves* in the unaffected side after therapy. Given that lower intensities of TMS were delivered after therapy (her thresholds decreased), this observed enhancement is not related to higher levels of TMS.

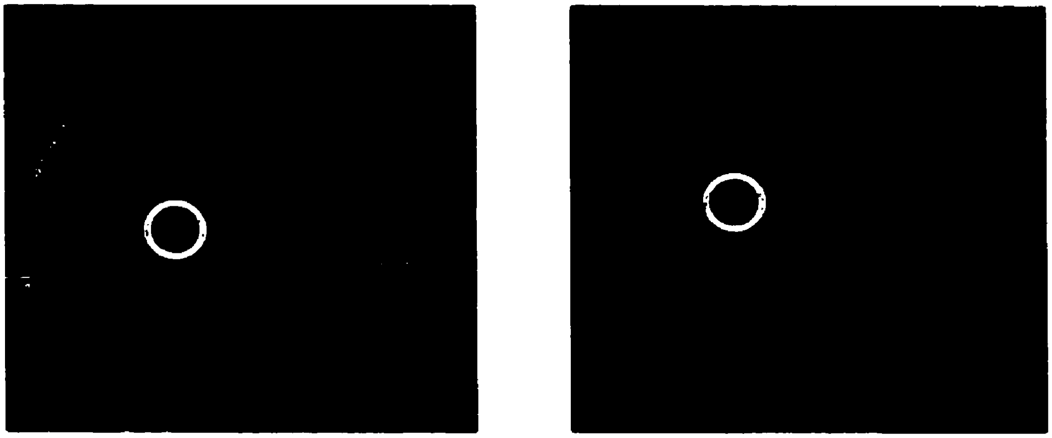
The increased excitability on the unaffected side could in part be explained by use (because she was also constantly training her good arm during Mirror Therapy in tandem with the weak arm); however, it was expected that this enhancement would also occur on the affected side. Nevertheless, JM displayed behavioural motor improvements in her affected arm after therapy, and this leads to the possibility that changes responsible for these improvements might have occurred in the unaffected hemisphere and / or at the spinal level. Decreases in the *silent period* duration towards normal levels were also observed on both sides after therapy. It was hypothesized that because *silent period* durations are altered in stroke patients, improvement in stroke deficits might parallel a return to normal levels. This was indeed the case in JM, and may indicate recovery.

4- CI Therapy and Neurophysiological Changes

The present study aimed to improve motor ability in two patients: one patient suffered a stroke in adulthood, and the other displayed hemiparesis since early infancy, possibly due to a perinatal lesion. Both patients met the inclusion criteria described above for Mirror Therapy. The rehabilitative intervention was very similar to the one used by Taub's group at the University of Alabama at Birmingham except that our patients received three weeks of CI Therapy, whereas Taub's patients received two weeks of therapy.

Patient SM

Patient SM was a right-handed 40 year-old man. His MR scan showed a lesion encompassing the left internal capsule and the left external globus pallidus (Figure 20). Originally from Ghana, Africa, he came to Montreal to study social work. He suffered a major ischaemic stroke in 1996 that left him with a right-sided hemiparesis. On the WAIS-R, SM obtained a Full Scale IQ rating within the low average range (85) with a significant discrepancy (16 points) between a Verbal IQ (93) and a Performance IQ (77) rating.



L R L R

Figure 20. The above MR shows coronal and horizontal views in Patient SM. The images reveal a lesion that encompasses the left internal capsule and external globus pallidus.

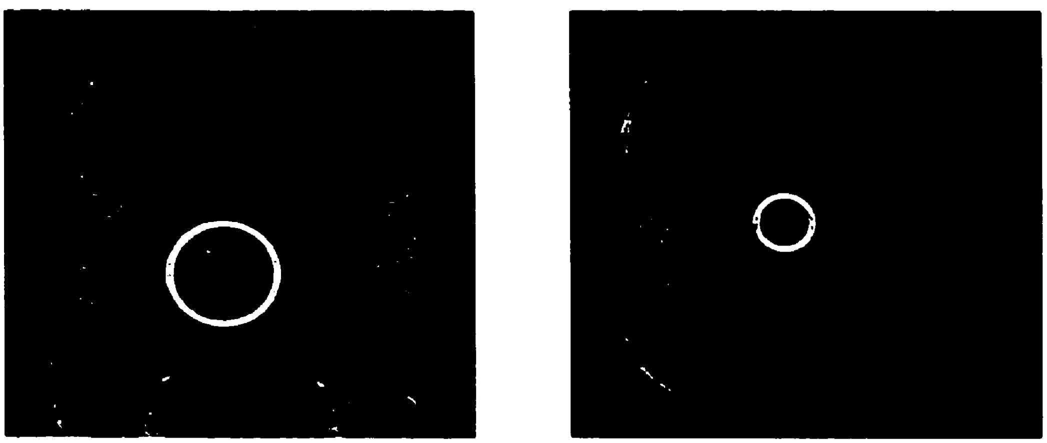


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Figure 21. The above MR shows coronal and horizontal views in Patient JM. The images reveal lesions in the left red nucleus, left crus cerebri, and a small lesion in the left thalamus.

Patient CS

Patient CS was a mandatory left-handed 40 year-old man. He suffered a right-sided hemiparesis in early infancy and his MR scan revealed two lesions (Figure 21). One lesion located in the left red nucleus affecting white matter in the left crus cerebri, and a second lesion was located in the left thalamus. Determining the precise location of a lesion in the thalamus is often difficult, but in his case, the location encompassed at least the ventral lateral nucleus, a motor-related area. CS came to Montreal in childhood from India; he has a Ph.D. in History and is currently a University lecturer. On the WAIS-R, CS obtained a Full Scale IQ rating within the high average range (111) with a highly significant discrepancy (43 points) between a Verbal IQ (130) and a Performance IQ (87) rating.

Method

The two patients underwent three weeks of intervention for which they trained their weak arm in the laboratory by shaping, for approximately six hours a day, five days a week. A selection of 40 tasks was available for shaping exercises, from which a subset of 18 was chosen for each individual depending on his specific deficit. Each task involved a simulation of an activity of daily living (ADL) and was directed towards different muscles. Some tasks were designed to strengthen a specific muscle group, and others concentrated on co-ordination of different muscle groups. In addition, patients were required to wear a padded safety mitt on their unaffected arm both in the laboratory and at home, but only in situations where safety was not compromised. *Safety was always the first consideration.* A formal home treatment contract was made with the patient outlining the agreed-upon activities in which the patient could and could not participate while wearing the mitt. This was to encourage patients to perform ADLs with their weak arm while avoiding any activity in which safety would be compromised while wearing the mitt. Patients were asked to wear the mitt for 90% of the time they were awake at home.

Measurements were taken in order to chart improvement. Behavioural measurements were documented, and the TMS / EMG procedures were used before and after therapy to monitor CNS changes. The MAL was also administered daily (Taub et al., 1993), and two additional behavioural measurements were also employed. These two tests were the Wolfe Motor Function Test (Wolfe et al., 1989; Taub et al., 1993) and the Actual Amount of Use Test, or the AOUT (Uswatte and Taub, 1999). In contrast to the daily administration of the MAL, the Wolfe and the AOUT were administered before and after therapy only.

The Wolfe documents performance time and functional ability (FA) for 17 simple limb movement tasks ranging in difficulty. Patients have to complete each task within 120 seconds, and if unable to do so in the allocated time, they receive a score of 0 out of 5 and the examiner moves on to the next item. The AOUT measures spontaneous use of the weak arm in the laboratory setting, and addresses differences arising in functional ability and amount of use when a task is requested versus when a task is not requested. For this latter test administration, the setting is informal and patients are unaware that they are being evaluated. The examiner prompts the patient to carry out predetermined activities routinely used in everyday life. Such a task would be to give the patient the morning newspaper and ask him or her to read an article that may be of interest. Overall, the MAL, the Wolfe and the AOUT were chosen and employed not only to measure motor ability, but also to the measure the usefulness of the weak arm in ADL.

Results for Patient SM

Patient SM showed remarkable improvement in his affected hand. His AOU scores on the MAL were 1.8 / 5 at the beginning of his therapy and 3.3 / 5 at the end of his therapy. These scores correspond roughly to little use of the affected arm at the beginning of therapy to substantial use after. Improvement in functional ability (FA) in the Wolfe was also remarkable with a score of 2.9 / 5 before therapy (median time to complete a task = 7.08 seconds) and a score of 3.9 / 5 after therapy (median time to complete a task = 3.44 seconds). These FA scores correspond roughly to a performance level that is fair to a performance level that is almost normal. The AOUT scores also showed substantial improvement in the usefulness of the affected arm. His AOU score in the AOUT prior to therapy was 0.2 / 2 and 1.5 / 2 after therapy. These scores correspond to no use of the affected arm at the beginning of therapy to substantial use after. His FA scores in the AOUT prior to therapy was 0.7 / 5 and 2.3 / 5 at the end of the therapy.

SM's electrophysiological data revealed trends similar to those observed for Patient JM. SM's active thresholds were higher compared to those of control subjects and these decreased with therapy (Figure 22). Resting thresholds were not obtained on the affected side for before and after therapy, because stimulation intensities were too high for the patient's comfort. His resting thresholds on the unaffected side increased with the therapy from 67% before therapy to 78% after. Conversely, his active thresholds on both sides decreased from 60% on the unaffected side to 52%, and from 65% on the affected side prior therapy to 60%.

Not all the necessary data for full resting *recruitment curves* were obtained because we were unable to find the patient's resting thresholds on the affected side. On the unaffected side, the stimulation intensities were too high for the patient for us to acquire a full set of data (Figure 23). Nevertheless, motor excitability on the unaffected side was lower than that seen in control subjects. Sufficient data were collected to obtain full active *recruitment curves* (Figure 24). Before therapy, these active curves were within the range of control values for both sides, and a substantial increase in motor excitability was seen after therapy on his unaffected side only. At the same time, SM's *silent period* durations were substantially higher on both sides than the control subjects and decreased towards normal levels after therapy, more so on the affected side (Figure 25).

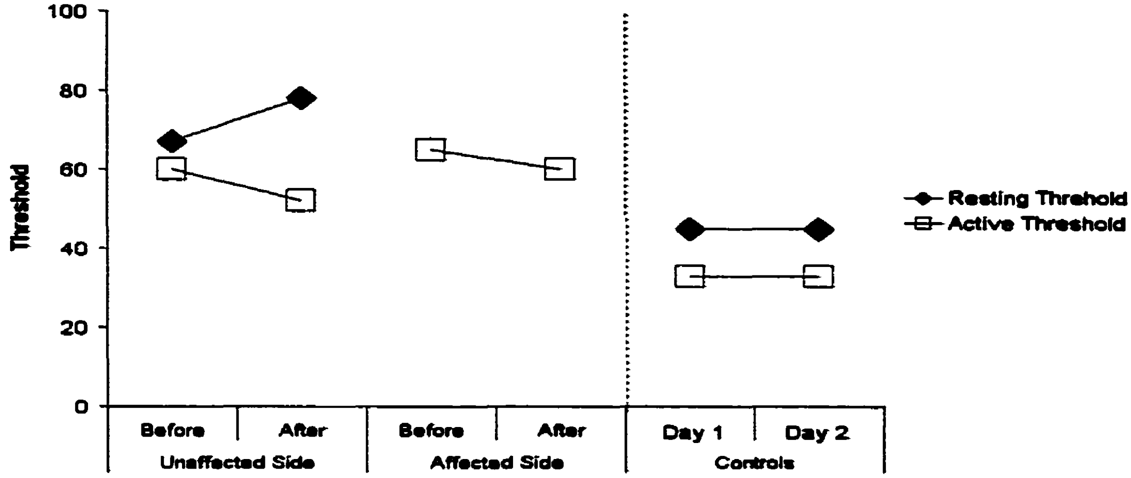

Figure 22. Illustrates resting (black diamonds) and active (white squares) threshold values in Patient SM: the Y-axis represents threshold values and the X-axis represents the unaffected and affected sides before and after treatment. Also shown are control data obtained in the seven healthy subjects. Active thresholds after therapy decreased on both sides, and resting thresholds after therapy increased on the unaffected side. Resting thresholds were too high to be obtained.

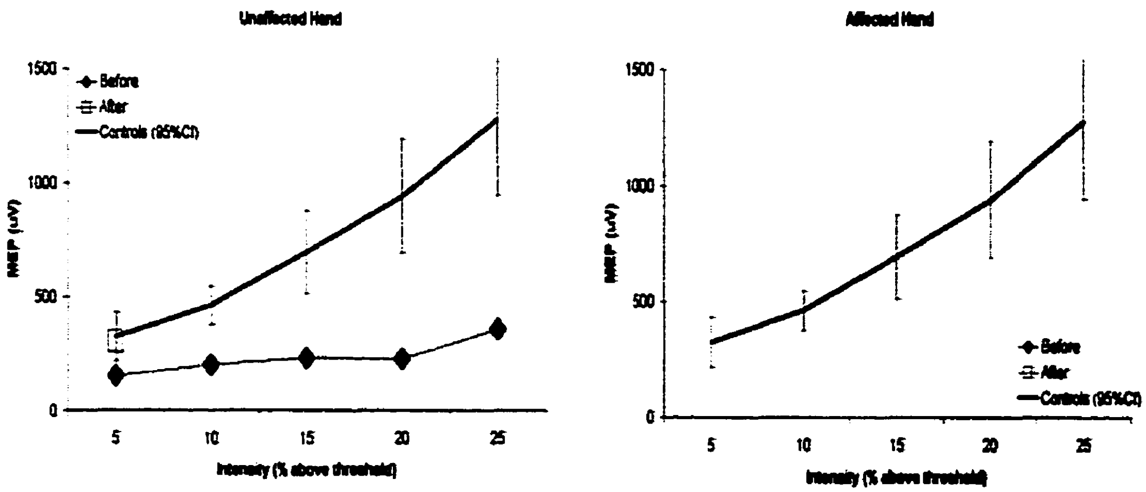

Figure 23. Illustrates the resting MEP amplitudes in Patient SM before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs in microvolts and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI.

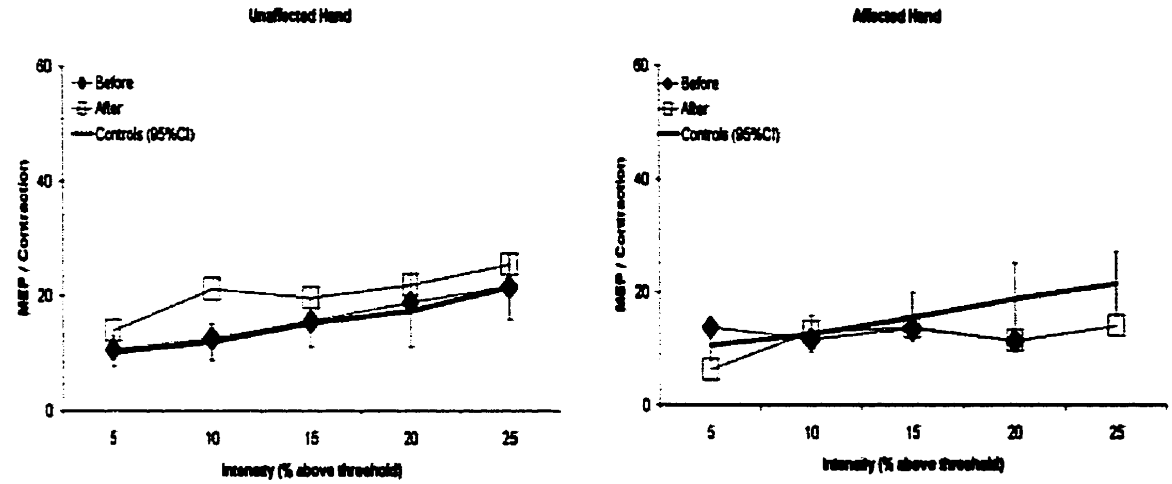

Figure 24. Illustrates corrected active MEPs in Patient SM before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs expressed as a ratio of MEP to EMG contraction and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. An increase in *recruitment curves* after therapy was seen on the unaffected side.

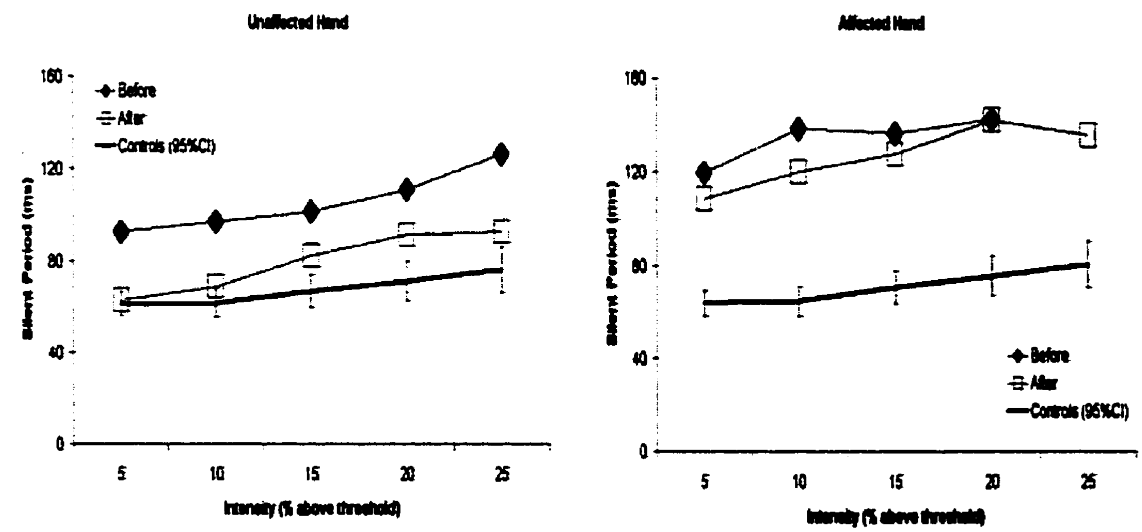

Figure 25. Illustrates *silent period* durations in Patient SM before (black diamonds) and after (white squares) treatment: the Y-axes represent the *silent period* in milliseconds and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. Decreases in the *silent period* after therapy were seen on both sides.

Results for Patient CS

Patient CS showed dramatic motor improvements with CI Therapy. His AOU scores on the MAL were 1.7 / 5 before the therapy and 3.7 / 5 after the therapy. These scores correspond to little use of the affected arm at the beginning of therapy to a substantial use after. FA scores on the Wolfe also demonstrated that his therapy was effective: prior to therapy his FA score was 3.3 / 5 (median time to complete a task = 2.60 seconds) and after therapy his FA score was 4.2 / 5 (median time to complete a task = 2.20 seconds). These FA scores correspond roughly to a performance level that is fair to a performance level that is almost normal. Substantial improvement in the usefulness of his affected arm was also observed on the AOUT. His AOU score in the AOUT was 0.7 / 2 before therapy and 1.8 / 2 after therapy, corresponding to little use of the affected arm at the beginning of therapy to substantial use after. His FA scores in the AOUT prior to therapy were 1.1 / 5 and 3.2 / 5 at the end of therapy.

CS's electrophysiological data, compared to the other two patients showed different patterns of change with therapy. Although his resting and active thresholds were also higher than control values, these thresholds either increased or decreased after therapy (Figure 26). His resting thresholds on the unaffected side increased from 60% to 70%, and decreased on the affected side from 69% to 68%. Conversely, his active thresholds increased on both sides from 43% on the unaffected side to 48%, and from 43% on the affected side to 54%. Because of his high resting thresholds, not all data necessary to acquire full resting *recruitment curves* were obtained; nevertheless, these curves decreased after therapy (Figure 27). Active motor

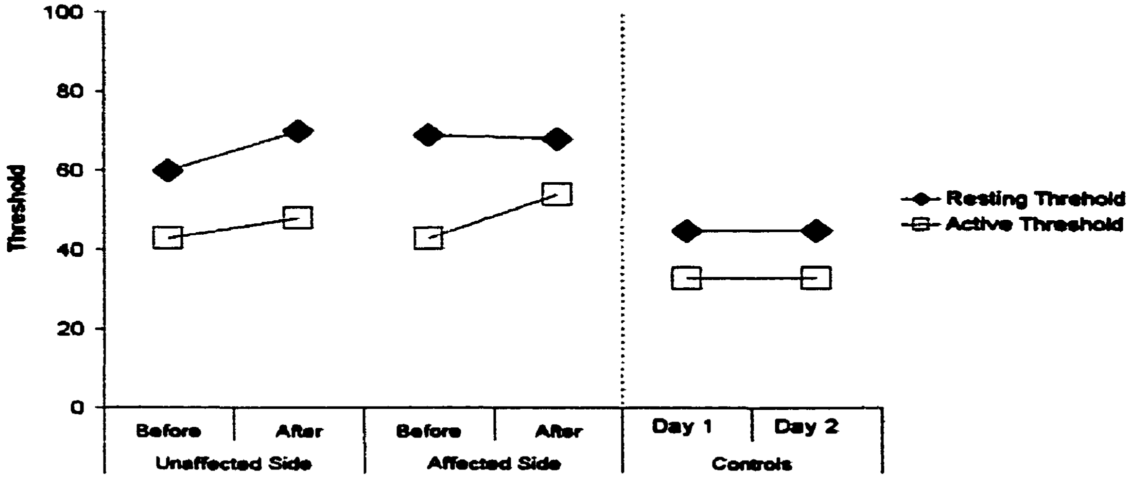

Figure 26. Illustrates resting (black diamonds) and active (white squares) threshold values in Patient CS: the Y-axis represents threshold values and the X-axis represents the unaffected and affected sides before and after treatment. Also shown are control data obtained in the seven healthy subjects. Resting and active thresholds had a tendency to increase after therapy.

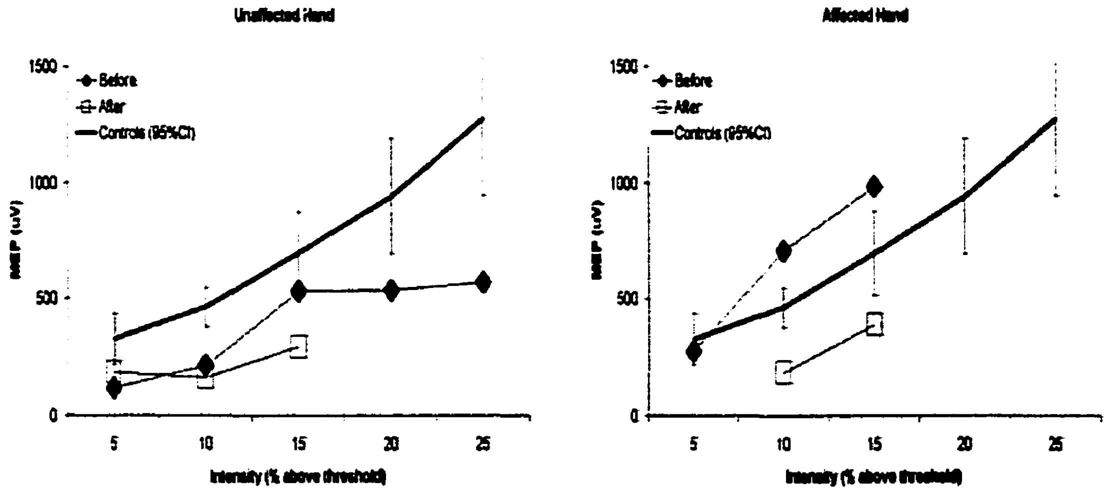

Figure 27. Illustrates the resting MEP amplitudes in Patient CS before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs in microvolts and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. Decreases in *recruitment curves* after therapy were seen on both sides.

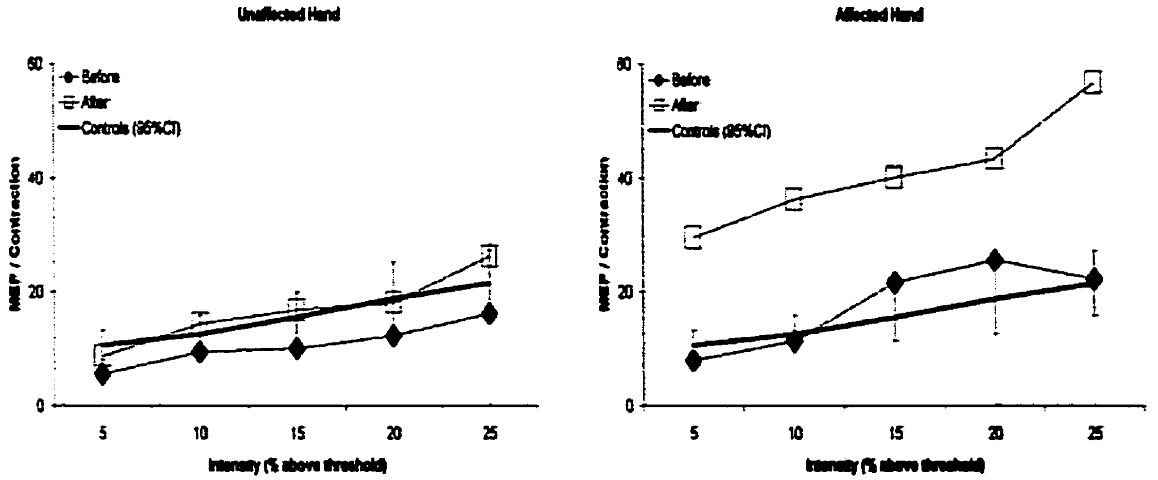

Figure 28. Illustrates corrected active MEPs in Patient CS before (black diamonds) and after (white squares) treatment: the Y-axes represent MEPs expressed as a ratio of MEP to EMG contraction and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. Increases in *recruitment curves* after therapy were seen on both sides, a more substantial increase was observed on the affected side.

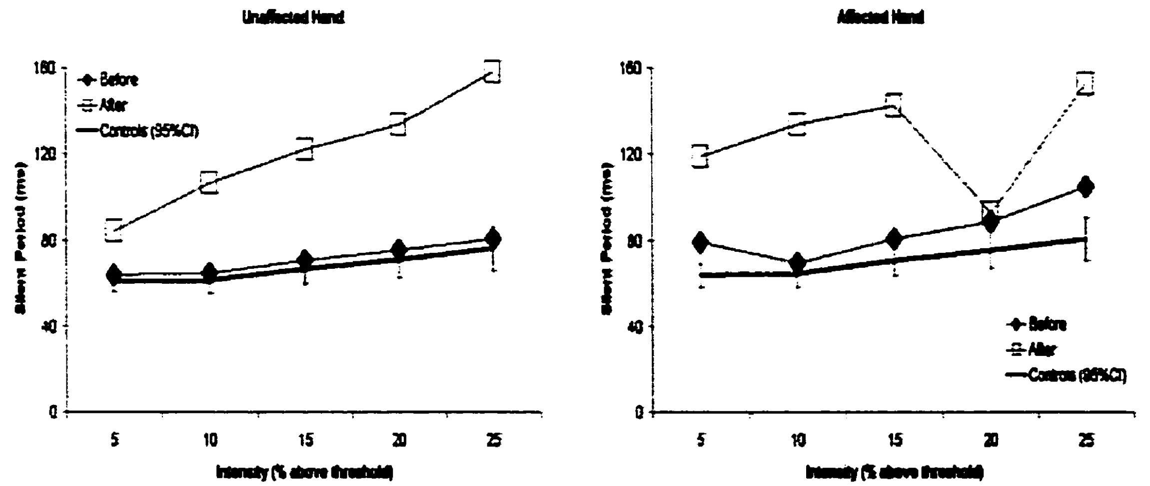

Figure 29. Illustrates *silent period* durations in Patient CS before (black diamonds) and after (white squares) treatment: the Y-axes represent the *silent period* in milliseconds and the X-axes represent TMS intensities as a percentage above threshold. Also shown are control data in the seven healthy subjects with 95-CI. Increases in the *silent period* were seen on both sides

recruitment curves changed in the other direction after therapy as the curves increased, and substantially more so on the affected side (Figure 28). Also, *silent period* durations were comparable to control values on both sides prior to therapy, but increased after therapy (Figure 29).

Comment

Both SM and CS showed remarkable improvement in their behavioural tests, indicating improved usefulness of their affected arm in ADL, and these benefits were maintained outside the laboratory setting. These results coincide with changes in electrophysiological measures, and given that both patients were different with respect to sites of lesion and time of stroke onset, it is perhaps not surprising that they showed different patterns of CNS change.

Patient SM's MR scan showed a capsular lesion, and he showed similar changes in electrophysiological measures to those observed in JM who had undergone Mirror Therapy. As revealed by the lack of change in SM's active *recruitment curves* on the affected side, change in the excitability of the motor pathways to the affected FDI was minimal; however, some increased excitability of the motor pathways to the unaffected FDI was indicated by the enhancement of the *recruitment curve* on the unaffected side. Given that lower intensities of TMS were delivered after therapy to obtain his active *recruitment curves* (his active thresholds decreased), this observed enhancement is not dependent on higher levels of TMS.

Unlike JM who underwent Mirror Therapy, the increased excitability observed in SM cannot be explained by use because SM's unaffected arm was constrained with a restraining device. This finding was therefore unexpected, and it was thought that this increased excitability would only occur on the affected side. Nevertheless, SM did display behavioural motor improvements in his affected arm after therapy, and this leads to the idea that changes in *recruitment curves* of the unaffected motor pathways might translate to behavioural improvements observed in the affected arm. This in turn may reflect neurophysiological changes in the unaffected hemisphere and / or at the spinal level.

By contrast, increased excitability of the motor pathways to the affected FDI was substantial in CS with the enhancement in *recruitment curves*, while changes in the excitability of the motor pathways to the unaffected FDI was minimal with little change in *recruitment curves*. Although higher intensities of TMS were delivered after therapy (his thresholds increased) and could have facilitated the muscle response, a real neurophysiological change is likely to have occurred because *recruitment curves* were greatly enhanced. In addition, CS's changes in *silent period* duration were unexpected. It was predicted that *silent periods* in our patients would initially be affected and would return to normal levels, this was indeed the case for SM but not for CS. *Silent periods* were at normal levels prior to therapy and about doubled in duration after. Perhaps, this difference between SM and CS might reflect different neurophysiological patterns of recovery.

In this project, we validated an electrophysiological method that could be useful in examining treatment related changes in stroke patients. Our first study served to validate the electrophysiological procedures employed by assessing the reliability of measurements between repeated sessions in healthy subjects who did not receive any intervention. It was assumed that no CNS changes between the two sessions would occur, and therefore it was also assumed that measurements taken between repeated sessions would remain consistent provided that the electrophysiological procedures were reliable. The study revealed that both resting and active threshold values were reliably reproducible over time, as were corrected active MEPs and *silent period* durations.

By contrast, low reliability was documented for the amplitudes of resting MEPs. Past experiments have shown that this variability is a real neurological phenomenon related to changing excitability of the cortex (Kiers et al., 1993). Changes in coil positioning affecting variability cannot be entirely ruled out. It is possible that reliability could have been increased had M1 stimulations precisely been delivered in the same position between sessions. With frameless stereotaxy (Paus, 1999), which first acquires an MR image of a subject's brain, then registers the subject's head with this image, and finally places the coil in the appropriate coordinates to target the brain region of interest, it would then be possible to monitor coil positioning throughout the experiment and ensure that the same position is achieved in repeat examination.

There has been recent interest in applying Mirror Therapy clinically to ameliorate certain neurological conditions. Altschuler and colleagues (1999) propose that their Mirror Therapy works by recruiting neurons in the premotor area, which thus provide a parallel corticospinal projection as a substrate for functional substitution (Dum and Strick, 1991). In the monkey, intracellular recordings in premotor area F5 reveal a group of specialized neurons coined *mirror neurons* by Rizzolatti and colleagues (1996a). These neurons are active both when the animal performs an action and when the animal observes the visual presentation of a similar action. Positron emission tomography (PET) studies have examined patterns of activations during the visual presentations of hand actions (Rizzolatti et al., 1996b), and show that homologous premotor areas show increases in cerebral blood flow (CBF) in humans.

In addition, visual presentation of movements can facilitate the execution of the same actions (Fadiga et al., 1995, 1999; Strafella and Paus, 2000), and it might therefore be possible that CNS changes can occur in the motor system when sufficient visual stimuli are provided over a period of time. Based on this possibility, it was predicted that Mirror Therapy would produce a permanent enhancing effect in motor ability; in the same way as professional athletes use mental imagery to enhance their performance and refine their skills (Annett, 1994; Blair et al., 1993; Madigan et al., 1992). It was hoped that the mirror would be effective because this could lead to exciting research and new clinical alternatives. With the increasing sophistication of computer graphical software, user interface, and virtual reality, effective home-treatment programs could be offered to chronic stroke patients on their computer.

Altschuler and colleagues (1999), however, failed to demonstrate convincingly that motor enhancements were directly related to the mirror. In our study of normal subjects, we differentiated the effects of repeated limb use from the putative effects of the mirror, and the results were more in keeping with limb use being the key in achieving motor improvement. No statistical difference was observed between groups that practised while observing their reflection in a mirror and those that used a cardboard and did not see a reflection. Greater improvement in the less adept hand occurred in groups that performed exercises in both hands than groups that performed exercises in their good hand only, illustrating the importance of use. The study also shows that groups performing exercises in the good hand only can also improve the other less adept hand, thus illustrating transfer from one hand to the other (Allen, 1948; Cook, 1933; Ewert, 1926). Yet, transfer may not apply in stroke: stroke patients already extensively use their good arm and this does not help them. According to Taub's theory of learned non-use (1980), the constant use of the good arm is actually problematic because it reinforces patients to avoid using their affected arm by preferring their good arm.

Patient JM who received Mirror Therapy reported that she was sceptical about the effects of the mirror, and felt that her motor enhancements were likely a result of the mass practice of her affected arm during training sessions. Nevertheless, her intervention helped her regain motor ability, and although her behavioural improvements were not as impressive as those demonstrated in Patients SM and CS who underwent CI Therapy, her improvement is significant given she received her intervention for only one week whereas SM and CS underwent three weeks of therapy. Whether or not Mirror Therapy has a placebo effect, it still may have some clinical value because it might encourage patients to use their affected arm.

On the other hand, CI Therapy is recognised as an effective intervention (Morris et al., 1997) and both SM and CS were extremely pleased with the outcome of their intervention. Behavioural results obtained on the MAL, Wolfe, and AOUT were impressive, and are consistent with those obtained by other groups (Miltner et al., 1999, Morris et al., 1997, Taub 1993). As an avid writer, CS set himself the goal of being able to type with both hands. Although he did not achieve this goal, he learned to effectively use a mouse with his affected hand, and reports that he continues to do this whenever he works on a computer.

The effectiveness of CI Therapy for remediating other neurological problems besides stroke has been demonstrated in musicians with focal hand dystonia (Candia et al., 1999). Focal hand dystonia involves a loss of motor coordination of one or more digits and is sometimes associated with repetitive synchronous movements of the digits made while playing instruments over many years. In one study, the combination of magnetoencephalography (MEG) and delivered tactile stimulation to the distal phalanx of the hand fingers, revealed cortical fusion of digit representations in the somatosensory cortex of dystonic musicians (Elbert et al., 1998). Based on this consideration, immobilization by splint(s) of the digits other than the dystonic finger(s), and the mass practice of repetitive exercises in coordination with one or more of the other fingers, was successful in remediating the dystonia (Candia et al., 1999).

Neurophysiological Patterns of Recovery

The strengthening of ipsilateral corticospinal connections is one of two possible mechanism of compensation underlying sparing of function after stroke (Hicks and D'Amato, 1970). Consistent with this suggestion are results obtained in functional imaging studies using TMS and EMG. In this regard, Caramia and colleagues (2000) demonstrated an unmasking of ipsilateral pathways in which greater ipsilateral MEPs were induced by TMS in patients with hemiparetic stroke compared to healthy control subjects. In addition, many studies using PET, or functional MR imaging, have revealed ipsilateral activation during the execution of movements by the affected hand in post-stroke patients (Nelles et al., 1999; Cao et al., 1998; Seitz et al., 1998; Weiller et al., 1993; Chollet et al., 1991).

Another possible mechanism mediating post-stroke improvement is the reorganization of pre-existing motor pathways in the affected hemisphere. Candidate areas for substitution are regions rich in direct corticospinal projections, namely the premotor areas (Dum and Strick, 1991). Following bilateral ablation of forelimb M1 in the rat, Castro-Alamancos and Borrell (1995) have shown that with microstimulation of adjacent cortical areas, functional recovery in recovered animals was due to the reorganization of adjacent areas. Ablation of the reorganized forelimb areas reinstated the forelimb behavioural impairment, while the same lesion in normal animals had no effect on performance.

Further studies in the adult monkey demonstrate that the size of motor cortical representations is highly correlated with motor performance (Nudo et al, 1996; Nudo et al., 1992). For example, motor cortical representations of the dominant hand are larger than corresponding regions for the non-dominant hand (Nudo et al., 1992). Likewise, when animals are trained to make specific movements, they show greater representations in the motor cortex for these trained movements than for other movements (Nudo et al., 1996). This latter finding clearly demonstrates that motor cortical representations are plastic in the adult monkey.

In human studies using functional imaging techniques, the phenomenon of skill-associated nervous system plasticity has been demonstrated. A TMS mapping study showed that the process of skill acquisition in non-musicians through sustained performance of playing a five-finger exercise on the piano is associated with an increase in motor cortical representations (Pascual-Leone et al., 1995). Concurrent with improvement in performance, the size of motor cortical outputs increased compared to control groups that did not undergo training. TMS mapping has demonstrated that blind subjects proficient in Braille reading have enlarged motor cortical representation of the reading finger compared to control blind subjects (Pascual-Leone et al., 1993). Recordings of sensory evoked potentials induced by the tactile stimulation of the reading finger, showed similar increases in sensory cortical representation in blind subjects with proficient Braille reading skills compared to control blind subjects (Pascual-Leone and Torres, 1993).

Although the combination of TMS and EMG employed in this project could not directly test whether ipsilateral or contralateral compensatory mechanisms were underlying improvements in motor ability, careful examination of the data provides some insight. The electrophysiological procedures examined changes in the excitability of the motor pathways to both the affected and unaffected first dorsal interosseus (FDI) muscles by measuring *recruitment curves*. It was predicted that behavioural motor enhancements consequent to therapeutic intervention, Mirror Therapy or CI Therapy, would result in increased excitability of motor pathways to an affected limb muscle.

Change in the *recruitment curves* of the affected FDI was minimal in JM and SM; however, enhancement of *recruitment curves* of the unaffected FDI was observed. This increased excitability in JM could in part be explained by use because she was also constantly training her good arm during Mirror Therapy in tandem with the weak arm. Unlike JM, this increase in excitability in SM cannot be explained by use because his unaffected arm was constrained with a restraining device. Nevertheless, both JM and SM displayed behavioural motor improvements in their affected arm after therapy, and this leads to the idea that the enhancement in *recruitment curves* of the unaffected arm might translate to improved motor ability in the affected arm, perhaps involving the recruitment of ipsilateral pathways. Recruitment of ipsilateral pathways might be likely in patients with capsular lesions, such as JM and SM who have a reduction in the number of corticospinal fibres in the affected hemisphere and have less neural substrate available for recruitment of adjacent fibres. Perhaps, their neurophysiological mechanisms for recovery also involve changes at the spinal level, but this remains to be elucidated.

Electrophysiological measures in CS reflect different patterns of change to those seen in JM and SM, which are likely related to lesion site and time of stroke onset. His lesions were located in the left red nucleus area, including surrounding white matter in the crus cerebri, and the left thalamus, which included at least the motor-related ventral lateral nucleus. As shown by his *recruitment curves* before and after therapy, increased excitability of the motor pathways of the affected FDI was substantial with large enhancement in *recruitment curves*, and changes in the excitability of the motor pathways to the unaffected FDI was minimal with little change in *recruitment curves*. A possible explanation is that CS may have had sufficient corticospinal substrates in the affected hemisphere for the recruitment of adjacent fibres.

Another difference in CS was his changes in the *silent period* duration. The *silent period* is a neurophysiological phenomenon driven by local inhibitory interneurons in M1 and inhibitory mechanisms in the spinal cord, including Renshaw inhibition (Hallett, 1996), and is relevant in stroke because it is frequently shortened or prolonged (Ahonen et al., 1998). Abnormal *silent period* durations reflect motor physiological impairment, and therefore it was predicted that they would return towards normal levels with motor recovery. JM and SM showed prolonged *silent period* durations prior to therapy that, as predicted, returned to normal levels after therapy, whereas CS had *silent period* durations that were comparable to healthy subjects prior to therapy and that grossly lengthened with behavioural motor improvements. Perhaps this difference reflects different neurophsyiological changes in the patients, yet our understanding of the *silent period* and how this parameter can change is still limited. Further examination of this possibility and a better understanding of these different mechanisms may allow more effective interventions specific to an individual.

Future Directions

The procedures employed in this project had two important limitations. The first is we did not directly test the recruitment of ipsilateral pathways, however, this could be resolved by recording induced muscle activity in the ipsilateral hand muscles with EMG electrodes. Prior TMS studies have tested ipsilateral MEPs and ipsilateral *silent periods* after stroke (Caramia et al., 2000; Turton et al., 1996), but this is more difficult than it appears. Special consideration must be taken because higher stimulus intensities are required for examining such pathways.

The second limitation is that the procedures did not directly test where and at what level of the CNS changes take place. Changes can occur at the cortical, subcortical, or spinal cord level. To determine whether these changes take place at the spinal cord level is feasible: spinal excitability can be measured by recording the H-Reflex for a given muscle (Nielsen et al., 1999), and any changes in spinal excitability would thus indicate a change at the spinal level. However, to differentiate changes in cortical and subcortical structures is more difficult. Imaging techniques such as PET and functional MR can only provide a pattern of activation sites, and reveal little information on how these sites are functionally connected. Current advances in combining TMS and PET may provide the opportunity to delineate more precisely the functional state of connectivity between a selected cortical area and other CNS structures (Paus et al., 1997). This is achieved by stimulation of a cortical area by TMS and measuring CBF with PET, and represents an exciting area for further research.

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