

**THE REHABILITATION
OF MOTOR AND COGNITIVE DISORDERS
AFTER STROKE**

by

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A thesis submitted to

The University of Birmingham

For the degree of

DOCTOR OF PHILOSOPHY

School of Psychology

College of Life and Environmental Sciences

The University of Birmingham

February 2014

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BIRMINGHAM

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ABSTRACT

Following a stroke there can be a large range of different deficits, with poor motor function and cognition being particularly important for outcome. Rehabilitation of these deficits is thus an important priority for clinicians. In this thesis, I present 5 experimental chapters aiming to generate cognitive and motor benefits for the stroke survivor. In Chapter 2, prolonged Mirror Therapy was applied to chronic stroke survivors. In Chapter 3, Mirror Therapy was applied in a home based for chronic stroke survivors. In both these Chapters 2 and 3 benefits in unimanual performance of the affected limb and functional improvements of daily activities are being reported. Chapter 4 considered the application of Mirror Therapy to early subacute stroke participants and tested the neural correlates behind any effect. Changes in brain activation within both the ipsi- and contralesional hemispheres were noted. Functional Electrical Stimulation was applied to chronic stroke patients in Chapter 5. Improvements in motor performance were noted, along with the amelioration of visuomotor neglect. Linked changes in activity in the ipsi- and contralesional hemispheres were again noted. Finally, in Chapter 6, Computer Progressive Attention Training was applied in early subacute stroke patients, comparing performance with patients who received no extra intervention. Importantly, the training not only improved the tested functions but also other cognitive processes not targeted in training (e.g., long-term memory). Taken together, the experimental work provides evidence of strategies that can be followed by clinicians to improve functional ability after stroke. In the final chapter the above findings are being discussed together with clinical implications of motor and cognitive rehabilitation approaches.

ACKNOWLEDGMENTS

There is only one way to start: my greatest gratitude to my PhD supervisor, Professor Glyn Humphreys. I believe that there are only a few people that could well act as PhD supervisors. By far the best and most ideal for me is Glyn. Glyn is the person that I would choose again to do a PhD with if I was about to start from zero point tomorrow. My supervisor was not only a mentor of my research projects but in a way he was a member of my extended family and always found the right way to advice me. PhD is a hard route to follow and Glyn is the only person that could find the strength in me and bring it to the surface during the hard times. From the first meeting that we did discussing the possibility for me being awarded with a PhD scholarship I had a solid impression that Glyn is by far the most intelligent person I ever met. Four years later this is not an impression, it's a fact. Half way through my PhD Glyn moved to the University of Oxford to undertake an exciting role and act as the Head of the Experimental Psychology. Despite, running through the busiest days of his career he was always next to me. His office door both in Birmingham and Oxford were always wide open for me to ask for guidance and to respond to my queries. Glyn is efficient and the positive energy and enthusiasm that emerges on his face combined with his uniquely humble personality will always be the good model for me and my children tomorrow. I am so looking forward to collaborate with Glyn at any stage of my career. Thank you!

It is with great pleasure to express my special thanks to my second supervisor Dr. Pia Rothstein. Her enthusiasm and hardworking character inspired me every minute and without her

MRI analysis will be still 'all Greek to me'. Pia is an incredible person and her friendship together with the long discussions that we had regarding future plans honors me.

Next and related to the academic field I would like to thank Professor Jane Riddoch for always giving me a smile and helping throughout the research projects, Professor Alan Wing for his endless support and Jill Ramsay for baptizing me in the world of research. Special thank to my great friend Dr. Amalia Tsanaka for her endless support to this thesis but above all for her constant positive energy that gives me joy at all times. I am indebted to my friends and colleagues at the University who have all contributed, whether knowingly or not by encouragement and practical assistance and having faith that I could complete this PhD.

There are people that you meet in this life and are here to stay not for less or more but forever. These lifelong friends are always next to you even if they live where you grow up, in Greece, or anywhere in the world. Without these amazing friends I wouldn't make it not only through my PhD but in general I wouldn't be the person that I am today. Eftihia, Tzoanna, Katerina I will always be next to you when you need me as you did all these years. Also, great friends here in UK: Kamen, Sarah, Crisa, Evi, Maria, Basilis, Ilias, Amalia, Katerina, Mel, Saheeda, Nele.

Last but not least, I thank my family, my parents for giving me the opportunity to pursue a career in Physiotherapy and to encourage me to continue my studies abroad. Their endless love and support is something that I would like to return to my children one day in the future. I also thank my brothers for their love and support. There are two more people in my extended family

that supported me through this thesis both emotionally and financially that I would like to express my gratitude to, Eva and Sini.

The last person that I would like to thank and is the most important one is my fiancée and future wife Sissy. These four years might bring me a PhD but above all brought me the person that I dreamed to have a family with. Sissy is the most compassionate, sweet person and has this amazing ability to calm me down when on my blues and to bring the smile back to my face. My beloved Sissy you make me proud and happy every minute. You have changed my life. Thank you so much!

Δημήτρης Σ. Σαμπάνης

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Stroke was first described by the father of medicine, Hippocrates, approximately 2.500 years ago. In his reports Hippocrates used the term ‘apopliksia’ or ‘apoplexy’ (αποπληξία) in order to refer to the sudden loss of consciousness and motor control (paralysis) associated with stroke. The current clinical description of stroke by the Royal College of Physicians (National Clinical Guidelines for Stroke, 2012), presents it as a clinical syndrome with a vascular cause that has the clinical image of rapidly occurring signs of focal or global disturbance of cerebral functions lasting more than twenty-four hours or leading to death (term originally given by WHO – 1978).

Stroke affects around 200 people per 100.000 yearly in England and Wales and 11% of the total deaths in the UK can be attributed to it (Mant, Wade and Winner, 2004). The majority of strokes have been associated with cerebral infraction (85%), whereas fewer cases have also been associated with cerebral haemorrhage (10%) and subarachnoid haemorrhage (5%). Approximately half of the patients who suffer from stroke die during the first year of the episode (Hankey et al., 2000), whereas 55 to 75% of the survivors have mild to severe hemiparesis on the upper limb (Jorgensen et al., 1995). Importantly, recurrence rate of 26% within five years and 39% within 10 years have also been reported in stroke survivors (Mohan et al., 2011). The sensorimotor and functional rehabilitation of stroke survivors has become a major priority and challenge for clinicians as stroke is now considered to be among the major causes of disability worldwide (WHO, 2008). As different rehabilitation techniques have been described in the literature, especially over the last two decades, it is important for the most effective ones to be

identified so that clinicians can promote motor recovery and daily living activities, which may reduce the burden of stroke (Thieme et al., 2013). Mirror therapy (MT), originally described by Ramachandran et al. (1995) to alleviate phantom limb pain, was first considered for the rehabilitation of stroke survivors in 1999 (Altschuler, 1999). Although previous research has assessed the effects of mirror therapy, what remains unclear is the effectiveness of the intervention over the long term and what neural mechanisms are involved during the rehabilitation process.

Another technique used for the rehabilitation of hemiparesis following a stroke is Functional Electrical Stimulation (FES). FES, originally developed as a neuroprosthetic to replace limb function (Lieberson et al., 1961), has been used therapeutically in order to augment voluntary motor drive during motor rehabilitation (Merletti et al., 1975; Popovic et al., 2002, 2004). Although there have been a few studies outlining the beneficial therapeutic use of FES in stroke survivors, however it has not been clarified whether FES only modulates motor recovery or whether it also affects other symptoms associated with stroke, including deficits in attention, such as unilateral neglect.

1.1.1. Attentional deficits after stroke

In addition to the sensorimotor deficits following a stroke, many survivors have minor or more severe attentional deficits including a reduced ability to sustain concentration and mental slowness. Such non-spatial deficits have been observed in spatial disorders, such as unilateral

neglect, which are characterised by a failure to attend to stimuli on the contralesional side of space (Heilman and Valenstein, 1979). However, the effectiveness of cognitive rehabilitation programmes for impairments in attention and cognition remains unclear (Loetscher and Lincoln, 2013). To increase the potential of the benefit from the rehabilitation of cognitive impairments following stroke, clinicians can now use advanced technological equipment including computer based rehabilitation tasks (e.g., attentional training, memory tasks) that still need to be evaluated in terms of their effectiveness (Laver et al., 2012).

1.1.2. Outline of the thesis

The current thesis focuses on the effectiveness of sensorimotor and cognitive interventions in patients suffering from stroke. Following a literature review of the main topics of this thesis (Chapter 1), the central topic of Chapter 2 is the application of mirror therapy to chronic stroke survivors when mirror therapy is applied over a relatively long time period but at a low intensity. This study also evaluates whether the effectiveness of mirror therapy varies for unimanual and bimanual tasks. Since many everyday tasks require bimanual actions, it would be optimal if mirror therapy improved both unimanual and bimanual actions – although the latter may be subject to extra (attentional) constraints (see Punt, Riddoch and Humphreys, 2005). The effectiveness of mirror therapy in chronic stroke survivors was also examined in the study presented in Chapter 3, which, however, focused on the effects of a brief intervention using high intensity mirror therapy. In Chapter 4, the possible positive effects of mirror therapy in an acute stroke population were investigated, while an effort was also made to understand the possible

neural mechanisms behind mirror therapy and its effectiveness, using fMRI techniques. Chapter 5 moves from mirror therapy to present pilot data on the use of functional electrical stimulation in subacute stroke survivors, focusing not only on motor control (contrasting unimanual vs. bimanual movements) but also on the remediation of unilateral neglect. fMRI data are again presented in order to identify possible neural mechanisms that underlie the effectiveness of functional electrical stimulation on stroke rehabilitation. Finally, Chapter 6 presents a computer-based intervention for cognitive problems after stroke, using programs designed originally to improve different aspects of attention in children with hyperactivity disorders. More specifically, the possible benefits of a trial of this intervention for cognitive problems after stroke have been explored. In the final chapter of the present thesis (Chapter 7), different sets of results from the aforementioned studies have been summarised, whereas the potential limitations and contributions of the current studies, as well as the implications for clinical practice and the rehabilitation of stroke patients, have also been discussed.

1.2. Literature Review – Mirror Therapy

1.2.1. First Use of Mirror Therapy

Mirror Therapy (MT) typically involves the use of a mirror 30x40 cm that is placed vertically at the centre of the participant's body. In the case of stroke, the participant places his/her hemiplegic hand behind the mirror and the healthy hand on the reflecting side.

Participants look at the reflecting side of the mirror and they are asked to concentrate on the reflection of the intact hand. Due to the reflection of the hand in the mirror, the patient receives visual feedback of normal movement of the nonparetic upper limb. The therapist leading the training asks the participant to move both hands equally (mirroring movements) in a sequence of movements starting from simple observation to opening and closing fingers, flexion-extension of the wrist, supination-pronation of the forearm and of the elbow. Mirror therapy was first introduced by Ramachandran and Rogers-Ramachandran (1996), who created visual illusions through the use of a mirror and alleviated phantom limb pain (pain that feels like it's coming from a body part that's no longer there) in amputees. By superimposing the healthy hand on the amputated hand with the help of the mirror, patients have reported that they could move and relax the absent limb and that they experienced pain relief (Ramachandran and Hirstein, 1998).

1.2.2. Current Theories

Harris (2000) proposed that phantom pain may be partially triggered by the imbalance of different senses (vision and proprioception). More specifically, mirror induced visual feedback has been suggested to possibly restore the balance between motor output and sensory input (Ramachandran and Altschuler, 2009). Another possible explanation of the way that MT acts is based on mirror neurons (Rizzolatti et al., 1999). These premotor neurons can be found in the frontal and parietal lobes of the human brain (Rizzolatti et al., 1999) and they have been found to fire both when an individual observes an action and when an individual executes a reaching action to grasp an object. In addition, it has been argued that mirror neurons may be involved in

a range of higher-level cognitive functions including actions and intention understanding (Ramachandran and Altschuler, 2009). Mirror therapy may involve the activation of such neurons through visual perception, encouraging their subsequent involvement in actual movement. According to Ramachandran and Altschuler (2009) MT's success in phantom limb patients may be associated with the fact that mirror neurons may be inactive due to learned paralysis and that MT is a tool that can encourage relearning in the brain. The same authors proposed in their conclusions that there is a need to think that the brain acts in an equilibrium state and that it does not act with multiple autonomous areas for specific movements. One consequence is that neurological damage may not (only) disrupt connections within the brain but it may also produce a functional shift in equilibrium. If that is the case, we may be able to shift the equilibrium point back by using other areas of the brain and restoring the neural 'balance', through the use of simple non invasive techniques which alter neural feedback (such as MT),.

Alongside the above theories, Kasai et al. (1997) propose that the primary motor cortex is activated during mirror-based interventions, just as it is during imagined movements. This may operate in parallel with the mirror neuron system (Rizzolatti and Craighero, 2004). Supportive evidence comes from Sartori et al., (2011) who noted the activation of the primary motor cortex during action observation, which was greater when actions were viewed from an individual's perspective compared to a third-person's perspective.

1.2.3. Phantom Limb

The use of MT for phantom limb pain has been proved to be beneficial in some patients both when presented in isolation (Darnall, 2009) or when it is combined with other techniques. For example, Wilcher, Chernev and Yan (2011) presented a case study in which MT was combined with auditory feedback in order to enhance the effectiveness of MT. Auditory feedback was based on the sounds produced by the patient's mother's clapping hands when the patient was asked to clap his hand with the use of the mirror. Participants' Visual Analog Scale (VAS) ratings of pain were reduced from 8/10 to 6/10 in two weeks of MT combined with auditory feedback. Mercier and Sirigu (2009) were interested in assessing the multiple factors that might lead MT to be beneficial or not in different amputees. They recruited eight participants and they offered MT two times per week for eight weeks. The patients reported 38% pain relief on a VAS scale, with only three patients reporting decrease of less than 30%. From their observations of the patients the authors concluded that the effectiveness of MT for amputees is more likely to be related to differences in perceiving the visual feedback from the mirror than to causes related to the amputation, such as the time since the amputation. Chan et al. (2007) also found phantom pain on the lower limbs to be decreased when they ran a MT protocol in comparison with sham therapy and mental representation treatment. Indeed, in the other two non-MT groups, phantom limb pain remained unchanged during the four weeks of the intervention. The authors mentioned that although the mechanisms behind MT remain unclear, it might be possible that visual input (utilized through the mirror neuron system) reduces the activity of systems that receive protopathic pain.

In another study, Sumitani et al. (2008) showed there was better alleviation of deep pain when compared to superficial pain in amputees. Furthermore, Hanling and colleagues (2010) gave four patients daily MT for 2 weeks in the pre amputation period and eliminated pain in three individuals – and even in the fourth individual the pain was not serious enough for the patient to participate in physiotherapy treatment following the amputation. In sum, the work on phantom limbs, then, indicates that MT can encourage neural plasticity and lead to the modulation of perceptual experience in patients.

1.2.4. Complex regional pain syndrome

Similar to phantom limb pain, cortical abnormalities have also been recorded post-stroke in patients with complex regional pain syndrome type 1 (CRPS1) (Moseley, 2004). CRPS1 is one of the most complex impairments to treat following stroke (Forouzanfar et al., 2002) and it is characterized by increased pain, swelling and skin changes. Clinicians are also challenged in their effort to diagnose this syndrome that can develop both post stroke or after limb injury (van de Vusse et al., 2003). Sensory abnormalities in the syndrome may include burning sensations, allodynia and hyper-analgesia. Motor impairments might include a decrease of muscle strength, tremor and clone – spasms. The cause of CRPS1 is yet unknown and treatment is mainly focused on alleviation of peripheral symptoms by using steroids, physiotherapy and analgesics (Ramachandran, Stewart and Rogers-Ramachandran, 1992). Mirror therapy has been shown to be beneficial in stroke survivors with CRPS1 in various studies the most important of which will be reported below.

Moseley (2004) recruited thirteen chronic stroke patients with neuropathic pain who were randomly allocated to the motor therapy or to ongoing management program on a cross over experimental design. The motor therapy comprised six weeks of motor imagery (identifying a left or right hand; imagined imitation of a hand movement) and MT. Neuropathic pain scale was significantly improved in the experimental group and the same effect replicated following a cross-over of the initial control group. However, this study had limitations including a small number of recruits, low heterogeneity in the population and a lack of blindness of the participants giving self ratings. .

A more recent research study of MT in CRPS1 was reported by Tichelaar et al. (2007) who used MT combined with cognitive behavioural therapy in three patients. The researchers measured the VAS (a testing technique for measuring subjective or behavioral phenomena (pain) in which a subject selects from a gradient of alternatives (as from “no pain” to “worst imaginable pain” or from “every day” to “never”) arranged in linear fashion), range of motion, muscle power and topography of painful regions. Pain was found to be improved in all patients following a four to six weeks intervention course. They also reported two patients to be improved in the range of motion and one patient in muscle strength. It is important that, in this study, one of the patients who felt that their affected limb did not constitute part of their body (anosagnosia) following the stroke was found to be less improved when cognitive behavioural therapy was combined with MT. Anosagnosia has been thought to constitute part of the neglect syndrome (Kinsbourne, 1987), suggesting that neglect may be relatively resistant to MT – an idea tested here (Chapter 4).

Selles, Shreuders and Stam (2008) investigated the positive effects of MT in Complex Regional Pain Syndrome Type II (Causalgia – differs from Type I in terms of evidence of nerve

damage) following peripheral injury. The authors reported two case studies in which MT was used in patients with neuroma and burning pain following a glass injury. Although positive reductions in pain were reported immediately after the MT, there was no long term benefit.

Research on the application of MT extends to hand surgery cases. For example, Rosen and Lundborg (2005) found that MT was beneficial to patients with incoordination. In addition, patients increased their active and passive range of motion and they were able to perform movement in smoother ways. In another study by Altschuler and Hu (2008), the authors reported a case study of MT application to a patient with no active wrist extension following wrist fracture. Following a prolonged internal fixation with open reduction the patient developed stiffness and pain. The patient was able to actively extend wrist following a short period of functional electrical stimulation but this only took place during the FES sessions. Following this period researchers combined FES with MT and found that the patient's ability to actively extend the wrist progressed to 35° a month later. The authors attributed the active wrist extension even after therapy to MT.

Freysteinson (2009) published a review paper on therapeutic MT interventions from a nursing point of view. In this paper the implications for nursing were discussed and it was proposed that it is beneficial nurses to use mirrors as a therapeutic intervention in a variety of cases like post mastectomy, trauma, pain (phantom – CRPS1) and in individuals with body and eating disorders. In addition and surely in a different manner from MT as described in this thesis, the use of mirrors as a tool to decrease the risk of falling in patients with balance disturbances was discussed. The use of mirrors for the purpose of decreasing the risk of fall has also been proposed by Vailant et al. (2004) and Galeazzi et al. (2006). In another review, Ezendam,

Bongers and Jannink (2009) focused on the upper limb function and reviewed the application of MT to CRPS1, CRPS2, and amputation, stroke and hand surgery. The authors argued that despite the limitations in the methodology employed by previous studies, there was still adequate evidence for the effectiveness of mirror interventions and their benefits for alleviation of CRPS1 and upper extremity disorders in stroke.

1.2.5. Mirror Therapy in Stroke Rehabilitation

In stroke rehabilitation the results from different studies show variable effects and this suggests that MT could not be considered as ‘panacea’ – Ramachandran and Altschuler (2009) argue that the successful outcome of the procedure may depend on the geography of the lesion and the time window following the brain injury (Ramachandran and Altschuler, 2009).

In a randomized controlled study, Cacchio et al. (2009) compared the benefit of MT in forty-eight stroke acute patients who were allocated to the MT condition or to a control (conventional therapy at the hospital). Pain reduction and motor function were both measured and shown to improve. These results occurred immediately after the 4-week intervention time window and at six months follow up stage.

Yavuzer et al. (2008) conducted a randomised-control trial and examined patients at a sub-acute stage. Their study involved 40 stroke patients, all within 12 months of stroke, on four weeks course of MT and six months follow up. The authors reported significantly higher improvement on the Brunnstrom stages of the upper limb and on the FIM scale in the MT group compared to the sham therapy group. Although no significant differences were found on the

Modified Ashworth Scale (MAS) and in spasticity, it is noteworthy that the additional benefit of MT on the FIM and the Brunnstrom stages was maintained up to the 6 months follow up assessment.

Grunert-Pluss et al. (2008) provided a detailed report of the MT procedure that they used (the 'St. Gallen' protocol which was applied to individuals with CPRS, chronic pain disease, complex hand and nerve injuries and fractures). Their protocol required patients to participate gradually in a home based rehabilitation program according to which MT was applied five to six times a day for five to ten minutes. Grunert-Pluss and colleagues (2008) did not report the full findings for the fifty two patients that they treated; instead they emphasized the positive effects in only two case studies. Therefore, the generalisation of the results is difficult to deduce.

More recently Thieme et al. (2013) evaluated the benefits of MT for acute and subacute stroke patients with severe hemiparesis. The sixty participants were randomly assigned to one of the following three groups: individual MT, group MT and control group (standard care). In order to assess sensory and motor modalities, activities of daily living (ADL) and neglect related deficits, the authors used the Fugl-Meyer Test and the action research arm test (ARAT), the Barthel Index and the Stroke Impact Scale. The star cancellation test from the Behavioural Inattention Test (BIT) (Halligan, Wilson and Cockburn, 1990) was used to measure neglect. Following a five week intervention protocol (20 sessions), additional to standard therapy at the hospital, there were no significant effects for MT in terms of improvements on the sensorimotor function and ADL measures but there was a significant effect on the amelioration of neglect (individual MT group compared to control group).

Another RCT was conducted by Sutebeyaz, Yavuzer, Sezer and Koseoglu (2007), this time focusing on motor recovery for the lower limbs in subacute stroke patients. Forty stroke participants with an inability to trigger ankle dorsiflexion were recruited and allocated randomly to control or MT groups. The control group underwent sham MT by performing movements on the non-reflective side of the mirror and both groups had conventional rehabilitation therapy. The results showed that MT combined with conventional therapy improved lower extremity motor recovery and functioning in the patients (measured in terms of Brunstrom stages of motor recovery and the FIM instrument). There were no significant findings in improving walking ability (Functional Ambulation Categories – FAC) or spasticity (Modified Ashworth Scale – MAS).

An interesting study published in 2012 by Kuys, Edwards and Morris assessed benefits of MT in chronic stroke participants in terms of upper limb sensory impairments, activity limitation and participation restrictions. In this study activity limitation and participation restrictions improved six weeks after the completion of six-week intervention period. In addition, MT was found to be partially beneficial for improving the light touch threshold and proprioception, both of which are key elements for functional activities in everyday life. Matsuo et al (2008) reported results from a cross over RCT of 15 subacute stroke survivors and they found that MT was superior to control treatment in terms of the Fugl Meyer assessment for the upper limb.

In their recent Cochrane review, Thieme, Behrens and Dohle (2012), reported that there is evidence for beneficial use of MT in motor function following a stroke, however the effects are not consistent between studies when MT is compared to sham intervention. In addition, they reported that there is evidence that MT might be helpful in patients with unilateral neglect.

Thieme and colleagues (2012) suggested that clinicians should judge the beneficial use of MT for each patient individually, as the profile of patients that will benefit more from MT is not clear, and that it may be best for MT to be applied as a supplementary rehabilitation technique, rather than a standard rehabilitation regime.

1.2.6. Mirror Therapy and Unilateral Neglect

In a case study report by Stevens and Stoykov (2004) MT was presented as a tool to simulate bilateral movement. Based on previous reports that poor bilateral movement may reflect motor neglect and extinction (Robertson and North, 1994), these data are relevant to the question of whether MT modulates neglect. The authors reported results from an individual who underwent three weeks intervention of MT and effects were shown on Fugl Meyer (four points difference pre and post intervention period) and Jebsen scores. The MT led to increased velocity of the hemiparetic hand during bilateral movements and therefore better bimanual task performance as depicted by the Jebsen test. Although the results of this single case study cannot be generalized, they are still important in providing preliminary evidence, which is consistent with the amelioration of motor neglect in bimanual action following MT.

In two more recent case studies, Watanabe and Amimoto (2007) positioned a mirror in the sagittal plane of the participants, who had to perform a task of reaching a ball by looking at the mirror. The ball was placed towards the visual neglected area and the patients could only see it through the mirror reflection (intact side). The Albert test was used to measure any changes in

neglect before and after the intervention. The results indicated that the patients improved in terms of unilateral visual neglect and, following MT, they were able to trace the ball when placed further away on the neglect-side.

Another study by Dohle and colleagues (2009) showed that MT benefited the hemiparetic arm and neglect in acute and subacute stroke survivors with severe hemiparesis. Six weeks of MT were provided to eighteen patients, whereas both MT and control groups received additional standard treatment consisting of physiotherapy and occupational therapy. The results indicated that the MT group differentially improved in their functional outcome measures of motor ability (the Fugl-Meyer test, the motor part of the Functional Independence Measure (FIM) and the Arm Research Action Test (ARAT)). Furthermore, the authors used a battery of tests (star cancellation, figure shape copying etc.) to assess hemineglect. Patients allocated to the MT group showed significantly greater improvement in their neglect scores compared to the control group. Similar results were also found for sensory impairments in the patients (i.e. light touch). It is important to mention that when the entrepreneurs of MT, Ramachandran and colleagues (1999), first used mirrors to ameliorate the impact of visuospatial neglect; they placed the mirror on the unaffected side of the patients. In contrast, Dohle et al.(2009) stimulated awareness of the affected side by placing the mirror towards the affected side. This method helped patients to focus on movements on the neglected side.

1.2.7. Neural Correlates Underlying Mirror Therapy

Several recent studies have attempted to elucidate the neural correlates of MT. Hamzei and colleagues (2012) randomly allocated 26 participants into two groups (MT and sham therapy groups) and measured brain activity by using pre- and post-intervention fMRI, when participants made a grasp action to a stimulus. The authors claimed that following a course of Mirror Therapy there was evidence that the two hemispheres increased their connectivity to perform unilateral tasks. In their analyses, the authors decoded information sent to the ipsilateral somatosensory cortex (SMC – left) and they found that both left and right premotor cortices increased their interaction with the somatosensory cortex. This means that moving the left hand was linked with increased activation of the ipsilateral (left) somatosensory cortex. The results indicated that, following MT training there was a shift in brain activity towards the ipsilateral SMC.

Nojima et al. (2012) examined whether mirror visual feedback can trigger neuroplasticity in the human primary motor cortex (M1). In this research, transcranial magnetic stimulation (TMS) was used to identify any traces of neuroplasticity during mirror visual feedback. They recruited sixty-three healthy individuals and, by using a mirror box for the experimental group, they reported evidence of increased excitability of the primary motor cortex, as EMG responses were triggered by a weaker TMS pulse to primary motor cortex. These findings indicate that neuroplasticity of the primary motor cortex is an important element of interventions using mirror visual feedback.

Matthys and colleagues (2009) used fMRI and compared brain activity when finger tapping movements were made in two different conditions (the authors did not mention any limitations due to concurrent effects). In the first condition a mirror was placed between the two hands so that the finger tapping of the right hand would be projected in the mirror as the tapping of the left hand (non-moving hand), whereas in the second condition, tapping of the right hand took place without the presence of a mirror (although participants were able to look at both of their hands). The right superior temporal gyrus (STG) and the right occipital gyrus were activated only during the mirror task (tapping was taking place with the right hand in the mirror condition). These two areas are related to the processing of visual signals and the STG in particular has been linked to the mirror neuron system (Rizzolatti et al., 1999). This result is consistent with the notion that the mirror neuron system is involved in the observation of body motion in a mirror.

Laepchen and colleagues (2012) also used TMS in order to explore the neural basis of MT. Twenty-four healthy individuals were randomised and allocated to the MT or control groups. Participants underwent MT (using only their right – dominant hand), whereas controls performed the same activities without the use of a mirror over four days for twenty minutes. The training tasks involved five different actions, such as moving cards from a predefined position. Both groups were unable to see their left hand or to move it (untrained hand). TMS was applied before and after the training session. Both hands were tested (in the above tasks) and no significant differences were found for the trained hand between the two groups. More interestingly behavioural results for the untrained hand showed greater performance in the mirror group compared to the control group. The authors did not find any significant difference of inter-hemispheric inhibition (IHI) between the M1's. However, it is important to note that both groups

changed their excitability levels following training but they followed different routes. The control group showed increased excitability of the left M1, whereas the right M1 remained the same. In contrast the mirror group showed decreased excitability on the left M1 and there was a disinhibition of the right M1. The authors concluded that although the two groups performed the same tasks during the training period, the lack of visual feedback in the control group led to different neural routes being involved during training and that MT induced neuroplasticity in the group with visual feedback.

Another study that tried to shed light on the neural correlates of mirror therapy, especially on the motor cortex, was conducted by Fukumura et al. (2007). Six tasks-conditions were tested, and right and left hand were appointed as the impaired and intact hand, respectively (all participants were healthy individuals). In the first task, participants were asked to make wrist movements in front of a covered mirror placed on the sagittal plane. In the second task, they imagined movements behind the covered mirror while they were moving their left hand (intact); in the third task, participants were able to see the mirror reflection while they were doing task one, while in task 4, they added mental representation of moving the impaired hand. In task 5, participants were asked to synchronise movement of their left hand with passive movements (assisted) of their right hand. Finally, in task 6, participants added mental representation of the affected hand moving while they were performing the task 5. The scope of this study was to evaluate the three possible factors that might be influenced during mirror-induced movements: observing the movement of the hand in the mirror, imagining the movement of the hand and assisting the movement of the hand. Results from the MEP amplitudes, as evoked by TMS, showed that when participants imagined moving the affected hand they showed greater numbers

of MEP's when the mirror was placed between the two hands. In addition, there was a significant increase of MEP's during the assisted movement tasks (5 & 6) compared to the non assisted tasks (1-4). Based on these results, the authors suggested that the use of mirror reflection between the impaired and intact hand when combined with motor imagery might have positive implications for the neuroplasticity mechanisms that are activated during rehabilitation. It was also found that the MEP's increased more during the assisted movement tasks (5 & 6). It is important to note, however, that this study was conducted in healthy controls and the hands (affected and non-affected) were predetermined; therefore, it would be important to test the same hypothesis in neurologically impaired participants. It is also important that in these neurological intact patients of this study there was not a differentiation between right and left side of the motor cortex activation levels

Interestingly, another study by Garry, Loftus and Summers (2005) provided evidence of neurophysiological changes during mirror-induced movements. Based on the fact that motor cortex is being activated both during movement of the ipsilateral hand and the observation of the contralateral hand, the authors tested the hypothesis that mirror therapy, which enables both the above approaches, might be useful for the rehabilitation of the paretic upper limb. Eight healthy participants performed a finger thumb opposition task over a period of sixty seconds and single pulse TMS was delivered every five repeats of the task (guided by a metronome). The same task was executed under the following four conditions: a) by looking at the moving hand, b) by looking at the non-moving hand (accordingly the other hand was covered), c) visually fixating in a target between the two hands and d) by looking at a mirror placed between the two hands in a way that participants perceived visual feedback of the non-moving hand as it was moving

(reflection of the active hand). All tasks involved movement of only one hand and both hands (dominant – non-dominant) were tested (non significant difference found during the analysis). Following the analysis of the MEP's during the different conditions and compared to the resting phase of the hands, it was found that there was increased excitability of the ipsilateral M1 during movements induced by the presence of mirror reflection. Less excitation was found when participants were looking at the middle distance of hands fixation point and on the looking the non-moving hand condition. The results showed that observation of the reflected hand enhanced excitability of primary motor cortex ipsilateral to a unilateral upper limb movement and this effect did not differ between the dominant and non-dominant hands (balance order of testing between the two hands). These findings add to the previous mentioned research papers and lead to the conclusion that mirror therapy can induce learning related neuroplasticity in the ipsilateral primary motor cortex (M1).

Funase et al. (2007) in their study recruited twelve healthy subjects to perform the following tasks while TMS was applied to the motor cortex of the left side: control (participants gazed on a fixed point at the covered mirror box so that they could not look at their left hand), performing bilateral arm movements by directly looking at both hands (no mirror box was placed between their hands) or by looking at the reflection of one hand in the mirror box. Motor evoked potentials of the left motor cortex were higher in both direct and indirect (mirror) movement conditions compared to the control task but there was no significant difference between the two experimental conditions. The authors concluded that there were no differences in the neural routes activated in the brain between self-observed or mirror-observed bimanual actions.

Tominaga and colleagues (2009) examined if the cortical response following stimulation of the median nerve (over the wrist) could be modulated by movements in front of a mirror placed between the two hands of the participants. All subjects (nine participants were analyzed) received right median nerve stimulation and the induced activity recorded on the left hemisphere. The following conditions were tested: a) resting, b) viewing the right hand holding an object with a transparent plastic, c) viewing the left hand holding an object through a transparent plastic and d) viewing the reflection of the left hand holding an object as it was being held by the right hand. Based on the idea that 20Hz of induced activity has been noted in the primary motor cortex following median nerve's stimulation actual movements (Salmelin and Hari, 1994 and Schnitzler et al., 1997), the authors examined if similar action would take place during viewing of the reflection of the hand in the mirror. The results of this study showed a reduction of 20Hz in all experimental conditions. When the participants were holding the object on their right upper limb (able to look through the transparent plastic), there was a strong suppression of the rebound of the 20Hz, whereas a slight suppression was noted when the subjects were viewing the reflection of the right hand in the mirror (perceiving feedback that the left hand is holding the object). When the participants were holding the object in their left hand there was a strong suppression during the reflection of the left hand task (subjects were looking at the reflection of left hand as the object was being held by the right hand), whereas less suppression was noted when the participants were holding the object with their left hand and it was able to be seen through the transparent plastic. These results indicated that despite the hand that was holding the object (right or left), the 20Hz induced activity was highly suppressed in the left hemisphere when participants received feedback that the right hand was holding the object and not when the participants were looking at the hand as the left hand was holding the object. Tominaga et al. (2009) findings

replicated previous findings revealing that the left primary motor cortex can be activated, not only during the observation of the right hand, but also during the observation of the reflection of the left hand in the mirror imitating the view of the right hand. These results suggest that mirror-related interventions may enhance neuroplasticity in the ipsilateral primary motor cortex. This finding may have implications for patient rehabilitation, as it may indicate that improvements in motor action can be achieved by utilizing the ipsilateral side of the intact hemisphere, instead of increasing the activity on the impaired motor cortex, which is often absent following the lesion.

Bhasin et al. (2012) recently examined the neural substrates of MT using fMRI. In this study thirty participants (twenty chronic stroke participants in the experimental group and ten healthy participants in the control group (the reason for the difference in number of participants in each group was not explained by the authors)) were recruited. The stroke survivors underwent an eight week bilateral movement-based physiotherapy regime, according to which the healthy hand was projected on the laptop inverted, as if the impaired hand was doing the task, consisting of one to one and half hour sessions, five days a week. According to Bhasin and colleagues (2012), although no significant differences were found on the Medical Research Council scale, significant differences were observed for both the Fugl-Meyer and the modified Barthel Index pre and post the intervention period for the experimental group. Neural correlates of treatment's benefits were also investigated through three fMRI sessions and diffuse tensor imaging (DTI) acquisitions at the following times: pre intervention, at eight weeks (duration of training) and at six months. The tasks that stroke participants had to perform in the scanner included fist flexion and extension with the paretic upper limb. On the other hand, both hands were used in the control group. The authors reported a laterality index without, however, reporting which exactly factors

this laterality index involved. Analysis of the laterality index pre and post intervention revealed that there was an increase in activation of the ipsilesional hemisphere (subjects were using only the hemiparetic hand in the scanner) and more specifically in the Brodmann areas 4 and 6 (BA 4 and 6). This increased activity of areas BA4 and BA6 in the ipsilesional motor cortex provides evidence of cortical reorganization induced by the mirror based bilateral movements – even in a chronic stroke population. It is important to note though that the improvement that was found at 8 weeks (end of intervention) did not fully maintain at 24 weeks follow up. These findings raise a question on whether top-up sessions are required for these types of interventions.

Michielsen et al. (2011) evaluated both the clinical effects and evidence for cortical reorganization following a home based MT protocol. Forty chronic stroke individuals (mean post-stroke time 3.9 years) were recruited into control and experimental groups and they participated in a six-week training program. The control group received bimanual exercises and practice in moving objects and the experimental group received MT. They reported results on Fugl-Meyer motor assessment along with evidence for fMRI activation. Michielsen and colleagues (2011) found that motor actions were significantly improved in the MT group in the post treatment assessment compared to the control group, however this improvement was not maintained at the 6-month follow-up. fMRI results (pre intervention vs. six weeks after – end of intervention period) confirmed a shift in activation balance in the primary motor cortex in favour of the ipsilateral to the hemiparetic hand hemisphere. According to the authors, this is the first study revealing evidence for neuroplasticity following a short course of MT. However, since the effects did not maintain at six months (it seems from this study that there is no long term motor

effect of MT), future research needs to focus on which patients will be the optimal population to undergo MT protocols (Michielsen et al., 2011).

Wang et al. (2013) performed a comparison of lateralized cerebral activations using fMRI in healthy individuals. Eighteen right-handed healthy individuals were recruited in this study (fifteen were finally analyzed). During the fMRI task subjects were asked to make unimanual hand movements and a video camera recorded the movement and projected it via LCD goggles. The following tasks were performed: a) relaxing hands, b) performing unimanual opposition thumb-index movements by perceiving feedback that they were moving their hand (i.e. right hand) or by perceiving inverted feedback (i.e. moving their left hand). Both hands were used in all conditions. Participants were also tested when viewing video-clips of movement observation tasks (observing someone else's movement). As expected, the results showed activation of bilateral motor networks in favour of the contralateral hemisphere (all movements were unimanual). The results suggested that mirrored inverted movements increased activation in primary visual and neighbouring, higher order visual areas (precuneus among others) contralateral to the hand viewed by the participant (similar pattern did not revealed during the observation of movement through video-clips), which lead to the conclusion that excitation of lateralized cerebral activations, can be triggered by inversion of visual feedback (mirror) but not by movement observation of the hand actually used in action.

1.2.8. Mirror Therapy in combination with other intervention techniques

More recent research has included protocols combining already existing techniques. The investigation of the effectiveness of intervention programmes combining two or more rehabilitation techniques at the same time is very important for clinical practice, as several different techniques are usually used with patients during a day of treatment in most rehabilitation centres. In a recent study, Kim, Lee and Song (2013) investigated the effects of a 4-week course that combined MT with Functional Electrical Stimulation (FES). The results were compared with those of a control group who received only FES, whereas both groups received conventional rehabilitation, as well. The results revealed more significant improvements in the MT and FES groups on the Fugl-Meyer assessment, the Brunstrom's motor recovery stage and the Box and Block test. The authors concluded that MT combined with FES might be a beneficial technique superior to FES alone in the rehabilitation of stroke survivors. One of the main limitations of this study is that there was not a MT only control group so that we could have evidence of which of the two interventions might be most beneficial for stroke survivors.

In another recent pilot study, Lin and colleagues (2012) combined MT with wearing a mesh glove (a two channel electrical stimulation system that has been used before to normalize muscle tone and to improve sensory-motor function; see Peurala et al., 2002). More specifically, there were sixteen chronic stroke patients who were randomly assigned to a MT or to a MT and Mesh glove group. All groups underwent a daily 90-minute training (5 days per week for over a period of four weeks). The benefits from training were significantly greater for the MT and Mesh glove group in the ARAT and FIM scores. The authors speculated that the two rehabilitation

techniques shared common pathways and gave rise to increased benefits when combined together. However, it is important to note the limitations of this study, including the small sample and the lack of a comparison group using only a Mesh glove, as well as the lack of a follow-up assessment for the investigation of long-term effects.

The above literature review indicates that MT can be added at least as a protocol on top of stroke survivors' rehabilitation but there is still no direct evidence for clinicians to follow and replace other interventions that have been proved to improve motor function. It seems that MT could be potentially beneficial for activities of daily living but the results need to be interpreted carefully as they derive from a small number of studies. Also there is still no clear evidence and differentiation of the results of MT application in different stages of stroke. The aims of this thesis are to differentiate results of MT between chronic and acute stroke survivors and also to identify attentional benefits especially around motor extinction as will be discussed in the findings of experimental chapters 2, 3 and 4.

1.3. Literature Review – Functional Electrical Stimulation (FES)

According to Alon (2013), electrical stimulation approaches to rehabilitation have been described under a variety of labels including transcutaneous electrical stimulation (TENS), neuromuscular electrical stimulation (NMES), electrical muscle stimulation (EMS) and therapeutic electrical stimulation (TES). In the current thesis the term FES will be used to refer to

electrical stimulation applied to the paretic upper limb to facilitate volitional functional movement.

The term 'therapeutic FES' is used to describe the application of peripheral nerve stimulation applied to several muscle groups in order to produce functional movements as an amplification of voluntary motor activation. The projected stimulation is delivered through different types of transcutaneous or implanted electrodes placed over the motor points of the target muscles and follows specific time courses in an effort to mimic functional physical movements. The role of FES is to facilitate and not to replace the voluntary activation of paretic muscles and the sensory input to the central nervous system (CNS). It has been proposed that proprioceptive feedback delivered by FES activates the somatosensory cortex and that this activation may play a key role in the neural changes that sub-serve the rehabilitation procedure (Harding and Riddoch, 2009). When FES is compared to conventional rehabilitation techniques, it has been demonstrated to lead to significantly better motor recovery, including hand function (Popovic et al., 2002) and walking (Mazzaro et al., 2006).

In a comprehensive review of the literature Sheffler and Chae (2007) stated that, despite difficulties in the clinical implementation of FES and its costs, there is sufficient evidence for researchers to investigate FES in large, multicentre, randomized clinical trials. Glinsky and Harvey (2007) reviewed the effects of electrical stimulation and suggested that there are clear benefits for stroke survivors when compared to conventional physiotherapy and sham electrical stimulation. In a meta-analysis, Glanz et al. (1996) reported that there is evidence that FES promotes recovery of muscle contraction following stroke and is likely to have clinical efficacy.

However, the neural mechanisms underlying FES effects on movements remain poorly understood (Blickenstorfer and Kleise, 2009). Kimberley and Lewis (2004) in their research on stroke survivors found that activation in the somatosensory cortex ipsilateral to the stimulation post-FES increased, suggesting that neuromuscular electrical stimulation may stimulate the cortical sensory areas, which in turn lead to improved motor function ipsilateral to the stimulation to the hand used in the subsequent task. Iftime-Nielsen et al. (2012) further report that, when FES was combined with voluntary movement, there was greater activation of the cerebellum and a decrease of activation in the secondary somatosensory cortex (contralateral), when compared to FES applied alone. Thus movement may be particularly facilitated when voluntary and electrical forces are joined, leading to a better reorganization of the cortical areas that are responsible for movement. However, further investigation of neural routes by Christensen and Grey (2013) suggested that FES-related activation of S2 area mainly derives from sensory input (rather than the movement component).

Sasaki et al. (2012) evaluated the effects of FES in five chronic stroke participants (mean time post stroke 2.8 years) that had already reached a plateau in their recovery. Three patients had right hemiparesis, whereas two patients had left hemiparesis. The training protocol was applied for over a period of twelve weeks and enabled finger flexion and extension (Bioness Inc, NESS H200). Behavioural outcome measures included the Brunnstrom stages, grip strength, passive range of motion, the Fugl-Meyer Assessment and the manual function test. Also, fMRI was used to measure brain activation pre intervention, at 4 weeks, at 8 weeks and at 12 weeks (end of intervention period), following the beginning of the intervention. Participants were asked to perform active gripping in the scanner. Participants were found to be improved on all behavioural

outcome measures at the end of the 12 week- FES trial. The authors were not clear if the task in the scanner was uni- or bimanual. However, they reported two different pathways of activation in their participants. According to the first pattern, FES activated somatosensory cortices (SMC) bilaterally; this effect maintained over the 12-week period of the intervention and there was always stronger activation in the involved hemisphere. According to the second pathway, there was a bilateral extensive engagement before the intervention period that was focused on SMC and areas in vicinity following the intervention period. Interestingly, Sasaki et al. (2012) argue that brain plasticity changes were traced four weeks after the intervention. Although Sasaki et al. (2012) findings revealed possible pathways of brain reorganization, they need to be replicated by future studies including larger samples and employing more conservative MRI data filtering processes.

It has been suggested by Powell et al. (1999) that neuromuscular electrical stimulation of the wrist extensors may enhance the strength of wrist extensor in stroke patients. In their randomized controlled study sixty stroke survivors were recruited on a daily FES course two to four weeks post stroke. The FES course included three thirty-minute sessions over a period of eight weeks. Powell et al. (1999) findings revealed a significant increase in performance on the Action Research Arm Test (ARAT) scores of the intervention group when compared to controls. More specifically the ARAT score increased by a mean of 21.1 (SD 12.7) in the FES group, when compared to 10.3 (SD, 9.0) observed in the control group at the end of the intervention period.

Despite this positive outcome, the same results were not found to be significant at thirty two weeks following the intervention. The authors recommended the use of FES as a low cost

intervention, especially in highly motivated patients with moderate impairments. This suggestion is consistent with Pandyan and Granat's (1997) findings revealing an improved range of extension in the wrist joint as a result of a two-week FES intervention in eleven stroke subacute survivors. However, these benefits were not maintained at two weeks following the intervention. These results suggest that FES can be used as a tool to prevent contractures, as well as that it is important that the devices that were used at that time have been improved technologically so that the equipment can deliver better stimulation which might lead to better functional outcome.

Knutson et al. (2009) used contralateral-controlled (the other hand used to control the trigger-time of the activation) functional electrical stimulation (CCFES) in a group of stroke survivors, such that patients could control the time of the initiation of the stimulation. The authors recruited three participants for a twelve-week training period and found increased finger extension in two out of three subjects. The small sample does not allow for general conclusions to be derived, although it seems that there is a positive effect following the self administration – initiation of the FES by the patient. Similarly, Sullivan and Hedman (2004) reported a case study of a stroke survivor that underwent an eighteen-week program of sensory stimulation combined with FES five years following the incident. Functional improvement in ARAT scores from 27 to 42 out of 57 following the intervention period was observed. Although this finding needs to be validated by larger scale studies, it provides preliminary evidence for the potential benefits of functional electrical stimulation even for chronic stroke survivors.

FES can initiate muscle contraction, activating Golgi tendon organs, proprioceptive receptors and other mechanical sensors of the periphery that could, in turn, activate specific areas of the brain (Kimberley et al., 2004, Smith et al., 2003). Kimberley et al. (2004) investigated

neuromuscular electrical stimulation (NMES) and its beneficial use for wrist and finger extensors in eight stroke survivors using grasp and release outcome measures, and characterized the changes in brain activity using fMRI. Participants underwent a 60-hour self-administered course of NMES over a period of 3 weeks and the results were compared to a group of eight stroke subjects who received sham treatment. Based on suggestions by Chae and Yu (2000), Kimberley et al. (2004) recruited stroke patients with mild to moderate impairments in a time period of 35.5 (+/- 25.1) months post-stroke. The results indicated significant improvement of grasp and release measures (Box and Block Test and Jebsen Taylor Hand Function Test), when compared to sham treatment. Both groups improved in isometric finger extension strength. Cortical activation, measured by the fMRI BOLD response, did not change significantly, although the authors reported an increase in activation of the somatosensory cortex pre- compared to post-intervention. Importantly though, Kimberley et al. (2004) highlighted the lack of evidence for changes in the motor cortex following the treatment.

Interestingly, Joa et al. (2012) compared changes in brain activation when FES was applied, when compared with voluntary contraction, or the combination of both techniques. More specifically, the authors recruited nineteen healthy individuals and examined the activation of the brain in three conditions: a) voluntary contraction only, b) FES applied on wrist extensors only and c) simultaneous application of FES during voluntary contractions. The same authors reported that during the voluntary contraction only session a range of brain areas were activated, including the contralateral primary cortex (M1), the thalamus, the bilateral supplementary motor area (SMA), the primary sensory cortex (SI), the secondary motor cortex (SII), the caudate and mainly ipsilateral regions of the cerebellum. The regions that were activated during the FES session

included the contralateral M1, SI, SMA, the thalamus, the ipsilateral SII and the cerebellum. Finally, when the two techniques of rehabilitation were combined, the brain regions that were activated included the contralateral M1, the anterior cingulate cortex (ACC), the SMA, the ipsilateral cerebellum, and the bilateral SII and SI. Strikingly, when FES was combined with voluntary movements, the number of voxels that was activated in the regions of M1, SI, the cerebellum and SMA were larger, compared to that one activated when only one technique was applied. Joa et al. (2012) concluded that it might be more beneficial for patients to combine FES with voluntary movements in clinical practice, and prioritise voluntary movements over FES, as a rehabilitation technique that enables overall more brain activation, compared to FES alone.

However, a notable effect of FES stimulation is the increase in awareness of the contralesional side in patients with post-stroke unilateral neglect (Harding and Riddoch, 2009). Unilateral neglect is mainly linked to right hemisphere lesions and is commonly characterised by a failure to attend to contralesional stimuli (Kerhhooff and Schenk, 2012). The dramatic effects of neglect following a stroke are associated with poor rehabilitative outcomes and severe disability in daily functional activities (Punt and Riddoch, 2006). Harding and Riddoch (2009) applied a mild form of FES in 4 patients with unilateral visual neglect and found that most (3 out of 4) participants benefited even 6 months after the intervention, which included 4 weeks of daily FES application. The authors suggested that FES may increase the proprioceptive excitation of the right parietal lobe, which in turn stimulates the interactions of the hemiplegic hand and attention with the environment. Polanowska and Seniow (2009) contrasted the effects of FES combined with scanning training to the effects of scanning training alone in a randomized, double blind study of patients suffering from neglect. They found that patients who received the combined

treatment on the contralesional hand experienced a greater alleviation of the symptoms of unilateral neglect relative to a group of patients who only received scanning training.

In the present thesis therapeutic FES will be used to improve motor and attentional functions in chronic stroke patients, and fMRI will be employed to measure any associated changes in brain activity.

The aim of this literature review around FES was to determine if FES increases voluntary muscle strength and ameliorates attentional deficits such as visual neglect and motor extinction. Although the FES literature provides evidence of the benefit of its application in terms of motor strength there is still a need for more evidence regarding the improvements in the attentional domains that have been impaired following stroke. This comes in parallel with this thesis aim to use FES to promote motor and attentional function in chronic stroke survivors. Also fMRI will be applied before and after the intervention to measure any associated changes in brain activity.

1.4. Literature Review – Computer Based Cognitive Training

Attentional impairments in stroke survivors can have a dramatic consequence on subsequent recovery and are the main cause of poor attention during the rehabilitation regime (Heruti et al., 2002). Attention refers to how we actively process specific information present in our environment. Impaired attention is also linked to the development of affective problems such as chronic depression (Hackett et al., 2005).

There has recently been a lot of interest in the idea of ‘brain training’ and in particular in the notion that engagement in immersive computer games can specifically enhance attentional functions. Green and Bavelier (2003) first reported this in a contrast between young participants who were ‘game players’ and participants who were not. They found that the game players performed significantly better than the non-game players on a range of laboratory-based measures of attention. They subsequently used an intervention approach in participants, who were either trained using immersive games or on the game Tetris, which is less immersive and demanding of rapid switches and control of attention. The individuals, who were trained on immersive games, performed better on attention tests than those trained on Tetris. These results have extended previous findings supporting computer-based cognitive rehabilitation for stroke survivors (Lynch, 2002), elderly participants (Gontkovsky et al., 2002) and dementia patients (Stern, Jeako and Millar, 1999). More specifically, previous studies that have used computer interventions on attentional and other cognitive functions, including memory, problem solving and daily functional skills, have reported beneficial outcomes in stroke patients (Nuechterlein et al., 2005, Sohlberg and Mateer, 1987, Ben-Yishay, 1978, Gray, 1992). In addition, Ben – Yishay (1978) found positive outcomes in concentration and sustained attention in forty adults with acquired brain injury, following a computer intervention. One of the most important findings of this study was the fact that improvements were found not only in focused and sustained attention procedures, but in all aspects of attention following the computer intervention program.

More recent studies in brain training have focused on problem solving and memory procedures. However, the results have been controversial. Although there is a general agreement that participants improve on the tasks they train on, studies have reported that generalization of

the training benefits is not guaranteed. In the largest scale study to date by Owens et al. (2010), 11,500 individuals underwent 6 weeks of brain training (focused on problem solving and memory). Improvements on the training tasks were clear, but did not generalize to other tests (e.g., measures of short-term visual memory). However this study involved normal individuals aged 11 to 65 years, who were likely to be self-selecting and possibly already with excellent cognitive functioning skills. The null result should not be interpreted as evidence that brain training will not be beneficial in other populations – e.g., stroke survivors. In a recent Cochrane review (2013) on cognitive training of individuals with acquired brain injury or other non-progressive forms of acquired brain damage, Chung et al. concluded that there was insufficient high quality evidence for the benefits of brain training. Only a small number studies used training tasks, especially designed to stress critical cognitive processes, whereas only a few included control groups in order to measure effects of repeated testing and time. The authors highlighted the need for high quality research, which would provide a fine-grained test of whether targeted cognitive training can improve cognition in neurological populations, whether training benefits can be generalized, and whether training effects supersede improvements produced by recovery over time and through engagement in other ongoing activities. Loetscher and Lincoln (2013) in their review on cognitive rehabilitation of attention deficits further suggest that cognitive rehabilitation may improve aspects of attention in a short period of time. However there has been no evidence so far showing that these results are maintained and therefore offer stroke survivors a long term benefit.

In the present thesis I examined brain training in stroke survivors, focusing on patients who present with cognitive problems in attention and at least one other cognitive domain, such as

language or memory. The patients were trained using attention-weighted tasks, which are game-like, give visual feedback after each session and cumulatively motivate involvement. Patients were assessed by using the attention training tests, as well as tests of other cognition functions on which they did not receive training, in order to also examine whether there was generalization to other aspects of cognition.

**CHAPTER 2: EFFECTS OF MIRROR THERAPY ON HAND
FUNCTION AND MOTOR EXTINCTION IN CHRONIC
STROKE PATIENTS**

ABSTRACT

Data are reported on the effects of Mirror Therapy (MT) on everyday action and on motor performance in a group of chronic stroke patients under conditions of unimanual and bimanual hand actions. MT improved functional performance and unimanual actions by the contralesional limb, however there were no improvements in bimanual actions in treated participants when compared to controls. The results suggest that MT can have a beneficial effect on motor recovery after stroke, but there can remain constraints induced by attentional competition when bimanual actions are performed.

2.1. INTRODUCTION

Stroke is one of the most serious causes of long-term disability in adults (Jongbloed, 1986) with impairments in upper limb function being a critical factor (Spieler, Lanoe and Amarenco, 2004). Around 80% of stroke survivors experience limitations in the upper limb following a stroke (Stroke Association, 2011). The upper limb impairments that can follow a stroke cause limitations in functional mobility and reduce the ability of stroke survivors to work and maintain their pre-stroke habits (Legh-Smith, Wade and Hewer, 1986). A variety of rehabilitation protocols have been reported to improve motor control and the function of the paretic upper limb, including exercise training focused on the hand or arm (Duncan et al., 2003), bilateral movement arm training (Summers et al., 2007), robotic assisted rehabilitation (Masiero et al., 2007), constraint induced movement therapy (Grotta, 2004) and functional electric stimulation (Ring and Rosenthal, 2005). Many of these approaches have limitations though. For example constraint induced therapy can disrupt a patient's function as it forces actions to be performed with the impaired limb. Functional Electrical Stimulation (FES) requires some experience in positioning the electrodes to induce action. Robotic assisted rehabilitation is expensive and not ready or available in most rehabilitation settings. One relatively newer approach with fewer restrictions, however, is Mirror Therapy (MT). MT provides a simple, low cost, patient-directed treatment that may help improve the function of the upper limb (Yavuzer et al., 2008).

MT is easy to administer and there is the possibility for self-administration in home environments even for participants with severe motor impairments. In MT, patients watch an image of their affected limb in a mirror, based on the reflection of the good limb, which provides

visual feedback for the motor action. Ramachandran and Rogers-Ramachandran (1996) were the first to describe MT in the treatment of phantom limb pain following amputation. After watching the reflection of their intact limb in place of the amputated digit, patients experienced movements and relaxation on the phantom limb, in addition to pain relief (Ramachandran and Hirstein, 1998). Since then MT has been found to effectively reduce pain and to enhance upper limb motor function in complex regional pain syndrome I and II (Cacchio et al., 2009, Moseley, 2004, Selles, Schreuders and Stam, 2008). Similarly, MT has led to motor improvement when applied to patients who have undergone hand surgery and experienced subsequent dyscoordination (Rosen and Lundborg, 2005).

There are also previous research reports on the effect of MT on stroke. Yavuzer et al. (2008) evaluated the effects of MT on upper extremity motor recovery, spasticity and hand-related functioning in 40 subacute stroke patients. Improvements were found in hand functioning with no effect on spasticity. In addition Altschuler et al. (1999) showed significant improvement in the range of motion (ROM) as well as the speed and accuracy of arm movements in 9 stroke patients before and after MT. Sütbeyaz et al. (2007) included MT for the lower limb with a conventional stroke rehabilitation program and they found a significant difference in functional performance. Stevens & Stykov (2003) applied MT for 3-4 weeks to two sub-acute stroke patients and had found an increase in their Fugl-Meyer Assessment score, active ROM, movement speed and hand dexterity. Grünert-Pluss et al. (2008) used MT in 52 patients with a variety of neurological disorders and confirmed the positive effect of MT intervention in 42 patients (80%), with pain reduction and improvements in movement and sensibility. In another report of patients with a chronic lesion, Sathian, Greenspan and Wolf (2000) found that after 2 weeks of MT, there was a significant improvement in grip strength and hand movement for the

paretic upper limb. A recent Cochrane Review (Thieme et al., 2012) concluded that there is evidence for the effectiveness of MT on motor function after stroke, but there is a need for more research to be conducted to address questions regarding the intervention protocol concerning the optimal dose, frequency and duration of MT.

The neural mechanisms underlying the efficacy of MT are not clear (Sathian et al., 2000) and they need not be interpreted in the same way across different disorders (e.g. phantom limb pain vs. hemiplegia). Nevertheless, for stroke patients there is evidence (Altschuler et al., 1999) that the visual feedback provided by MT, which provides input consistent with normal movement of the paretic limb, may in turn lead to the activation of neuronal areas linked to motor action (Nelles et al., 1999, Garry, Loftus and Summer, 2005). For example, Fukumura et al. (2007) investigated the effects of MT using electromyographic signals (EMG) and reported larger increase in motor-evoked potential (MEP) amplitudes during motor imagery in patients who had undergone MT compared with those who had not. The authors state that synergistic effects of afferent information and motor imagery led to the increase in MEP's and this may facilitate movement and promote neuronal reorganization. Michielsen et al. (2011) reported some effectiveness for MT in chronic stroke patients and linked the effects of MT to cortical reorganization. The same authors also showed that, during bimanual movements, the mirror illusion increases brain activity in the precuneus and the posterior cingulate cortex, areas associated with awareness of the self and spatial attention, but it should also be noted that there was relatively poor functional outcome in that study and no evidence for long term benefit. Garry et al. (2005) further argued that motor effects are mediated by the mirror neuron system, whose neurons become active during imagery stimulation, action execution and action observation.

The present study examined the behavioral effects of MT on a group of chronic stroke patients (stroke occurrence more than 2 years before) and measured not only unilateral but also bilateral arm movements. The results were compared with a matched control group of chronic stroke patients who did not receive MT. Under conditions of bilateral movements, patients with lesions to motor and pre-motor regions can show motor extinction, where movement of the affected limb can decrease relative to the degree of unimanual movement that can be achieved by the same limb (Laplaine & Degos, 1983). Punt and Riddoch (2005) described the syndrome of motor neglect as the under utilization of a limb opposite a brain lesion that cannot be fully explained by primary sensory or motor deficits and may reflect instead attentional competition under bimanual action conditions. Consistent with this, motor extinction is reduced by manipulations that cue a patient's attention to the affected limb (Punt, Riddoch and Humphreys, 2005). Motor extinction comprises a relatively under-recognized deficit by clinicians, but it may have a significant impact on patient performance and recovery following stroke. Here we ask whether MT may functionally improve motor extinction as well as unimanual motor actions. In addition we assess whether the effects of MT on subsequent motor performance are maximized when actions are performed with the eyes open rather than closed, as this might throw light on the mechanisms underlying MT effects. For example, if the effects of MT arise due to visual input enhancing motor activation, and re-learning based on the presence of this enhanced activity, then we might expect that actions post-therapy will be optimized when the input is again present when participants perform with eyes opened but not when they perform with eyes closed.

2.2. METHODS

2.2.1. Participants

Fourteen chronic patients were recruited in this study from the School of Psychology, University of Birmingham. All participants provided informed consent under ethics approved by the University of Birmingham ethics committee. Seven chronic stroke patients were allocated randomly to the Mirror Therapy group and seven chronic stroke survivors were allocated to the control group (no MT was applied). All of the patients, met the following inclusion criteria: (a) a first episode of stroke diagnosed at least 24 months before (the length between study participation start and stroke was at least 2 years), (b) a score between 1-3 on the Brunnstrom stages of motor recovery for the upper extremity, (c) cognitive skills that would not affect the ability of the participant to follow the instructions during the MT intervention (the capacity to follow the program) and (d) no orthopedic or neurological dysfunctions that could affect the upper limb prior to stroke. Demographic and clinical characteristics of all participants showed a mean of 2.5 +/-0.5 in Brunnstrom stages. In the MT group four of the participants had right side hemiparesis and 3 left side. This was matched in the control group. In all participants MRI scans showed impaired areas of the primary motor cortex or motor related areas (i.e. internal capsule). All participants were males with a mean age of 64 years +/-10 and the mean

time post stroke was 14 years (+/-5 years). None of the participants that were allocated to the MT group missed more than one session in a row.

| Demographic | | | Group | | Years post |
|-------------|-----|-----|-------|---------|------------|
| Subject | Sex | Age | MT | Control | stroke |
| 1 | M | 65 | o | | 7 |
| 2 | M | 78 | o | | 16 |
| 3 | M | 68 | o | | 17 |
| 4 | M | 71 | o | | 21 |
| 5 | M | 63 | o | | 13 |
| 6 | M | 57 | o | | 20 |
| 7 | M | 34 | o | | 13 |
| 8 | M | 69 | | o | 8 |
| 9 | M | 63 | | o | 20 |
| 10 | M | 70 | | o | 21 |
| 11 | M | 67 | | o | 8 |
| 12 | M | 71 | | o | 14 |
| 13 | M | 55 | | o | 13 |
| 14 | M | 69 | | o | 9 |

Table 1: Demographic data of participants - Chapter 2

2.2.2. Procedure

Each intervention session lasted about 40min and the sessions were conducted on a weekly basis for a period of 6 months. A mirror (50x70cm) was used to facilitate visual feedback. Patients did not participate in any other rehabilitation during the MT intervention. The potential role of an imagery component and visual feedback in the therapy was reinforced by instructing each participant to imagine that the reflected limb was his/her affected limb moving physically in space (Grunert-Pluss et al., 2008) in synchrony with the movement of the patient's spared hand. For the first 3 weeks of the intervention the patients learned to identify the reflected arm in the

mirror as their own and to try to perform bilateral movements. Subjects were placed in a sitting position while the mirror was positioned between their upper limbs perpendicular to their midline, with the nonparetic arm facing the reflective surface. The patients were not allowed to wear anything that enabled them to differentiate between their two limbs. The patients then observed the reflection of the nonparetic upper limb while flexing and extending fingers, wrists and elbows for a period of around 40 minutes.

Consistent with Punt and Riddoch's (2006) suggestion for adjusting rehabilitation protocols to each patient needs, each patient followed his/her personally designed protocol according to the functional level of his paretic limb. Each patient began by making single flexion and extension movements of the spared hand, but this was then extended to include functional movements such as grasping a glass or a pen (~15 trials per session) and rolling a ball. Patients were asked to move the affected limb as well as they could during the functional movements together with moving the intact hand (2 glasses or pens were placed – one of each side of the mirror). The therapist reinforced all movements by verbal feedback and also pantomimed the correct movements to patients at the start of a session. Where necessary and very occasionally (only when a new functional movement was going to be introduced to the participant), the therapist also assisted the affected paretic upper limb when movement was poor, for no more than 2 consecutive sessions.

2.2.3. Outcome Measures

Outcome measures of motor performance that were taken: (a) the number of taps made on simple counter device and (b) the Action Research Arm Test (ARAT) (Yozbatiran et al., 2008).

2.2.3.1. Tapping Task

Tapping counter device: The device consisted of two counters 20 cm apart attached on a wooden base. The force to press the button was similar to the force applied to press a ballpoint pen (1 Newton). Participants tapped with each index finger, either making unilateral or bilateral movements, over a period of 20 seconds. Patients were asked to make as many taps as they could under the unilateral and bilateral action conditions, with and without their eyes open. 1 week before the start of the intervention and 1 week after the end of the 6 months intervention period baseline assessments were taken (eyes opened). Pre- and post-intervention measurements were also taken in every single session (Figure1). The control group underwent two measurements, at the School of Psychology, spaced 6 months apart, but they did not undergo any specific therapy in-between

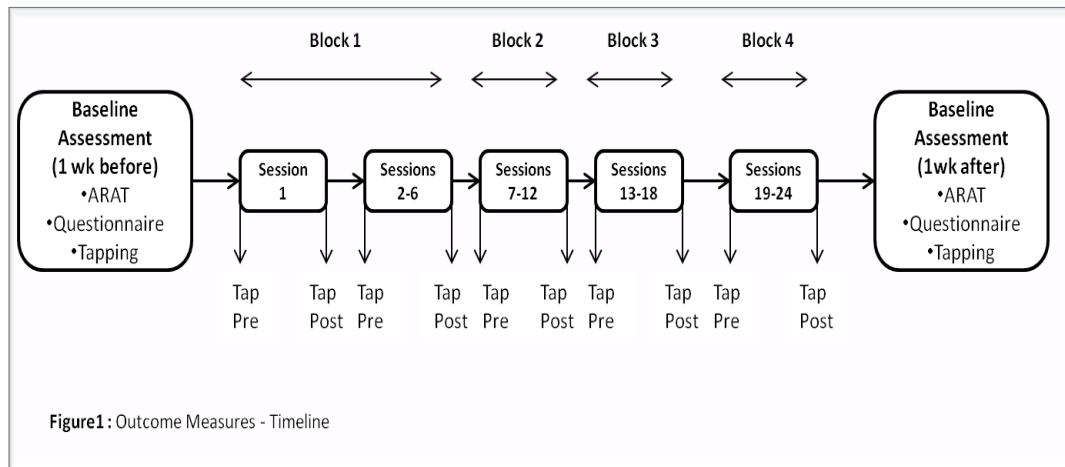


Figure 1: Outcome Measures - Timeline

2.2.3.2. Action Research Arm Test (ARAT)

The Action Research Arm Test was completed by two blinded assessors who saw videos of each patient's performance (for confidentiality reasons only the hand of the patient could be seen on the videos) in specific tasks before and after the total period of the intervention. The two raters were not aware of the nature of the intervention and all raters received training and information sheets on the tests used. The action videos of the patients were recorded before the first and after the last session of MT. Measurements across the same time period were also taken for the control group. The Action Research Arm Test has been validated for stroke (Hsieh et al., 1998) and consists of 4 different subscales. These subscales are related to grasping, gripping, pinching and gross movement. The test enables 19 movement tasks and the total score ranges from 0 to 57 (each task can be graded from 0 to 3). Measurements were taken before the start of the intervention and one week after the end of the 6 months mirror therapy.

2.3. RESULTS

2.3.1. Tapping performance

The outcomes of the intervention were initially assessed using the baseline tapping assessments that were taken prior and after the completion of the 6 months intervention period. A 2x2x2x2 ANOVA (within-subjects factors - time: before – after, task: unimanual – bimanual, hand: ipsilesional – contralesional; between-subjects factor - group) returned significant main effects for: time ($F(1, 12) = 29.471$; $p < 0.001$), task ($F(1, 12) = 11.726$; $p = 0.05$) and hand ($F(1, 12) = 106.910$; $p < 0.001$). There was no significant main effect for group ($F(1, 12) = 2.289$, $p = 0.156$). There were also significant interactions between time x group ($F(1, 12) = 29.471$, $p < 0.001$), between hand x group ($F(1, 12) = 5.524$, $p = 0.037$), between time x hand ($F(1, 12) = 5.274$, $p = 0.04$), between time x hand x group ($F(1, 12) = 5.274$, $p = 0.04$). There were more taps made using the impaired limb post- relative to pre-treatment for the intervention only group, but this held across the other factors-conditions (uni- and bimanual) and hand (ipsi- and contralesional) (Figure 2).

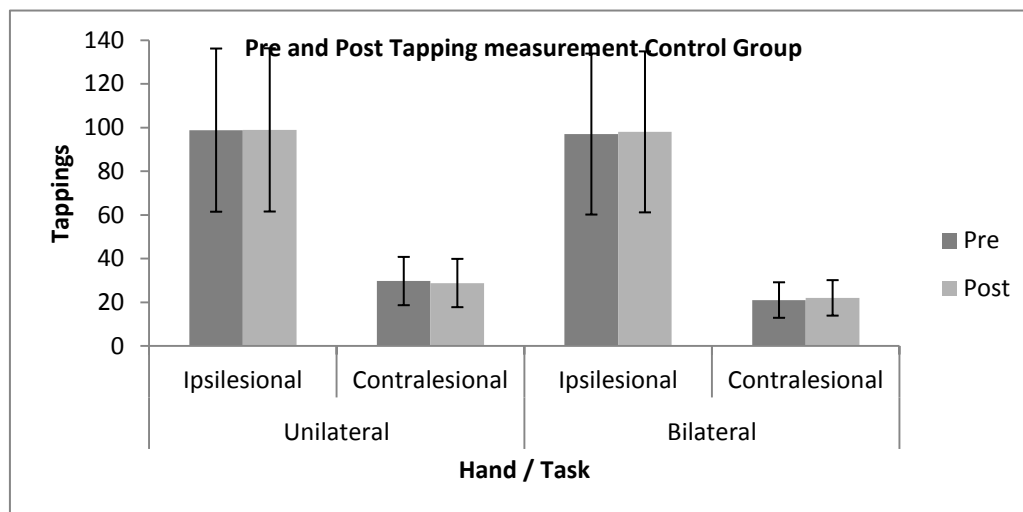
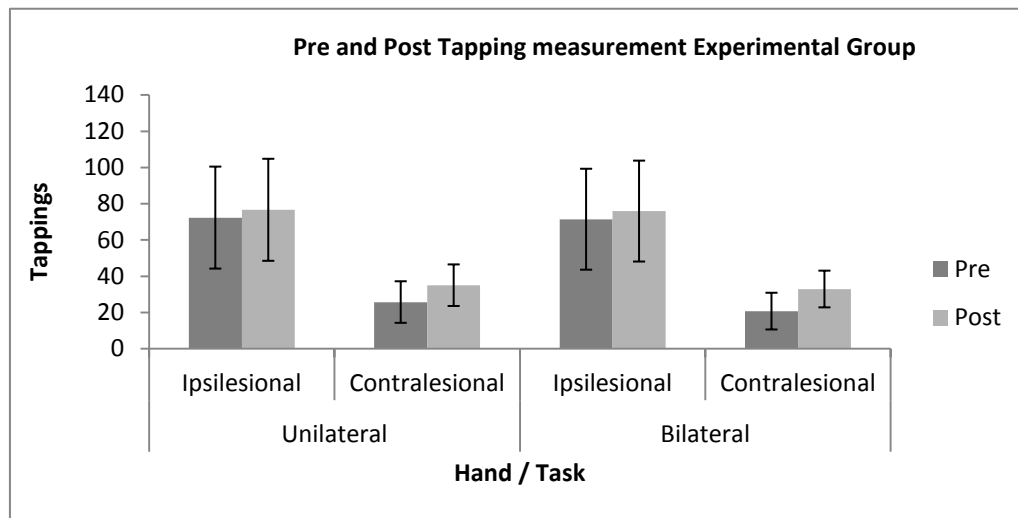


Figure 2a and 2b: Pre and Post mirror therapy tapping performance (in terms of N(Taps) for a) Experimental and b) Control Group. Error bars depict 1 SE on each side of the mean

Further analyses were conducted to decompose the 3-way interaction of time x hand x group. Two separate 2x2 ANOVAs were run for each group averaging across the tasks (uni- and bimanual actions). For the experimental group significant main effects of time ($F(1, 6) = 29.471$, $p = 0.002$) and hand ($F(1, 6) = 22.792$, $p = 0.003$) were returned and there was a borderline interaction between these two factors ($F(1, 6) = 5.274$, $p = 0.061$). There was improved performance post- vs. pre-training and for the intact over the impaired hand, The improvement

was larger for the impaired (contralesional) hand, but it was reliable for both (for the intact [ipsilesional] hand $t(6)=-2.48$, $p=0.048$; for the impaired [contralesional] hand $t(6)=4.49$, $p=0.002$). For the control group there was a main effect of hand ($F(1, 6) = 133.762$, $p < 0.001$) but not for time ($F(1, 6) = 0.462$, $p = 0.522$) (Figure 3).

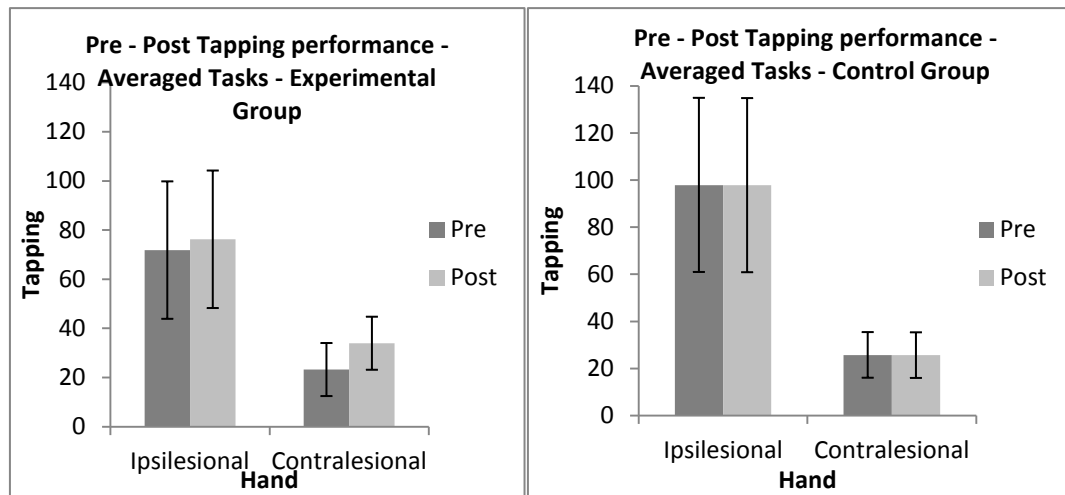


Figure 3a and 3b: Pre and Post mirror therapy tapping performance – averaged tasks-(in terms of N (Taps) for a) Experimental and b) Control Group. Error bars depict 1 SE on each side of the mean

To assess the effect of initial performance level on training, participants in the MT group were separated according to their level of functional ability to perform taps. If the participant initially scored fewer than ten taps on the unimanual task with the impaired hand they were allocated to group A (more impaired) and if they were able to tap more than ten times they were allocated to group B (less impaired). Three participants were allocated to group A, and four to group B. Performance was averaged across unimanual and bimanual movements (Figures 4 and 5).

For group A (more impaired), the analysis returned a significant main effect of hand (ipsilesional – contralesional): $F(1, 3) = 28.364$; $p = 0.013$). No other main effects or interactions

were reliable ($p's > 0.05$). Performance was worse for the contra- relative to the ipsilesional limb, but this did not improve post- vs. pre-treatment. For group B (less impaired), the analysis returned a significant main effect of time (before – after): $F(1, 2) = 25.900$; $p = 0.037$). All other main effects and interactions were not significant ($p's > 0.05$). For these patients there was a general improvement which held across movement type and hand.

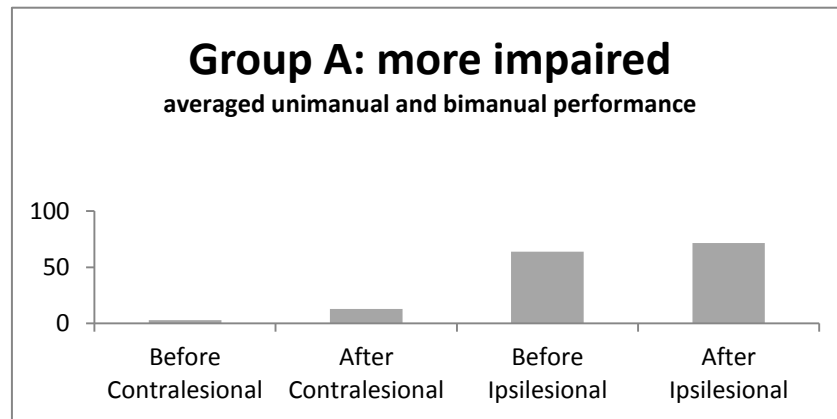


Figure 4: Tapping performance (N(Taps)) pre and post mirror therapy of more impaired participants (Group A)

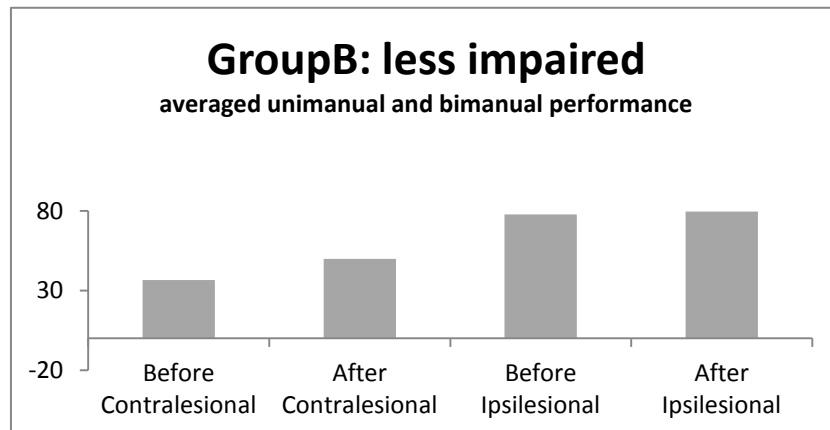


Figure 5: Tapping performance (N(Taps)) pre and post mirror therapy of less impaired participants (Group B)

A further analysis of the tapping data took place using the measurements that were taken on a weekly basis (only for the intervention group) during the six months of the MT. In order to assess the effects of therapy, the scores were broken down into 4 time periods across the therapy

period and performance was averaged across the therapy sessions contributing to each block. This smoothed out slight differences across patients when individual therapy sessions were missed. The data are shown in Figures 6-9. Tapping performance for the paretic upper limb was assessed using a repeated measure ANOVA with five factors: block (blocks 1-4), pre – post session (pre intervention and post intervention), eyes (opened versus closed), task (bimanual versus unimanual) and hand (contralesional versus ipsilesional). All main effects were significant: block ($F(3, 18) = 7.580; p=0.002$), pre – post session ($F(1, 6) = 13.045; p=0.011$), eyes ($F(1, 6) = 7.069; p=0.038$), task ($F(1, 6) = 29.304; p=0.002$) and hand ($F(1, 6) = 20.351; p=0.004$). The effects of block and pre – post session indicate that there was a significant improvement in tapping both across the therapy blocks and within each therapy session. There were significant interactions between pre – post session and task ($F(1, 6) = 7.546; p=0.033$) and between pre – post session, task and hand ($F(1, 6) = 8.685; p=0.026$). No other interactions were significant (all p 's > .05).

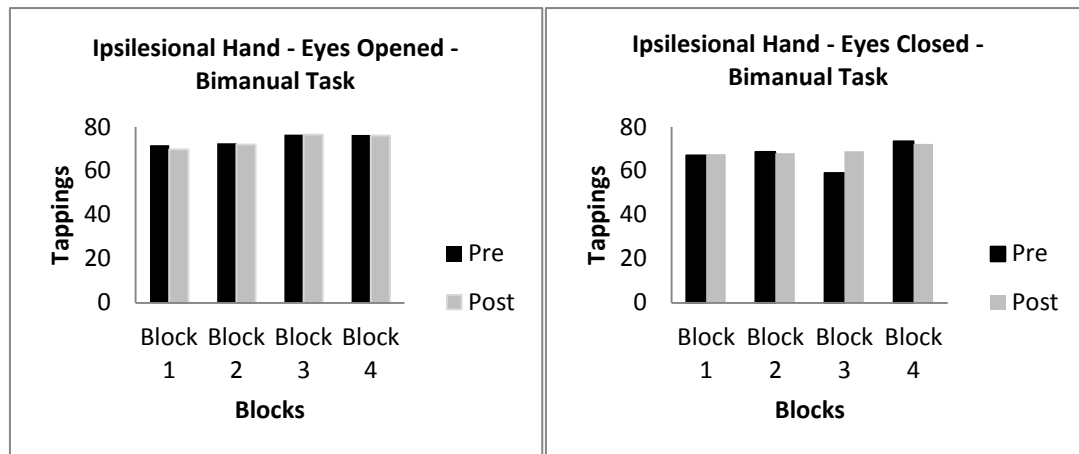


Figure 6a and 6b: Tapping performance (N(Taps)) pre and post mirror therapy for Ipsilesional Hand, Bimanual Task a) Eyes Opened b) Eyes Closed

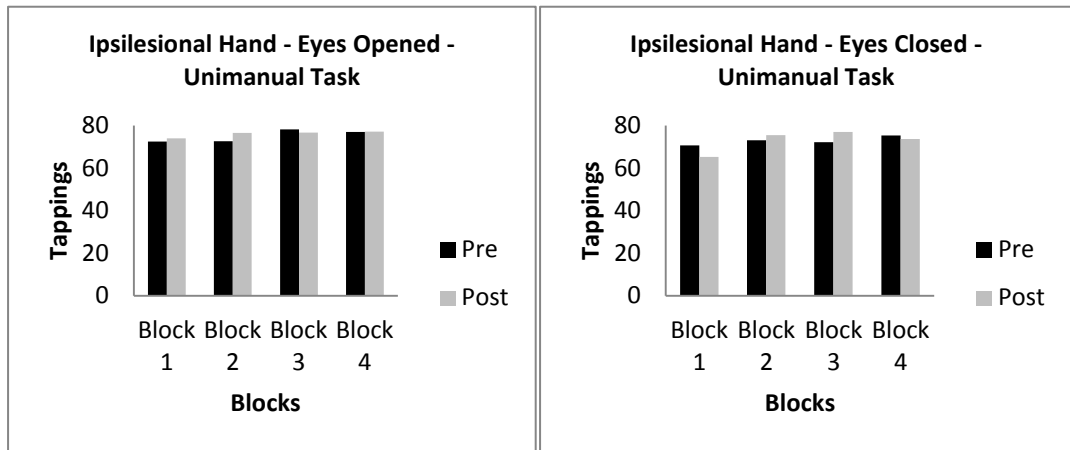


Figure 7a and 7b: Tapping performance (N(Taps) pre and post mirror therapy for Ipsilesional Hand, Unimanual Task a) Eyes Opened b) Eyes Closed

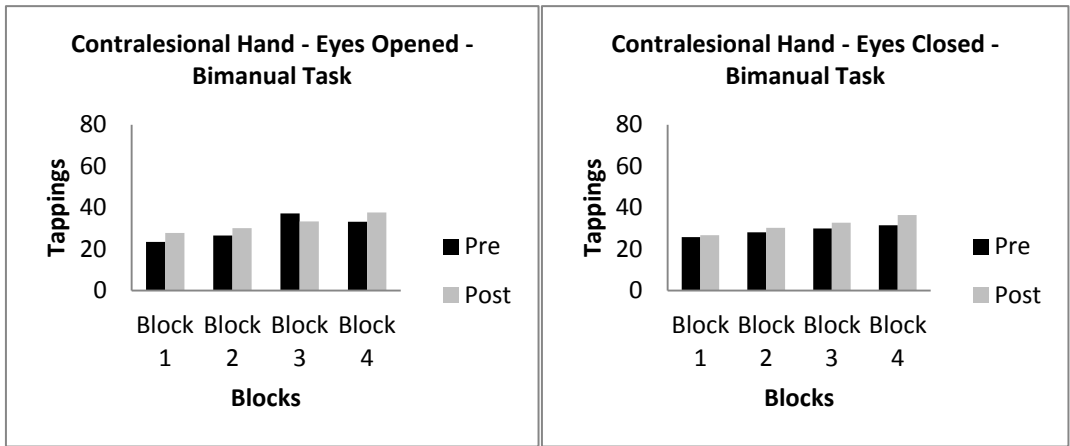


Figure 8a and 8b: Tapping performance (N(Taps) pre and post mirror therapy for Contralesional Hand, Bimanual Task a) Eyes Opened b) Eyes Closed

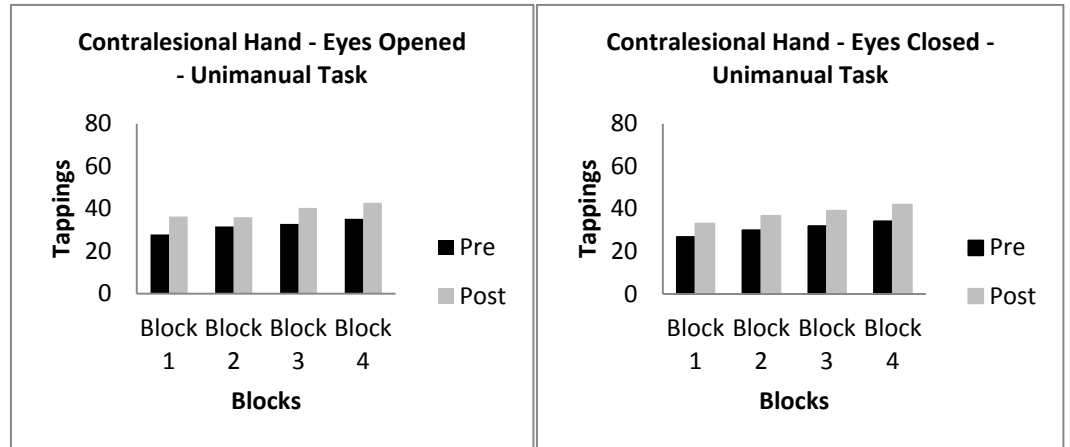


Figure 9a and 9b: Tapping performance (N(Taps) pre and post mirror therapy for Ipsilesional Hand, Unimanual Task a) Eyes Opened b) Eyes Closed

Since the effects did not vary as a function of whether the participants had their eyes open or closed or the block, further analyses were conducted averaging over these factors. The interaction pre – post session, task and hand was assessed by two 2-factor-ANOVAs, one for each hand. For the contralesional upper limb there were reliable main effects of pre-post session ($F(1, 6) = 9.501$; $p=0.022$) and task ($F(1, 6) = 16.482$; $p=0.007$), and there was also a significant interaction between these factors ($F(1, 6) = 21.180$; $p=0.004$). The interaction arose because there was a post-session improvement that was greater in the unimanual than the bimanual condition (Figures 9-12). In the pre-session measures there was no difference between the unimanual and bimanual actions ($t(6) = -1.23$, $p=0.266$), while there was a unimanual advantage in the post-test session ($t(6) = -7.58$, $p<0.001$). There was no improvement post vs. pre session for bimanual movements ($t(6) = -1.46$, $p=0.195$) while there was a reliable improvement for unimanual movements ($t(6) = -4.27$, $p<0.01$). The data are shown in Figures 10a and 10b.

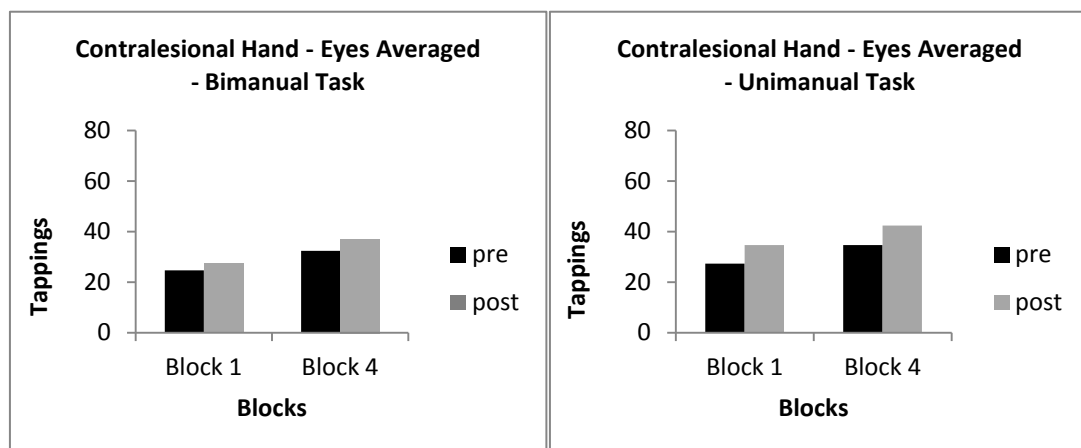


Figure 10a and 10b: Tapping performance (N(Taps)) pre and post mirror therapy for Contralesional Hand, Eyes Averaged a) Bimanual Task b) Unimanual Task

For the ipsilesional upper limb there was a significant effect task $F(1, 6) = 13.252$, $p=0.011$). There was no main effect of pre-post session ($F(1, 6) = 0.912$, $p= 0.376$) and no interaction between these factors $F(1, 6) = 0.070$, $p= 0.857$. The data are shown in Figures 11a and 11b.

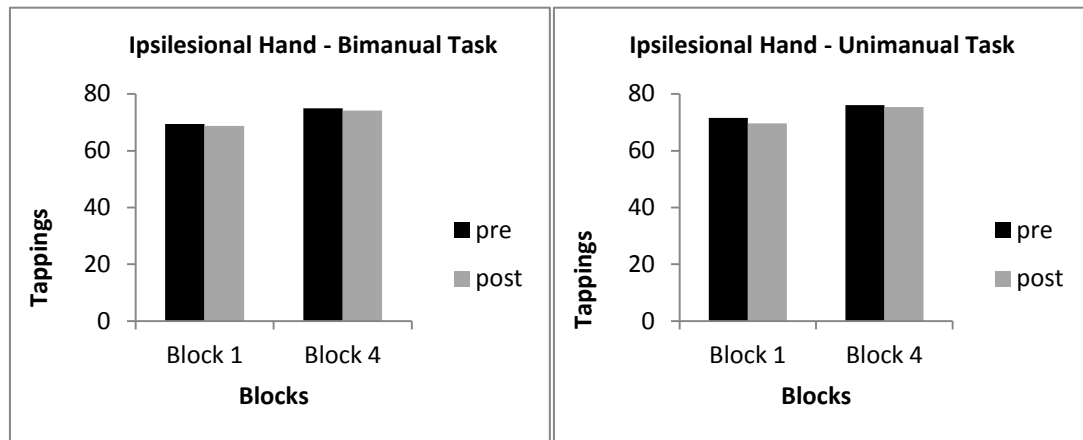


Figure 11a and 11b: Tapping performance (N(Taps)) pre and post mirror therapy for Ipsilesional Hand, Eyes Averaged a) Bimanual Task b) Unimanual Task

2.3.2. Action Research Arm Test (ARAT)

Data from the action research arm test were analyzed by comparing the mean ratings across the raters prior to any therapy and after the last therapy session. Initial ANOVA was performed for the pre vs. post performance as per group. There was a significant effect of time ($F(1, 12) = 161.485$, $p < 0.001$) and a significant interaction of time by group ($F(1, 12) = 170.036$, $p < 0.001$). When same analysis ran for the control group, there was no significant amelioration in ARAT score ($t < 1.0$). There was significant improvement across the patients that were allocated to the MT group ($t(5) = -12.254$, $p < 0.01$) (Figure 12a).

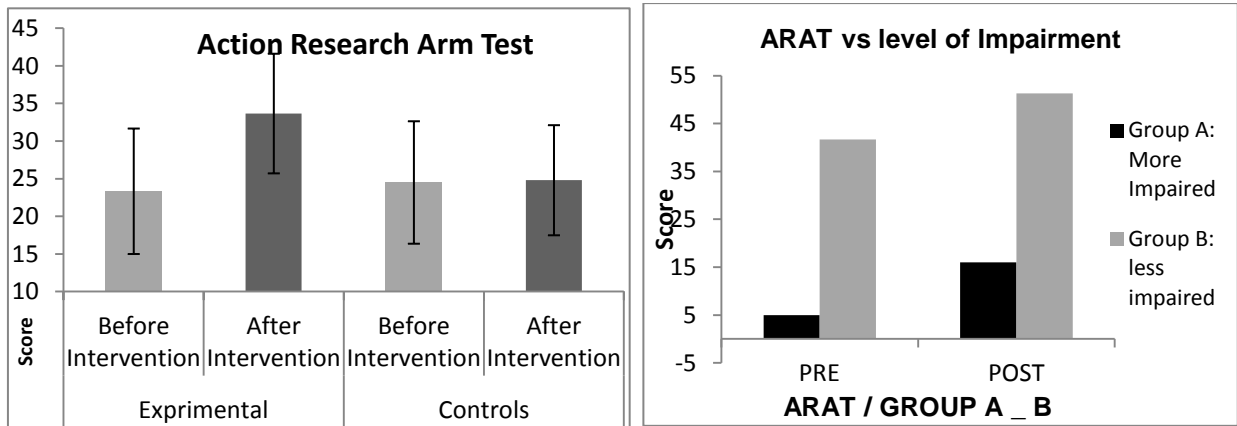


Figure 12a and 12b: ARAT performance before (pre) and after (post) mirror therapy comparing (a) experimental and control groups (error bars show Plus/minus one SE around mean) (b) more (black) or less (grey) impaired.

In order to identify any effect of initial motor performance level, participants of the MT group were allocated to two different groups, identical to the allocation during the tapping task. Three participants were allocated to group A (more impaired) and 4 patients were allocated to group B (less impaired). Level of performance was assessed using an ANOVA with time (before-after) as a within subject factor and group (A – B) as a between subject factor. The main effect of time was highly significant, $F(1, 5) = 196.829$; $p < 0.001$. There was no significant interaction between group and time. The results are shown in Figure 12b. Similar analysis returned no significant effect for the control group.

The Brunnstrom stages that were used to categorize the patients' characteristics remained unchanged before and after the intervention period.

2.4. DISCUSSION

There were significant improvements in functional motor outcome for chronic stroke patients given prolonged and regular Mirror Therapy (MT) whereas control participants not given therapy across the same time period showed no improvement. On the ARAT, functional movements improved only in the MT group, and this improvement was at least as marked for the patients who were initially more impaired, as for those who initially performed better. On the tapping task, there was a less clear improvement in the more dysfunctional group compared with the more functional group, which might reflect a floor effect in the tapping data for the very impaired patients. No improvement was noticed in the control group.

For the tapping tasks performed before and after each session, there were more differential effects of unimanual and bimanual actions across the MT group. Unimanual actions with the contralesional hand showed clear evidence of improvement within a session (pre vs. post session), and this held across the test blocks (see Figures 9-12). In contrast, tapping by the contralesional hand under bimanual action conditions did not improve within a session. These data indicate that, even when there is an improvement in motor activity (indexed by the unimanual conditions), performance can still be limited by attentional constraints when bimanual actions are demanded – when competitive motor regimes are activated. Punt and Riddoch (2006) have shown that motor extinction (the underutilization of a limb contralateral to a brain lesion under bimanual conditions) can decrease when the patient makes bimanual actions to virtually

grouped stimuli. It may be that attempts need to be made to group the visual cues involved in MT in order to promote recovery that is robust to competition in motor programming

It is also important to note that, during the tapping task, the participants were instructed to look at the centre, and it may be that they focused their attention on the ipsilesional hand when bimanual actions were performed. We compared performance while eyes were opened or closed and found little effect of this manipulation. However, we did not explicitly manipulate where patients attended, and again this might be critical for overcoming any competition for motor training between the ipsilesional and contralesional limbs when bimanual actions are made. The lack of an effect of vision (eyes open vs. eyes closed) also indicates that we did not have to generate subsequent benefits on action production. This is also consistent with Kim & Kramer (1997) who suggested that visual feedback might reduce importance once a motor skill has been reeducated.

It has been suggested that corticospinal excitability activation on the superior occipital gyrus is connected and influence areas of posterior parietal cortex (which is considered a part of the motor system – crucial for visuomotor transformations) (Matthys et al., 2009). This can be translated as a suggestion that MT generates visual illusory feedback to increase the functional ability of the hand. Carson (2005) suggested that by engaging the nonparetic limb during motor training, in bilateral tasks, there will be increased activation in the homologous motor pathways of the hemiplegic upper limb, and functional recovery will result (and this is referring to bilateral symmetric aimed movement (as opposed to tapping as fast as possible with each hand)). Fukumura et al. (2007) also found that an even greater increase in the amplitude of MEPs has been observed when the affected hand's movement is assisted.

Our data also indicate that there was greater improvement on tapping in patients who scored higher during the assessment outcome measures. This contrasts with results reported by Dohle et al. (2009) both in acute and sub-acute stroke patients, where recovery after MT was most prominent for those patients who had no initial distal function. This difference might be due to the lower capacity of brain plasticity in the chronic stroke patients when compared to the acute group. Further research is needed to clarify. Also, future research needs to examine the positive effects of synergistic application of 2 or more interventions (i.e. FES combined with MT). Yun et al (2011), showed synergic effect on hand function when MT is combined with neuromuscular stimulation and they found larger improvement when compared to the groups that used only one of these two interventions.

Limitations. The present study had some limitations. The number of experimental participants' (n=7) was relatively small and this constrains generalization for clinical use. Also, it would be useful to document the neural mechanisms of motor improvement using fMRI recorded prior to and post the intervention (see Michielsen et al, 2011). It should also be noted that the 6 month period over which this intervention applies is not always clinically feasible as most likely patients might be discharged from rehab in an earlier stage. Interestingly however, MT is entirely possible in a patient's home, and it would be useful to investigate long-term effects of prolonged home rehabilitation, to assess if this could be substitute for the experimenter – directed intervention used here.

2.5. CONCLUSIONS

We showed that prolonged MT when compared to no therapy improved motor function post stroke, particularly for patients scoring higher in their initial motor abilities. On the other hand, there was minimal effect of measuring action with and without vision, and the benefits of MT did not overcome motor extinction. MT can be a useful approach to improve, motor function after stroke, though attentional limitations can remain.

**CHAPTER 3: HOME BASED MIRROR THERAPY PROMOTES
MOTOR RECOVERY OF THE HEMIPARETIC UPPER LIMB**

ABSTRACT

Objective - To assess functional benefits in motor ability, along with motor extinction, following home-based mirror therapy in chronic stroke survivors with moderate hemiparesis of the upper limb.

Methods - Sixteen chronic stroke survivors (mean time post stroke 4.2 years) were randomly allocated to the experimental (n=8) or the control group (n=8) and they joined a 4 week rehabilitation program with weekly supervision. The outcome measures were performance on the Action Research Arm Test (ARAT) and tapping performance using the index finger.

Results - In the experimental group, patients regained elements of functional performance as translated by the ARAT, and there was also an improvement in both unimanual and bimanual tapping performance. There was no evidence of a differential improvement for bimanual actions.

Conclusions - MT in chronic stroke participants is a promising method for improving motor function but appears to operate by improving motor functions without necessarily changing attention to the affected limb.

Keywords: Stroke rehabilitation; mirror therapy; motor recovery

3.1. INTRODUCTION

According to the World Health Organization (2008) stroke is the primary cause for long term disability in developed nations and, when combined with ischaemic heart disease, it is the main cause of death worldwide. The percentage of stroke survivors with upper limb disability following stroke is approximately 80%, with the degree of recovery dependent on the severity of the hemiparesis (Nakayama, 1994).

Many current therapies to improve motor function after stroke depend on the stroke survivor having at least some minimal degree of voluntary movements (e.g., for robot-based rehabilitation [Zimmerli and Crewer, 2012] and constraint induced movement therapy [Taub, 2012, Grotta et al., 2004]. For patients without minimal movement, however, alternative approaches need to be sought. One such approach involves Mirror Therapy (MT) (Sutbeyaz et al., 2007). MT is easy to administer and there is the possibility for self-administration in home environments even for participants with severe motor impairments. Initially introduced by Ramachandran and Rogers-Ramachandran (1996) as an intervention to alleviate phantom limb pain in amputees, it has been widely used since then in different conditions such as peripheral nerve injury to alleviate pain (Gruenert-Pluss et al., 2008), complex regional syndrome (Moseley, 2004) and stroke (Altschuler et al., 1999, Sutbeyaz et al., 2007, Steven and Stoykov, 2003, Michielsen et al., 2011).

In MT, during the treatment session, the patient sits in front of a mirror placed parallel to his/her midline. The view to the hemiparetic upper limb is obstructed due to it being placed behind the non reflecting side of the mirror. During the intervention the patient moves the intact hand and watches its reflection in the mirror. This reflection appears to be the impaired limb

moving normally. It has been argued that this visual illusion stimulates cortical areas involved during the performance of the observed actions (Grezes and Decety, 2001), facilitating motor recovery.

Yavuzer and colleagues (2008) conducted a RCT on possible benefits of MT on hemiparetic hand's motor recovery, spasticity and hand related functioning in 40 subacute stroke patients. Significantly better performance was found in hand functioning with no effect on spasticity. Additionally, Altschuler and colleagues (1999) reported significant improvement in the range of motion (ROM) and on the speed and accuracy of arm movements in nine stroke patients following a MT course. Stevens and Stykov (2003) reported results on the application of MT for 3-4 weeks to two sub-acute stroke patients and found a significantly better outcome in terms of the Fugl-Meyer Assessment score, active ROM, movement speed and hand dexterity following training. In another report on chronic stroke patients Sathian, Greenspan and Wolf (2000) found that, after a two week course of MT, there was a better performance in grip strength and hand movement for the hemiparetic arm. Consistent with these results a recent Cochrane Review (Thieme et al., 2012) concluded that there is evidence for the effectiveness of MT and that improvements may occur in motor function for patients after stroke, but there is a need for more research to address questions regarding the intervention protocol, the optimal dose, frequency and duration of MT.

The present study assessed whether home-delivered MT would be effective in improving motor function in chronic stroke patients. Functional performance was assessed along with performance on a tapping task sensitive to bimanual as well as unimanual actions. Following a stroke, patients can be impaired at making bimanual actions when compared to unimanual actions using the affected limb. This deficit, known as motor extinction (LaPlane & Degos, 1983) has

been taken to reflect reduced attention to the affected side under conditions when there is competition for motor control with the ipsilesional limb. Consistent with this, motor extinction can be modulated by cueing patients to attend to the affected side (Edwards and Humphreys, 2002). To test motor extinction here, patients were asked to make unimanual and bimanual tapping actions and the drop in tapping performance with the contralesional limb was measured when bi- rather than unimanual actions were made. Does MT improve the relative degree of attention paid to the affected side, lessening the deficits specifically under bimanual conditions? Do improvements in motor extinction align with effects on functional actions?

3.2. METHODS

3.2.1. Participants

Sixteen chronic stroke patients were recruited. Participants were recruited from the panel of patients, School of Psychology, University of Birmingham. All participants provided informed consent under ethics approved by the University of Birmingham ethics committee. Eight chronic stroke patients were allocated randomly to Mirror Therapy group (mean age 70.8 +/-8.6, mean stroke incident 28.3mths +/-7.8) and eight chronic stroke participants were allocated to control group (mean age 66.5 +/-8.7, mean stroke incident 27.8 +/-5.3). All recruited participants met the following inclusion criteria : (i) they had had one episode of stroke diagnosed at least 12 months before (length of study participation and stroke incident was at least 12 months), (ii) scored between 1-3 on the Brunnstrom classification of motor recovery for the upper limb (Brunnstrom

classification consists of six stages of sequential motor recovery that leads to full recovery), (iii) were able to follow instructions related to MT and to maintain concentration for one hour-long sessions (capacity to follow rehabilitation regime) and (iv) had no other neurological related underlying conditions or orthopedic impairments that could affect upper limb's ability pre or post stroke. In the MT group five of the participants had right hemiparesis and 3 left and in the control group four had right hemiparesis and four left. Participants were males and they showed a mean of 2.3 +/-1.2 in Brunnstrom stages. Demographic data of participants:

| Demographic | | | Group | | Months post |
|-------------|-----|-----|-------|---------|-------------|
| Subject | Sex | Age | MT | Control | stroke |
| 1 | M | 69 | o | | 24 |
| 2 | M | 74 | o | | 31 |
| 3 | M | 68 | o | | 42 |
| 4 | M | 83 | o | | 37 |
| 5 | M | 63 | o | | 28 |
| 6 | M | 58 | o | | 19 |
| 7 | M | 82 | o | | 24 |
| 8 | M | 70 | o | | 22 |
| 9 | M | 54 | | o | 30 |
| 10 | M | 66 | | o | 18 |
| 11 | M | 64 | | o | 35 |
| 12 | M | 81 | | o | 27 |
| 13 | M | 64 | | o | 35 |
| 14 | M | 81 | | o | 27 |
| 15 | M | 73 | | o | 25 |
| 16 | M | 72 | | o | 28 |

Table 2: Demographic data of participants - Chapter 3

3.2.2. Procedure

In the experimental group all stroke survivors participated in a 4 week intervention of MT and controls participated twice to generate outcome measures with a monthly gap in-between the two sessions. The control group had no other rehabilitation during this month. For the experimental group participants visited the School of Psychology at the University of Birmingham before the intervention for an educational session of MT and practice with the

procedure. For the next four weeks they visited the university on a weekly basis to review their tolerance for MT and to take on new exercises in MT under the supervision of a qualified physiotherapist. During this visit, the therapist monitored that the patients did concentrate on the reflection of the spared hand in the mirror and not on the intact hand itself, when MT was performed. In between the weekly visits to the university the patients were instructed to perform hourly sessions of MT at home 5 days a week. Participants were instructed to log sessions in a diary and present it at the end of the intervention period to the research team. A commercially available Mirror Box was used (Reflex Pain Management Ltd, Stockport, UK). Subjects were placed in a sitting position while the mirror was positioned between their upper limbs perpendicular to their midline, with the nonparetic arm facing the reflecting surface. The patients were not allowed to wear anything that enabled them to differentiate between their two limbs. An important principle of MT and of any neurological rehabilitation approach is to adjust the treatment protocol to each patient's needs (Punt and Riddoch, 2006) and to vary the protocol during the progress of the treatment by increasing the level of difficulty. Accordingly, each patient followed his/her personally designed protocol according to the functional level of the paretic limb.

3.2.3. Outcome measures

The MT exercises consisted of functional movements mainly for fingers, wrists and elbows. Participants underwent finger flexion – extension, wrist flexion – extension, elbow flexion – extension, supination – pronation and shoulders abduction-adduction. The primary

outcome measure was the difference between performance pre- and post-intervention in the Action Research Arm Test (ARAT) (Yosbatiran et al., 2008). A blind assessor who was not aware of the nature of the intervention was used before and after the intervention period to score performance. The ARAT consists of four different subscales that are related to grasping, gripping, pinching and gross movement. The test involves nineteen movement tasks and the total score ranges from 0 to 57 with each specific task being rated from 0 to 3.

The second outcome measure was tapping performance. An electronic counter device was used consisting of two counters 15 cm apart mounted on a frame. Participants tapped (1N force required to press the button) the left counter with the left index finger and the right counter with the right index finger, either making unilateral or bilateral movements, over a period of 30 seconds, with their eyes open. Patients were asked to make as many finger taps as they could under both the unilateral and bilateral action conditions. This outcome measure has been shown to be sensitive by Cozens and colleagues (2003) for unimanual and bimanual movements. For this test, baseline assessments were taken 1 week before the start of the intervention and 1 week after the end of the intervention period.

3.3. RESULTS

3.3.1. Action Research Arm Test (ARAT)

Data from the action research arm test were analyzed by comparing the scored from the blind assessor prior to any therapy and after the last therapy session (Figure 13). An ANOVA

with a between-subjects factor of group (experimental vs. control) and a within-subject of time (pre- vs. post-intervention) performed. There was no significant effect of group ($F(1, 14) = .0, p = .786$). There was a highly significant main effect of time ($F(1, 14) = 41.653, p < 0.001$) and a significant interaction between time and group ($F(1, 14) = 29.300, p < 0.001$). To identify the nature of this interaction two t – tests were performed, one for each group. For the experimental group there was a significant effect of time ($t(7) = -6.333, p < 0.001$) but this did not occur for the control group ($t(7) = -1.488, p = 0.18$).

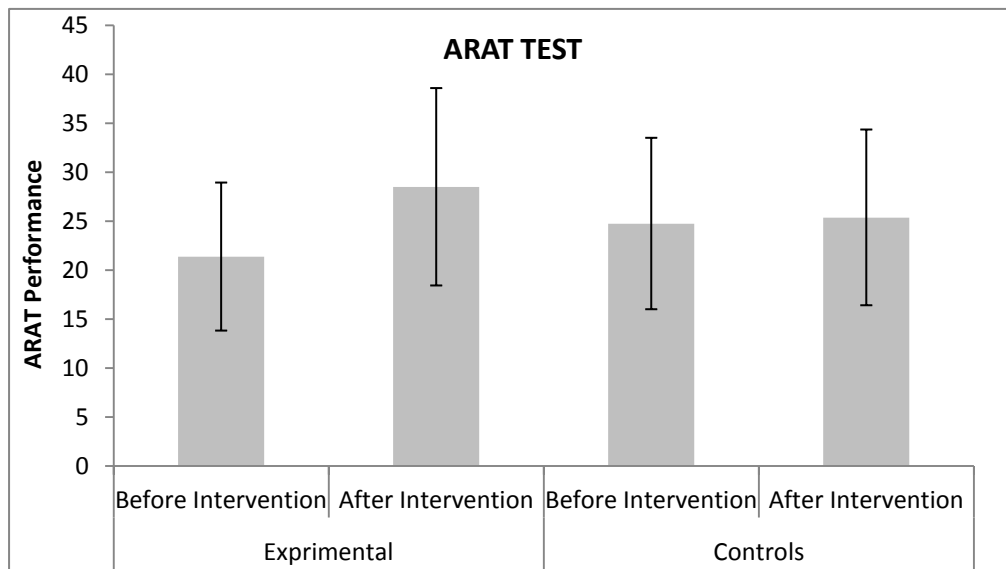


Figure 13: ARAT performance before (pre) and after (post) mirror therapy comparing experimental and control groups (error bars show Plus/minus one SE around mean)

3.3.2. Tapping Performance

For the tapping task we compared the number of taps made pre – and post-intervention (within-subjects factor: time), with the healthy vs. the impaired hand (within-subjects factor:

hand), for unimanual and bimanual movements (within-subjects factor: action) and across experimental and control groups (between-subjects factors: group). There was no overall effect of group ($F(1, 14) = 1.219, p = 0.288$). There were reliable main effects of hand ($F(1, 14) = 15.880, p = 0.001$), action ($F(1, 14) = 29.646, p < 0.001$) and time ($F(1, 14) = 239.471, p < 0.001$). There were also two 2-way significant interactions between hand and group ($F(1, 14) = 10.163, p = 0.007$) and hand and time ($F(1, 14) = 13.339, p = 0.003$). There were also two 3-way interactions between hand, time and group ($F(1, 14) = 9.603, p = 0.008$) and between hand, action and time ($F(1, 14) = 3.279, p = 0.034$). Figures 14-16.

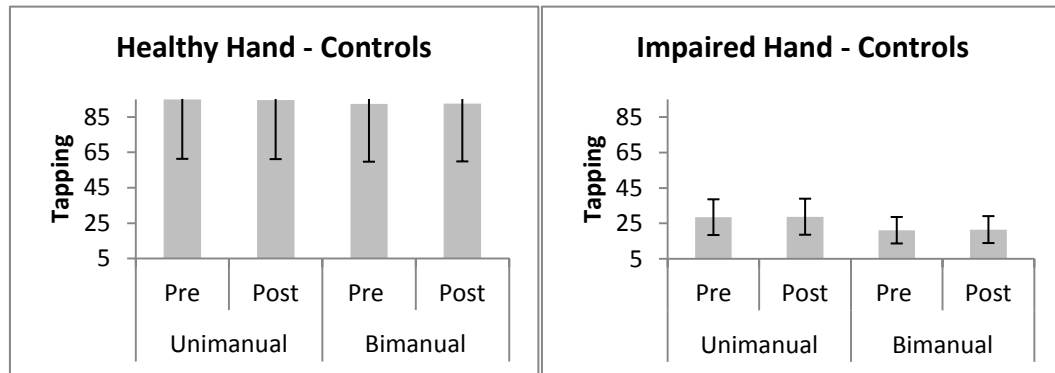


Figure 14a and 14b: Pre and Post mirror therapy tapping performance (in terms of N(Taps) for control participants a) Healthy Hand and b) Impaired Hand. Error bars depict 1 SE on each side of the mean

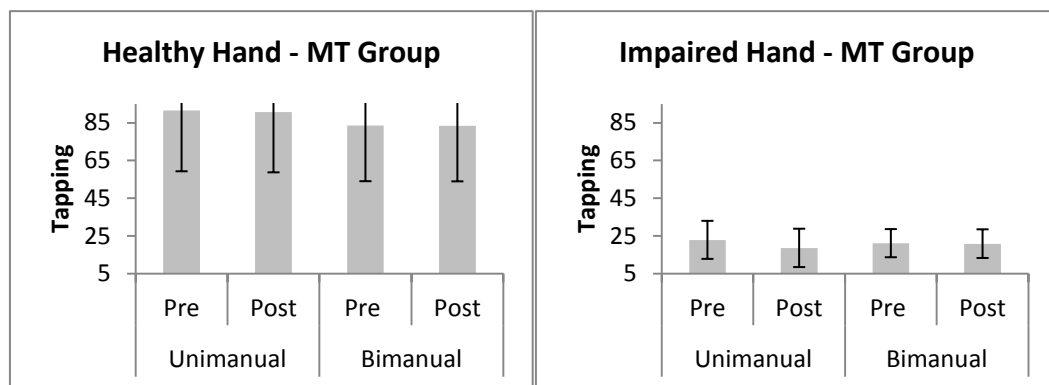


Figure 15a and 15b: Pre and Post mirror therapy tapping performance (in terms of N(Taps) for experimental participants a) Healthy Hand and b) Impaired Hand. Error bars depict 1 SE on each side of the mean

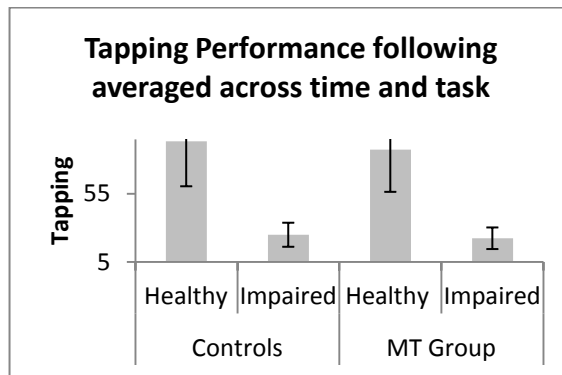


Figure 16: Pre and Post mirror therapy tapping performance (in terms of N(Taps)) for all participants per group following average of time and task. Error bars depict 1 SE on each side of the mean

The 3-way interaction between hand, time and group was broken down by running two 2-way ANOVAs, one for each group. For the control group, the ANOVA returned a significant main effect of time ($F(1, 7) = 93.659, p < 0.001$) and no significant effect of hand and no hand x time interaction (Figure 16). For the MT group there were significant effects of hand ($F(1, 7) = 18.481, p = 0.004$) and time ($F(1, 7) = 174.335, p < 0.001$). Also, there was a significant interaction between hand and time ($F(1, 7) = 13.803, p = 0.008$). In order to identify significant changes per time for the healthy and impaired hand separate t-tests were ran. There was a significant effect for the impaired hand per time ($t(7) = -6.517, p < 0.001$). The same t-test for the intact hand was not significant ($t(7) = .720, p = 0.495$).

The 3-way interaction between hand, action and time, was assessed by means of two 2x2 ANOVA's, one for each hand. For the healthy hand there was only a significant effect of time ($F(1, 7) = 20.896, p = 0.003$) revealing more taps post intervention. For the impaired hand there were significant main effects of action ($F(1, 7) = 30.822, p = 0.001$) and time ($F(1, 7) = 13.445, p = 0.008$). There were more taps post- relative to pre-intervention, and there were more

taps with uni- relative to bimanual actions. There was no significant interaction of action and time for the impaired hand ($F(1, 7) = 3.294, p = 0.112$).

3.4. DISCUSSION

The present study reports on the use of mirror therapy (MT) in chronic stroke subjects following a 4 weeks course of home based intervention. We demonstrated that MT generated functional improvements in motor performance. First, the data demonstrate chronic stroke participants may benefit from MT based on a clinical outcome measure, the Action Research Arm Test (ARAT). The change itself was relatively small in magnitude; specifically it was an averaged across the participants' change of 24 to 33 (increase of 37.5%) for the experimental group and no significant change for the control group. Similar results of improvements have been noted in mirror therapy research papers such as: in Thieme et al. (2013) a change of 3.2 to 8.2 had been found in the experimental group (increase of 156%); in Dohle et al. (2012) no significant improvement found; in Lin et al. (2012) an increase of ARAT score from 8.5 to 12 has been argued (change of 41%). Similarly in other intervention such as Functional Electrical Stimulation (FES) similar functional improvements have been reported: Powell et al. (1999) argued an increase from 6 to 10 in ARAT performance which is equal to 67% and Sullivan and Hedman (2004) found an increase of 27 to 42 which can be translated in 55.5% improvement.

Therefore our findings represent a significant result both functional and clinical given the short term rehabilitation protocol.

Second, MT improved both unimanual and bimanual taps, though it did not change the ratio of tapping actions for the uni- and bimanual actions (there was no interaction between action and time). More specifically the lack of interaction between unimanual and bimanual task indicates that MT had an effect on limb use but not necessarily on attention to the limb as there remained a drop under bimanual condition, though tapping improved in both the uni- and the bimanual conditions.

The evidence that tapping improved for both the uni- and bimanual conditions is consistent with the general motor improvement in the patients trained using MT. If MT had also improved attention to the affected limb, we might have expected to see a differential improvement under the more attentionally demanding condition of bimanual movements. We did not. We conclude that MT improved motor function without differentially generating improved attention to the affected limb.

The argument for an effect of MT on motor output is supported by Fukumura et al. (2007). The authors proposed that MT as motor imagery enables increase of activation of the motor cortex and that motor imagery combined with observation of the moving hand in the mirror could have beneficial implication during the rehabilitation process. Brain imaging studies have shown that MT can induce enhanced visual activation in the superior occipital gyrus and the posterior parietal cortex (Matthys et al., 2009). This suggests that, by generating illusory visual feedback, MT increases the functional ability of the hand and maybe even further to promote bimanual tasks that are crucial for activities of daily living. There was no evidence here however that any sensory-associated activation in relation to MT had an impact on attention (differential

improvement under bimanual action) as opposed to movement alone. Rather the data are consistent with an effect on motor activity, perhaps operating through the mirror neuron system (Rizzolatti and Craighero, 2004). The functional and neural mechanisms through which MT operates is clearly a question that requires additional research.

Limitations. The present study had some limitations. The number of experimental participants' (n=8) was relatively small and this constrains generalization for clinical use. Also, it would be useful to document the neural mechanisms of motor improvement using fMRI recorded prior to and post the intervention (see Michielsen et al, 2011). It should also be noted that the home-based approach adopted in this intervention applies is not clinically feasible in relation to the demands on monitoring the patient by the clinician.

**CHAPTER 4: MOTOR RECOVERY AND NEURAL
CORRELATES FOLLOWING MIRROR THERAPY IN
SUBACUTE STROKE PATIENTS**

ABSTRACT

Background and Purpose – We examined the effectiveness of Mirror Therapy (MT) in promoting motor recovery and changing neural activation in relation to movement of the hemiparetic upper limb in early subacute stroke survivors.

Methods – Fifteen stroke survivors (mean 68.3 ± 10.6 years old and 18 ± 11 days post stroke) took part in the study. Nine patients were randomly allocated to the mirror therapy group (MG) and six patients were allocated to the control group (CG). All patients received 4 weeks of upper limb MT for 40 minutes, 5 days per week, but only the MT group saw a reflection of the non-hemiparetic limb. Outcome measurements included the Hospital Anxiety and Depression Scale (HADS), the Barthel Index (BI), the Action Research Arm Test (ARAT) and fMRI data (collected from 4 patients of the MG and 2 patients of the CG).

Results – After 4 weeks of treatment, all patients showed a significant generalized improvement in terms of the upper limb's functional capacity, as depicted by the ARAT compared with the baseline measurements. This improvement was larger in the MT participants. These behavioural improvements were associated with increased responses in motor associated regions both within the intact and lesioned hemisphere.

Conclusions – Four weeks of MT, applied to subjects with early subacute stroke, improved their motor and functional performance. These improvements are mediated by neuroplasticity-induced changes in cortical motor associated activation of the affected and non affected regions and the potential generation of new neural pathway.

Key words: mirror therapy, rehabilitation, stroke, functional magnetic resonance imaging, fMRI.

4.1. INTRODUCTION

Hemiparesis is among the most devastating consequences following a stroke with implications for functional outcome including activities of daily living (Kwakkel, 2003). Various techniques have been introduced to help remediate hemiparesis (Thieme, 2013), with one recent innovation being Mirror Therapy (MT) (see Altschuler et al., 1999). During MT stroke survivors move their healthy upper or lower limb in front of a mirror, placed perpendicular to their midline, which enables a reflection of the healthy limb to be used as illusionary visual feedback. This feedback may be perceived by the participant as illusory movement of the affected upper limb (Sathian, 2000). MT was originally described by Ramachandran and Rogers-Ramachandran (1996) as an intervention that could alleviate phantom limb pain in amputees, however it has more recently been shown also to be effective in reducing post-stroke hemiparesis (Yavuzer et al., 2008).

The neural correlates of MT remain largely unknown. It has been suggested that observation of passive movements may trigger excitatory neurons of the ipsilateral M1 (Maeda, 2002). Garry et al. (2005) attempted to test this theory by applying TMS to the motor cortex in eight healthy volunteers during both passive and active movements in front of a mirror. The authors reported that M1 neurons ipsilesional to the hand behind the mirror became excited during unilateral movements and, more importantly, this excitation of M1 was higher when there was the mirror-induced reflection of the movement task compared to when the hand was actively moved without this visual feedback. This finding is important for clinical applications as it is possible to achieve recovery of the impaired hand by moving the healthy hand. In a similar study,

Nojima et al. (2012) investigated effects of mirror visual feedback on motor cortex using TMS. Sixty-three healthy individuals performed different tasks to compare the behaviour of M1 ipsilateral to the TMS in mirror versus action observation tasks. They reported evidence of increased excitation of the primary motor cortex, as EMG responses were triggered by a weaker TMS pulse to primary motor cortex. It was found by the same authors that excitation of M1 (both sides) can be expected in mirror visual feedback rehabilitation techniques.

Laepchen and colleagues (2012) also used TMS to explore the neural basis of MT. They randomised their 24 participants into two groups. Participants underwent MT over (using only their right – dominant hand, controls performed the same activities without the use of a mirror) four days for twenty minutes. The training tasks involved five different actions, such as moving cards from a predefined position. Both groups were unable to see their left hand or to move it (untrained hand). TMS was applied before and after the training session. Both hands were tested (in the above tasks) and no significant difference was found for the trained hand between the two groups. More interestingly behavioural results for the untrained hand showed greater performance in the mirror group compared to the control group. The authors did not find any significant difference of inter-hemispheric inhibition (IHI) between the M1's. Interestingly though, both groups changed their excitability levels following training but they followed different routes. The control group showed increased excitability of the left M1, while the right M1 showed no differences. In contrast the mirror group showed decreased excitability on the left M1 and there was a disinhibition of the right M1. The authors concluded that although the two groups performed the same tasks during the training period, the lack of visual feedback in the control group led to different neural routes being involved during training and that MT induced

neuroplasticity in the group with visual feedback. Wang and colleagues (2013) compared lateralized excitation of the human cortex during self-observed mirrored movements. The authors reported lateralised cortical activation in healthy individuals when self-movements were observed via a mirror, which, however, was absent during the simple observation of hand actions. This is also consistent with research published by Fukumura et al. (2007) who found that observation of one's own hand movement in the mirror makes similar movements for the other hand easier in healthy individuals.

fMRI data suggest that there are also specific visual areas that are activated during mirror induced movements, which are not activated to the same extent during the observation of simple (non-mirrored) hand actions. For example, Matthys et al. (2009) found increased activation of the ipsilateral superior temporal gyrus (STG) and superior occipital gyrus when mirrored visual feedback was given as a subject moved. However, these brain regions were not activated during movements in a non-mirror task (when actions were made in free view). The authors' main goal was to correlate mirror movements with areas of the mirror neuron system which has been found to be activated during both the execution and observation of movements (Rizzolatti et al., 2004). Although key topographical areas of this system include regions of the frontoparietal cortex, Matthys and colleagues (2009) did not find any association of MT with these areas. However, these findings do not exclude the involvement of the mirror neuron system during MT, as STG areas and superior occipital areas have also been associated with the mirror neuron system (Rizzolatti et al., 2004).

Hamzei and colleagues (2012) investigated possible neural connectivity mechanisms of MT using fMRI, again focusing on the role of the mirror neuron system (mainly areas of

ipsilateral sensorimotor cortex – SMC) during mirror induced movements. In the healthy subjects recruited in this study it was found that MT induces motor plasticity by connecting movements of the upper limb to the ipsilateral SMC. The results indicated that cortical activation of the non-trained hand side takes place during the mirrored movements of the contralateral hand. More fMRI results by Tominaga et al. (2009) in healthy individuals confirmed that the primary motor cortex in the contralateral hemisphere is activated in participants not only during the observation of action but also when participants look at the reflection of the ipsilateral hand on the mirror.

Although there is evidence for motor improvements following MT in stroke survivors (Yavuzer et al., 2008), there is very limited evidence of the neural changes in stroke survivor's cortex following MT training. The only RCT with fMRI data that has been conducted so far is the one by Michielsen and colleagues (2011). In this study forty chronic stroke patients were randomised into mirror or control groups. The experimental group followed a six week intervention protocol of daily home-based MT (with once per week sessions to be under supervision). The control group was allowed to directly view both hands while the experimental group could only look at the non affected hand and its reflection to the mirror projected as the impaired hand. The authors found behavioural changes in the Fugl Meyer Assessment scale (FMA) following the intervention, but the difference between the control and mirror therapy groups did not maintain across a six months follow up. fMRI analysis of the pre- and post-MT scans (end of intervention period) revealed that, in the mirror group, there was a shift in the proportional level of activation between the primary motor cortices in favour of the lesional side. Bhasin et al. (2012) also reported results on the application of MT in twenty chronic stroke

individuals. In this study participants underwent sixty to ninety minutes of mirror therapy for a period of over eight weeks using a laptop in which the healthy hand was projected as the impaired one (a mirrored image). When fMRI data from the pre- and post-intervention period were compared there was a significant improvement in the laterality index (the authors did not provide full details of the parameters of this laterality index), noticed in favour of the ipsilesional regions BA4 and BA6 (BA = Brodmann area). This is consistent with some degree of neuroplasticity induced by MT.

The aim of the present study was two-fold. First, behavioural data on the application of MT in early subacute stroke survivors are reported on motor and general clinical outcome measures. Second, in order to identify mechanisms of neuroplasticity and cortical reorganization during the crucial phase of stroke recovery, fMRI data were obtained pre- and post-intervention. To our knowledge this is the first fMRI study that has been conducted in an early subacute stroke population using MT on top of the standard rehabilitation regime.

4.2. METHODS

4.2.1. Participants

Out of twenty-three inpatients from Moseley Hall Hospital in Birmingham (UK) that were initially contacted, fifteen were recruited into this study. All patients provided informed consent under ethics approved by IRAS. Demographical data of the fifteen participants can be seen in Table 3. The experimental group included 7 males and 2 females (mean age 68.1 +/-11.4, mean

days post stroke 15 +/-5.14), whereas the control group included 5 males and 1 female (mean age 68.5 +/-10.1, mean days post stroke 13.8 +/-5.03). The participants fulfilled the following inclusion criteria: (i) first stroke, (ii) able to follow simple instructions and maintain concentration for at least forty minutes during rehabilitation sessions, (iii) had normal movement of the upper limbs prior to their stroke; (iv) scored between stages II and V on the Brunnstrom scale¹. Patients recruited to this study were given the option to attend the pre and post scan sessions or not. Additional inclusion criteria for patients agreeing to undergo two MRI sessions were: lack of epilepsy, lack of claustrophobia, ability to push down index finger (even with use of forearm's pronators), no metal implants or other implants that are contraindicated for MRI scans. Scans took place at BUIC (Birmingham University Imaging Centre) and the study was ethically approved by the NIHR (National Institute of Health Research) through the IRAS (Integrated Research Application System). Four patients from the MT and two patients from the control group gave consent to MRI (Figures 17 and 18).

| Demographic | | | Group | | Days post | | ARAT | | Barthel Index | | Anxiety | | Depression | |
|-------------|-----|-----|-------|---------|-----------|-------|------|------|---------------|------|---------|------|------------|------|
| Subject | Sex | Age | MT | Control | stroke | MRI | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | M | 70 | o | | 7 | - | 34 | 39 | 19 | 20 | 4 | 3 | 2 | 2 |
| 2 | M | 73 | o | | 16 | y (A) | 38 | 44 | 19 | 20 | 5 | 5 | 9 | 8 |
| 3 | M | 68 | o | | 17 | y (B) | 29 | 37 | 18 | 20 | 5 | 4 | 7 | 8 |
| 4 | F | 86 | o | | 21 | - | 42 | 47 | 20 | 20 | 8 | 6 | 6 | 4 |
| 5 | M | 56 | o | | 13 | y (C) | 14 | 21 | 10 | 14 | 3 | 3 | 2 | 2 |
| 6 | M | 54 | o | | 20 | y (D) | 8 | 17 | 15 | 16 | 1 | 1 | 1 | 0 |
| 7 | F | 84 | o | | 13 | - | 9 | 16 | 12 | 15 | 6 | 6 | 2 | 1 |
| 8 | M | 59 | o | | 8 | - | 18 | 23 | 16 | 18 | 1 | 1 | 4 | 3 |
| 9 | M | 63 | o | | 20 | - | 17 | 24 | 14 | 15 | 2 | 2 | 6 | 6 |
| 10 | M | 81 | | o | 21 | - | 25 | 27 | 17 | 20 | 1 | 1 | 5 | 5 |
| 11 | M | 61 | | o | 8 | - | 32 | 34 | 19 | 20 | 2 | 2 | 4 | 3 |
| 12 | F | 82 | | o | 14 | y (E) | 8 | 10 | 15 | 17 | 3 | 2 | 1 | 0 |
| 13 | M | 61 | | o | 13 | - | 12 | 15 | 8 | 16 | 6 | 4 | 8 | 7 |
| 14 | M | 62 | | o | 9 | y (F) | 14 | 17 | 16 | 17 | 6 | 6 | 10 | 8 |
| 15 | M | 64 | | o | 18 | - | 15 | 16 | 15 | 18 | 6 | 6 | 3 | 4 |

Table 3. Demographic and behavioural data pre post

Table 3: Demographic data of participants. Chapter 4

¹ Brunnstrom six stages are used to categorize stroke survivors according to their motor capacity, i.e. II minimal movement, VI good movement but not as detailed as in the healthy side.

4.2.2. Procedure

Nine patients were randomized to the MT group and six into the control group. Six out of these fifteen participants consented to undergo MRI scans (four from the MT group and two from the control group). Following the collection of informed consent, patients underwent the pre-assessment by completing the Hospital Anxiety and Depression Scale (HADS) (see Bjelland et al., 2002) and the Barthel Index (Sulter, 1999) to provide general outcome measures, the Action Research Arm Test (ARAT) (Hsieh et al., 1998) to measure motor function and, for those who agreed, the pre-intervention MRI. The same procedure was followed four weeks later at the end of the intervention when post-treatment measurements were acquired one week after the end of the intervention. During their hospitalization participants underwent a standard rehabilitation programme consisting of daily physiotherapy and occupational therapy (forty-five minute-sessions) along with language therapy and neuropsychology reviews, if required. The main focus of physiotherapy in the hospital was to restore balance and walking mobility and therefore MT was the main intervention that the patients received for the restoration of function for the paretic upper limb.

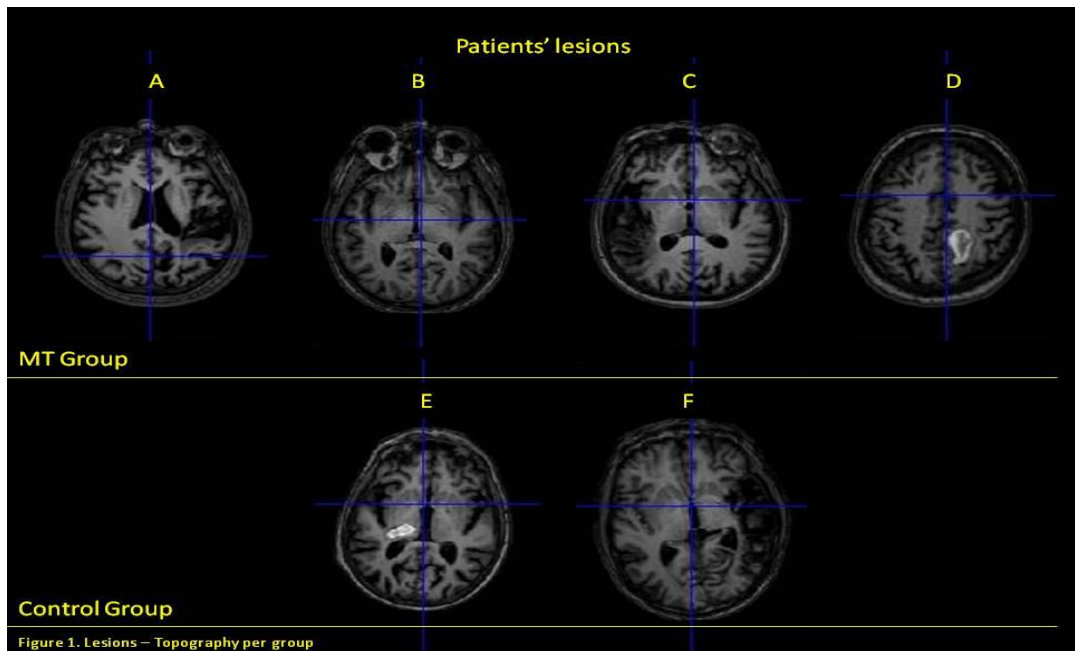


Figure 17: Lesions - Topography Per Group, Left refers to anatomical Left brain.

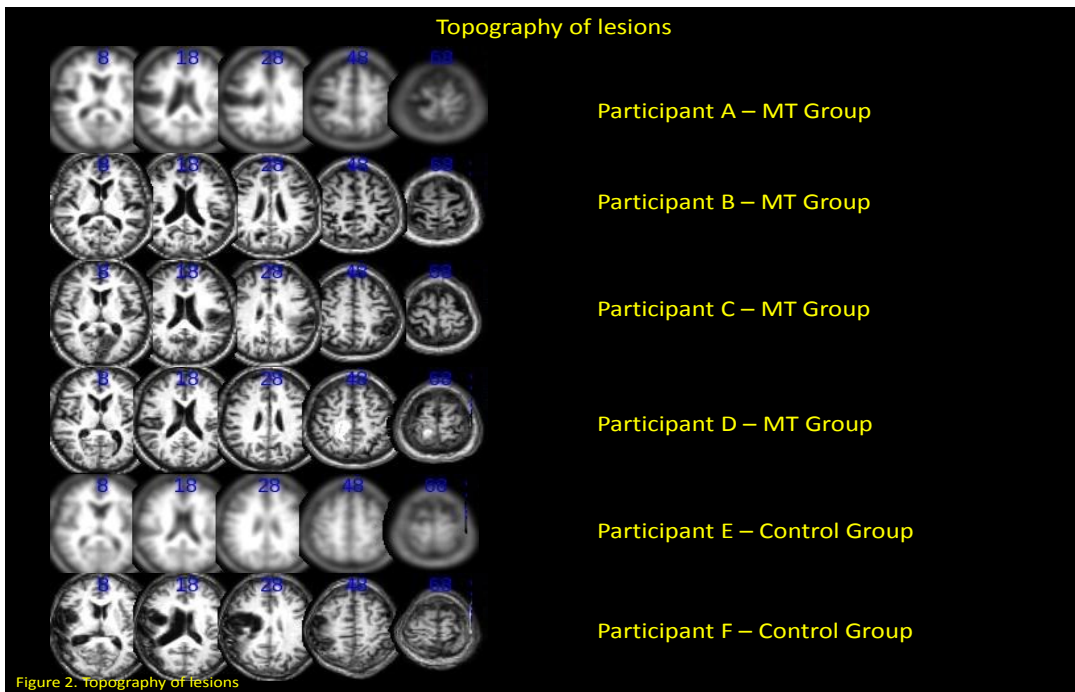


Figure 18: Topography of Lesions Left refers to anatomical Right brain.

4.2.3. Mirror Therapy – Sham Therapy

All participants underwent a four-week daily training programme and they were blind to the aim of this study. A mirror 40x60cm was placed perpendicular to the midline of the participants while they were seated. The mirror's reflecting side was placed towards the intact upper limb in the experimental group, whereas, in the control group, the mirror was covered during the sessions. Participants in the experimental group were asked to concentrate on the reflection of their good hand in the mirror. Participants in the control group were asked to imagine that they were able to see their impaired hand. During the continuation of the intervention period subjects were asked to perform bilateral movements starting with elbow flexion-extension and progressing to more detailed movements of pronation-supination, wrist flexion-extension, finger movements (i.e. thumb-index opposition). Functional tasks were introduced in the third week of the intervention period, including reaching a ball, grasping a cup, picking a pen. In all the sessions participants practiced under the close supervision of a physiotherapist and member of the research team. The duration of each session was approximately 40 minutes.

4.2.4. Outcome Measures

The behavioural outcome measures included the HADS, the Barthel Index, and the ARAT. The HADS was used as a generic outcome measure in order to identify effects on anxiety

and depression. The Barthel Index monitors capacity of basic everyday needs and the level of assistance that a patient requires. Finally, the ARAT test is an assessment of functional motor control. The ARAT consists of four subscales covering the following activities: grasp, grip, pinch and gross movement. Each task is graded between zero and three, and the maximum total score is fifty-seven. Results for the behavioural outcome measures can be seen in Table 1.

4.2.5. fMRI scanning

All six stroke survivors participated in two fMRI experimental sessions (four - five weeks apart) of equal duration. The first session took place, on average, three days prior to the start of the intervention course and the second one took place three days after the end of the intervention period. All participants were able to be transferred by taxi from hospital to BUIC, where the fMRI acquisitions took place. All scanner sessions were conducted using a 3T scanner (Achieva; Philips, Eindhoven, The Netherlands). EPI and T1-weighted anatomical (1x1x1 mm) scans were initially performed with an eight-channel SENSE head coil. All MRI sequences used gradient-echo EPI data that were applied by 34 axial slices with no gaps (repetition time = 2000ms, echo time = 35 ms, flip angle = 80°, 3x3x3 mm resolution). Three 180 second-EPI runs were performed. Patients read visual instructions projected on a screen and they were requested to tap using a standard MRI button response. During the fMRI acquisition a researcher was present in the scanner room to ensure that patients followed the instructions. The finger tapping sessions were randomized across participants with a resting interval in between. Each fMRI session

consisted of a block of 180 secs; during these blocks patients tapped on the button device with their index fingers while they performed three different tasks: right hand tapping, left hand tapping and bimanual tapping. The participants were unable to see their hands during the fMRI task. The tasks randomly alternated from right hand tapping, left hand tapping and bimanual tapping. Patients were instructed to press and release the buttons at a ratio of one squeeze every 1-3 seconds according to their functional capacity. Prior to each tapping block an instruction screen was presented for 20s to prepare the participants for the task, displaying the words 'get ready'. During each acquisition each tapping task was interspersed with a rest block where a 'relax' screen was displayed for 10sec. In addition, 10s fixation periods were added at the beginning and the end of each session.

4.2.6. Image analysis

The imaging data were analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, 2009) run in Matlab (version 2009). Realignment and unwarping of all acquired volumes took place to correct for all movement distortions (Anderson et al., 2001). Also all T1 scans were co-registered to the mean EPI image in order for the normalization parameters to be estimated. The next step was to use the unified segmentation algorithm so that all T1 scans were warped to the normalised MNI space (see Crinion et al., 2007). The last step was to smooth the EPIs using an 8x8x8 FWHM Gaussian model so that random field theory (Worsley et al., 1996) could be applied.

The main part of the analysis took place by analyzing the BOLD signal post- vs. pre-intervention separately for each patient. Patients were treated as individual case studies as there was a small sample size, different sizes of behavioural effect and heterogeneous lesions. Significant changes in BOLD activation during each functional task were presented and assessed for every participant separately according to the general linear framework. The model included the following regressors of interest: the onsets of the right, left and bimanual hand tapping blocks separately for the pre and the post sessions. Regressors of no interest included the ‘get ready’ and ‘relax’ periods and the movement parameters for each session. For each patient and each hand (unimanual right – left and bimanual) the following contrasts were computed: 1) tapping (pre + post) > relax; 2) tapping pre > post; 3) tapping pre < post. Here, we reported on results that survive family wise error correction at a voxel level with a cluster extent of 100.

In a second analysis, masking was used in order to identify changes in activation in motor and sensory motor related regions (Brodmann’s Areas 1 to 7, BA’s 1-7). This mask was applied on the following contrasts: healthy hand pre < post and pre > post, impaired hand pre < post and pre > post and bimanual hand tapping pre < post and pre > post. For this analysis cluster an error correction voxel level was chosen with a cluster extent of 50 voxels.

4.3. RESULTS

4.3.1. Effect of therapy in motor function, behavioural

4.3.1.1. General outcome measures.

The Barthel Index and HADS were used to compare any significant differences between the Mirror and Control Group. A 2x2 ANOVA ran, included group as a between-subjects factor and time (pre vs. post) as a within-subject factor. For the Barthel Index there was no significant effect of group ($F(1, 13) = 0.022, p = 0.884$) but there was a significant effect of time ($F(1, 13) = 22.157, p < 0.001$). There was no reliable interaction between time and group ($F(1, 13) = 1.809, p = 0.202$). For the anxiety scale of the HADS there was no significant effect of group ($F(1, 13) = 0.005, p = 0.943$) but there was an effect of time ($F(1, 13) = 5.406, p = 0.037$). There was again no significant interaction of time by group ($F(1, 13) = 0.019, p = 0.893$). For the depression scale of the HADS there was no significant difference across the groups ($F(1, 13) = .255, p = .622$) but there was a significant effect of time ($F(1, 13) = 6.050, p = 0.029$). There was again no significant interaction found between time and group ($F(1, 13) = 0.050, p = 0.827$). Table 1 shows initial pre and post results of the Barthel Index and depression and anxiety scales of HADS.

4.3.1.2. Action Research Arm Test (ARAT)

Data from the action research arm test were similarly analysed. An ANOVA with group as a between-subjects factor (Mirror Group (MG) vs. Control Group (CG)) and time as a within-subjects factor (pre vs. post intervention) was used. There was no significant effect of group ($F(1, 13) = 1.734, p = 0.211$). There was a significant effect of time ($F(1, 13) = 186.844, p < 0.001$) and there was a significant interaction of time by group ($F(1, 13) = 47.308, p < 0.001$). Two different t-tests were run for the MG and CGs separately, comparing post- vs. pre-treatment performance: MG ($t(8) = -13.811, p < 0.001$) and CG (Controls: $t(5) = -7.050, p = 0.001$). The results can be seen in Figure 19.

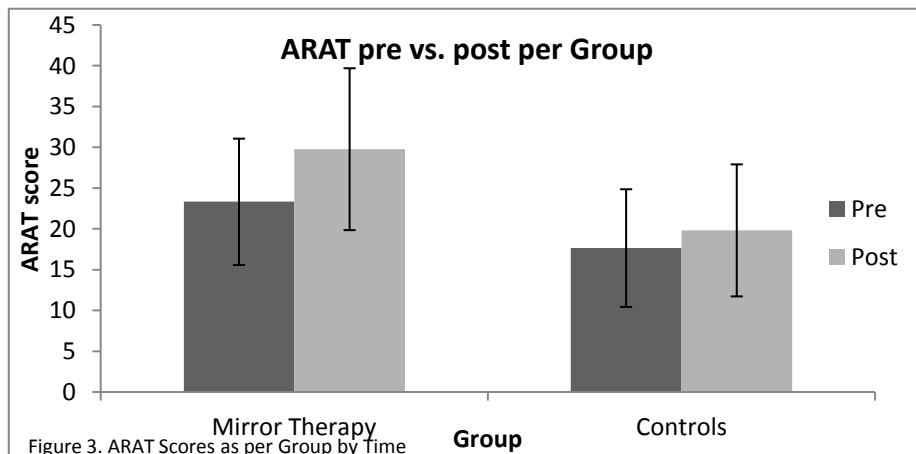


Figure 19: ARAT performance before (pre) and after (post) mirror therapy comparing (a) experimental and control groups (error bars show Plus/minus one SE around mean)

This time by group interaction occurred even when the analysis was confined just to the participants who underwent scanning ($F(1, 4) = 13.009, p = 0.023$).

The analyses indicate that all patients improved over time but the magnitude of improvement was greater for the patients who underwent mirror therapy.

4.3.2. fMRI Results

Each patient was analysed as a single case and so results are reported from the first level analysis focusing on six contrasts of interests: 1) healthy hand tapping (pre < post and pre > post); 2) impaired hand tapping (pre < post and pre > post); 3) bimanual hand tapping pre < post and pre > post. Both increases and decreases in the BOLD response were examined following treatment for both hands. The results are summarized in Tables 4 and 5. I next describe the findings for each patient separately. The topography of the lesions can be seen in Figures 18 and 19, and proof that the task was effective during the scanning can be seen by the activation during the healthy hand tapping in Figure 20.

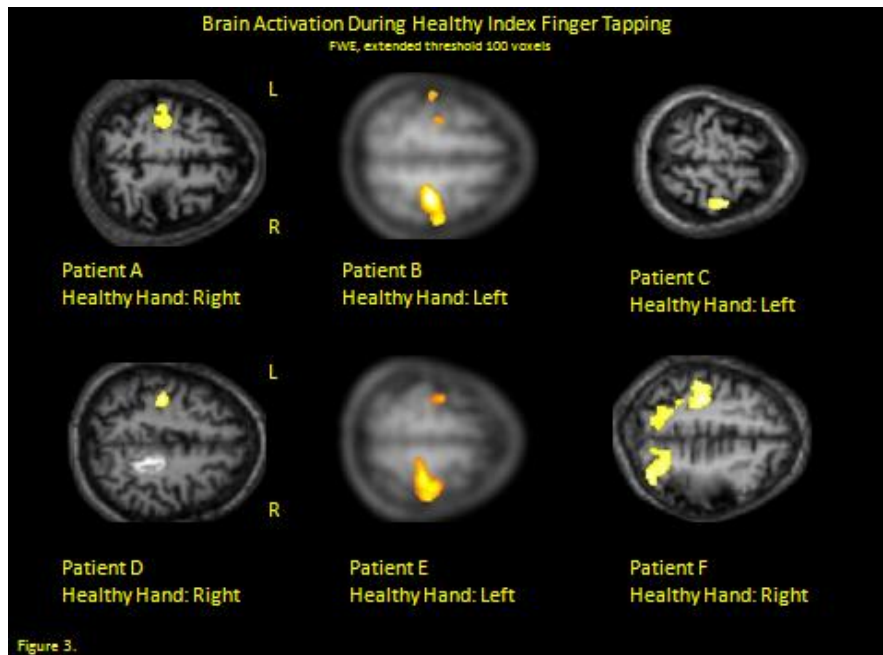


Figure 20: Brain Activation During Healthy Index Finger Tapping, Right refers to anatomical Right hemisphere

Participant A: This participant belonged to the MG and had extended lesions of the parietal and motor areas of the right hemisphere (Figures 17 and 18). During the functional outcome measure of ARAT his performance increased by 34 to 39 revealing an increase of 14.7%.

Voxel based analysis: Tapping with the healthy (right) hand was associated with strong activation in his left central sulcus (CS) and surrounding areas (Figure 20). Tapping with the impaired hand was associated with activity in extended areas of the rolandic operculum on the lesioned side and frontal and temporal areas of the non-lesioned hemisphere (Figure 21). During the bimanual tapping task, there was BOLD activation of the rolandic operculum, the paracentral lobule and precentral areas of the non-lesioned hemisphere. In the next part of the analysis and

following the application of a mask across the motor and somatosensory cortex, there was a significant increase of the BA's 1-7 areas that was noted in both hemispheres when tap were performed with the impaired hand (detailed areas on Table 5). There was no significant decrease on any of the activated areas post intervention. The data here suggest that there was takeover of performance by the somatosensory cortex ipsilateral to the impaired hand following upper limb MT intervention in this stroke survivor.

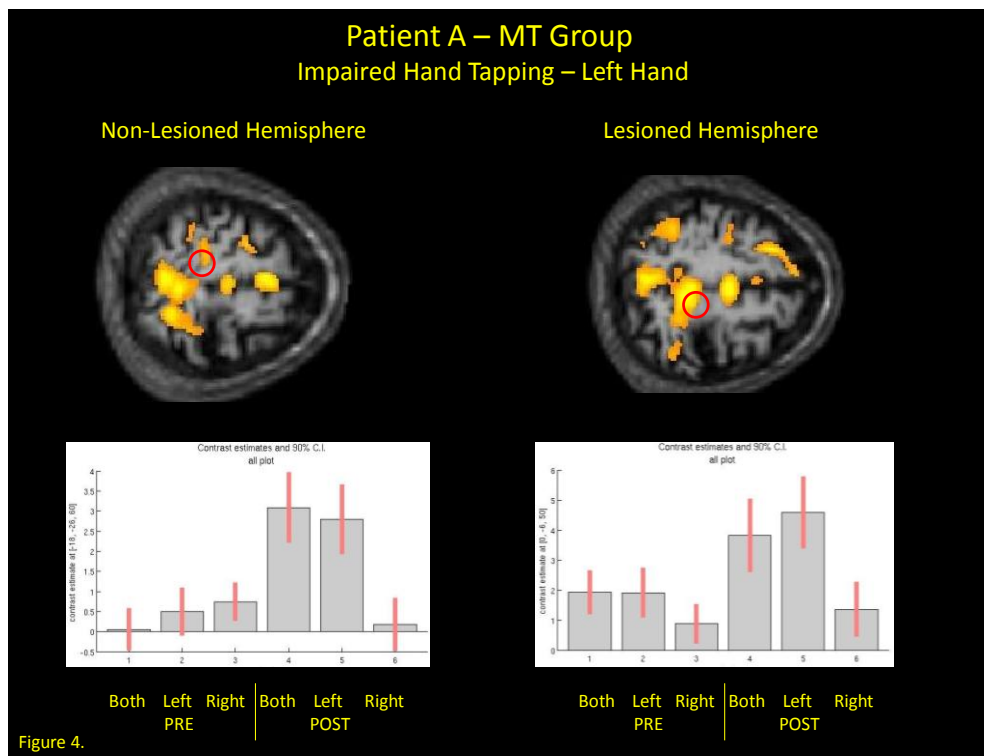


Figure 21: Patient A - MT Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

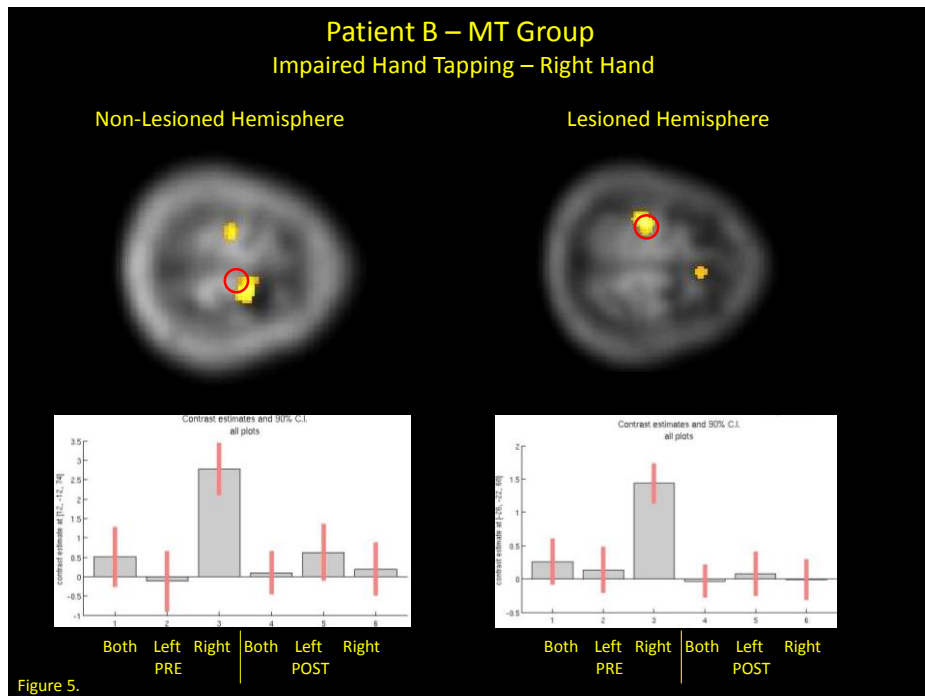


Figure 22: Patient B - MT Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

Participant B: This participant belonged to the MG and had multiple small (scattered lesions of the frontoparietal and somatosensory areas) of the left hemisphere (Figures 17 and 18). Following training his functional performance on the ARAT increased by 29 to 37 (an increase of 27.5%).

Voxel based analysis: Tapping with the healthy hand (i.e., left hand) was associated with strong activation in the right CS and surrounding areas (Figure 20). Similarly, during the impaired hand tapping there were notable activations in the lesioned hemisphere in areas of the middle cingulum and in the frontal supplementary area (Table 4). Activation post vs. pre intervention was associated within the hippocampus and precuneus in the damaged hemisphere

(Figure 22). More interestingly during the bimanual tapping task there was strong activation mainly around the CS on the lesioned side. When the mask was applied (Table 5) there were no differences in activation relative to tapping with the healthy hand. There was though a significant increase of BOLD signal relative to when tapping with the impaired hand for the following areas: SMA and precentral areas of the healthy hemisphere and for the precentral and parietal supplementary area of the impaired hemisphere. Also, there was a low level decrease only for the region of the precentral sulcus of the healthy side. During the bimanual hand tapping task there were only significant decreases in the cluster level of activation in the precuneus and precentral areas of the healthy hemisphere and in parietal inferior areas of the impaired one during the pre and post scans.

Table 4: fMRI Results per Task, all participants

| Subject | Group | Region | Cluster siz | Peak-Z | MNI Coordinates | | |
|--|-------|---------------------------------|-------------|--------|-----------------|-----|-----|
| | | | | | x | y | z |
| [Healthy Tap] | | | | | | | |
| A | MT | Motor Ctx NonLesional | 356 | 7.03 | -40 | -20 | 58 |
| B | MT | Motor Ctx NonLesional | | 6.31 | | | |
| C | MT | Motor Ctx NonLesional | 988 | Inf | 30 | -14 | 64 |
| D | MT | Motor Ctx NonLesional | | 5.48 | | | |
| E | CG | Motor Ctx NonLesional | 888 | 4.82 | -10 | 44 | 6 |
| F | CG | Motor Ctx NonLesional | | 4.31 | | | |
| [Impaired Tap] | | | | | | | |
| A | MT | rolandic oper Lesioned | 19596 | Inf | -52 | 0 | 6 |
| | | frontal inf tri Non-Lesioned | 354 | 7.16 | 42 | 42 | 10 |
| | | temp mid Non-Lesioned | 241 | 5.88 | 42 | -46 | 44 |
| B | MT | cicgulum mid Lesioned | 159 | 6.1 | 6 | 4 | 66 |
| | | hippocampus Non-Lesioned | 422 | 5.44 | -28 | -24 | 66 |
| | | precuneus Non-Lesioned | 369 | 5.35 | -2 | -60 | 54 |
| C | MT | front supp Lesioned | 134 | 5.24 | 12 | 12 | 76 |
| | | Precentral Lesioned | 115 | 3.97 | 28 | 2 | 48 |
| | | frontal mid Non-Lesioned | 1210 | Inf | -42 | 38 | 24 |
| D | MT | precentral Lesioned | 3310 | 7.73 | 10 | 30 | 24 |
| | | postcentral Non-Lesioned | 591 | 7.22 | -60 | -2 | 12 |
| | | insula Non-Lesioned | 464 | 6.84 | -38 | -14 | 62 |
| E | CG | front mid Non-Lesioned | 106 | 5.86 | -40 | 24 | 2 |
| | | precentral Non-Lesioned | 2064 | 6 | 38 | -16 | 42 |
| | | angular Lesioned | 935 | 4.6 | -44 | -64 | 28 |
| F | CG | front supp medial Lesioned | 1969 | 4.31 | -14 | -54 | 14 |
| | | front supp medial Lesioned | 2166 | 4.09 | -4 | 56 | 14 |
| | | temp supp Non-Lesioned | 780 | 3.8 | 64 | -36 | 10 |
| A | MT | postcentral Lesioned | 250 | 2.72 | -44 | -32 | 12 |
| | | front inf tri Non-Lesioned | 143 | 2.63 | 46 | 38 | 2 |
| | | front inf orb Non-Lesioned | 117 | 2.16 | 38 | 32 | -14 |
| E | CG | postcentral Non-Lesioned | 305 | 5.13 | -60 | 0 | 22 |
| | | cing ant Non-Lesioned | 216 | 4.77 | -8 | 50 | 4 |
| | | insula Lesioned | 379 | 4.7 | 42 | -14 | 30 |
| F | CG | postcentral Non-Lesioned | 193 | 4.43 | -62 | -8 | -2 |
| | | insula Lesioned | 454 | 4.4 | 30 | 26 | 16 |
| | | fron inf orb Non-Lesioned | 420 | 4.61 | 42 | 32 | -10 |
| A | MT | lingual Non-Lesioned | 16871 | 3.77 | 20 | -74 | 50 |
| | | postcentral Lesioned | 940 | 3.71 | -38 | -22 | 50 |
| | | occipital mid Non-Lesioned | 149 | 3.07 | 44 | -66 | -10 |
| D | MT | fron sup orb Lesioned | 314 | 3.07 | -22 | 42 | 6 |
| | | insula Lesioned | 429 | 2.6 | -44 | 6 | 24 |
| | | front sup med Lesioned | 378 | 2.51 | -10 | 58 | -12 |
| [Both Tap] | | | | | | | |
| A | MT | Rolandic_Oper_Non-Lesioned | 974 | Inf | -52 | 0 | 4 |
| | | Cerebelum 4_5_Lesioned | 602 | Inf | 12 | -54 | 14 |
| | | Paracentral Lobule_Non-Lesioned | 829 | Inf | -2 | -22 | 72 |
| B | MT | Precentral_Non-Lesioned | 155 | 6.31 | -34 | -18 | 56 |
| | | Rolandic_Oper_Lesioned | 102 | 6.03 | -50 | -6 | 4 |
| | | Precentral_Non-Lesioned | 430 | Inf | 36 | -16 | 66 |
| C | MT | Frontal_Mid_Non-Lesioned | 505 | 7.39 | 32 | 50 | 20 |
| | | Cingulum_Ant_Non-Lesioned | 1227 | 7.37 | 12 | 36 | 18 |
| | | Frontal_Mid_Lesioned | 209 | 7.22 | -34 | 40 | 30 |
| D | MT | Precentral_Non-Lesioned | 345 | 6 | -34 | -18 | 54 |
| At peak/cluster level $p < .05$ (FWE corrected), #voxels > 100. ; (for impaired at cluster level $p=0.001$) | | | | | | | |
| Table 2. fMRI results per task, all participants | | | | | | | |

Participant C: This participant belonged to the MG and had extended lesions of the parietal and frontotemporal lobes with an impaired motor cortex in the left hemisphere. During the functional outcome measure of ARAT his performance with the hemiparetic right upper limb increased by 14 to 21 (an increase of 50.0%).

Voxel based analysis: Tapping with the healthy hand (e.g. left hand) was associated with strong activation in his left CS and neighbouring areas (Figure 20). When tapping with the impaired hand participant C showed reliable activation of the BOLD signal in areas of the frontal middle, postcentral and insula regions of the healthy side and in the precentral gyrus of the impaired hemisphere (Figure 23). Similarly during bilateral tapping there was significant activation of the precentral, frontal middle and cingulum areas of the healthy hemisphere and frontal middle areas of the lesioned hemisphere (Table 4). Following the mask application there was a significant increase in activation pre compared to post MT intervention period in the postcentral cortex of the intact hemisphere when taps were performed with the healthy hand. There was also a decrease of activation for the postcentral and SMA areas in the healthy and impaired hemispheres respectively (Table 3). For the impaired hand there was a significant increase of activation in areas of the parietal supplementary areas of both hemispheres and the postcentral sulcus of the lesioned hemisphere. During the bimanual hand tapping task there was a significant increase in the parietal and postcentral sulcus clusters of the lesioned hemisphere and for the parietal supplementary areas of the non lesioned hemisphere (Table 5).

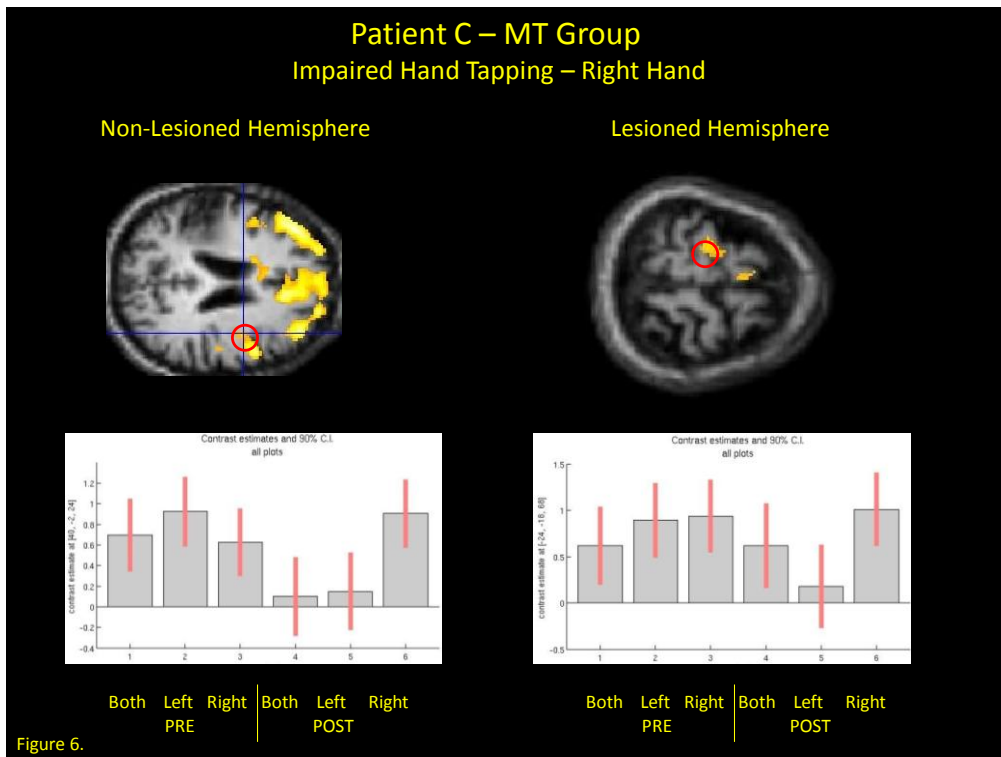


Figure 23: Patient C - MT Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

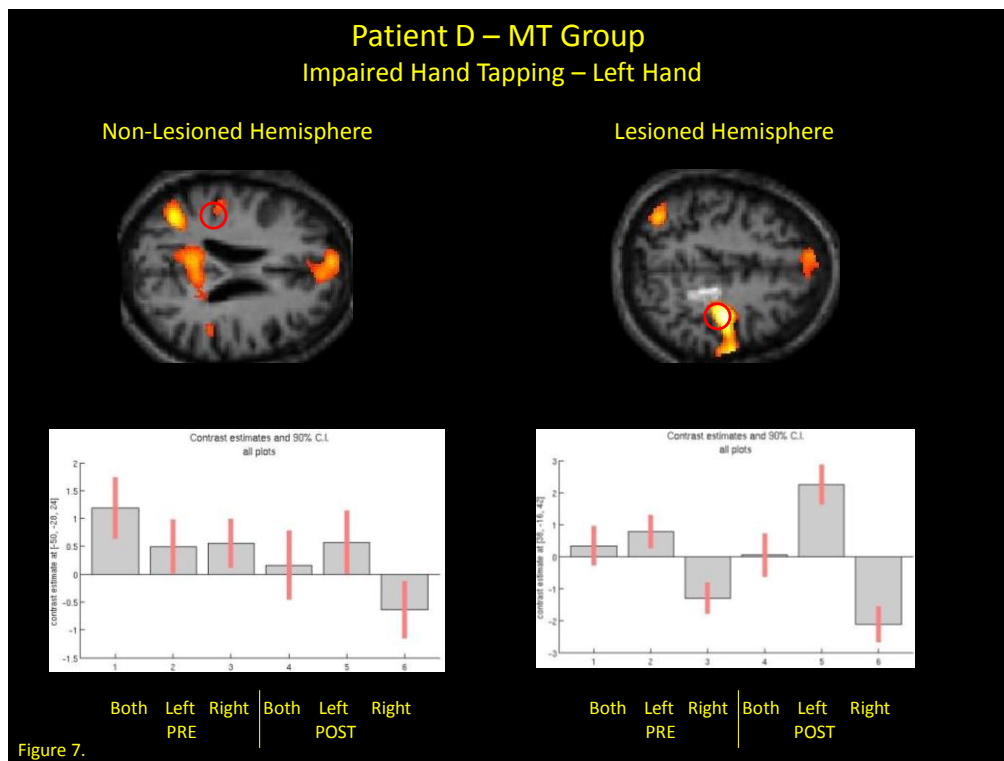


Figure 24: Patient D - MT Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

Participant D: This MG participant had a concentrated lesion of the white matter in a central region of his right hemisphere (Figures 17 and 18). His ARAT performance with the hemiparetic right upper limb increased by 8 to 17 (an increase of 112.5% in the post compared with the pre rehabilitation period).

Voxel based analysis: Tapping with the healthy hand (e.g. right hand) was correlated with strong activation in his left CS and areas in the vicinity (Figure 20). When tapping with the impaired hand there were areas of activation that survived FWE correction both in the intact and impaired hemispheres. More specifically (see Table 4) these areas for the lesioned hemisphere

were the angular, frontal supplementary area and postcentral sulcus and for the non-lesioned hemisphere the precentral lobule, temporal supplementary and frontal inferior areas. Following the application of the mask only one area was found to be activated more during the intact hand tapping which was the precentral cortex of the non-lesioned hemisphere. Tapping with the impaired hand, associated with an increase of activation in the postcentral region, ipsilateral to the impaired hand (in the intact hemisphere) and in the cuneus of the impaired hemisphere (Table 5). During the bimanual task there was a significant decrease of activity in the postcentral sulcus and frontal supplementary cortex of the non lesioned hemisphere and in the middle frontal, postcentral and angular areas of the impaired hemisphere.

Table 5: fMRI Results per Contrast following application of mask BA1 to BA7 only

| Subject | Contrast | Group | Region | Cluster siz | Peak-Z | MNI Coordinates | | |
|--|----------|-------|----------------------------|-------------|--------|-----------------|-----|----|
| | | | | | | x | y | z |
| [Healthy Hand Tapping] (masked[incl.] Bilateral_Motor&Sensory_BA1to7) | | | | | | | | |
| A | Pre<Post | MT | x | | | | | |
| | Pre>Post | | x | | | | | |
| B | Pre<Post | MT | x | | | | | |
| | Pre>Post | | x | | | | | |
| C | Pre<Post | MT | postcentral NonLesioned | 323 | 5.01 | -54 | -16 | 30 |
| | Pre>Post | | postcentral NonLesioned | 871 | 6.28 | -34 | -18 | 66 |
| | | | supp motor area Lesioned | 73 | 4.04 | 14 | 2 | 52 |
| D | Pre<Post | MT | precentral NonLesioned | 264 | 5.45 | 30 | -24 | 50 |
| | Pre>Post | | x | | | | | |
| E | Pre<Post | CG | x | | | | | |
| | Pre>Post | | x | | | | | |
| F | Pre<Post | CG | x | | | | | |
| | Pre>Post | | precuneus NonLesioned | 1726 | 4.81 | 12 | -68 | 50 |
| | | | precentral Lesioned | 103 | 3.61 | -24 | -14 | 52 |
| [Impaired Hand Tapping] (masked[incl.] Bilateral_Motor&Sensory_BA1to7) | | | | | | | | |
| A | Pre<Post | MT | front supp NonLesioned | 1634 | 6.81 | 8 | 0 | 68 |
| | | | rol oper Lesioned | 342 | 4.94 | -54 | 0 | 10 |
| | | | calcarine NonLesioned | 540 | 4.72 | 18 | -50 | 60 |
| | | | precuneus NonLesioned | 103 | 3.95 | -8 | -56 | 54 |
| | | | x | | | | | |
| B | Pre>Post | MT | supp motor area NonLesio | 330 | 5.74 | -10 | -8 | 68 |
| | Pre<Post | | precentral Lesioned | 163 | 5.73 | 34 | 4 | 48 |
| | | | precentral NonLesioned | 125 | 5.16 | -38 | -2 | 46 |
| | | | parietal sup Lesioned | 54 | 4.47 | 28 | -48 | 58 |
| | | | precentral NonLesioned | 128 | 5.31 | -22 | -22 | 70 |
| C | Pre>Post | | parietal sup Lesioned | 253 | 4.8 | 14 | -76 | 50 |
| | Pre<Post | | postcentral Lesioned | 85 | 3.76 | -16 | -34 | 72 |
| | | | parietal sup NonLesioned | 65 | 3.74 | -20 | -70 | 58 |
| | | | x | | | | | |
| D | Pre>Post | MT | x | | | | | |
| | Pre<Post | | postcentral NonLesioned | 2907 | 6.4 | 32 | -34 | 52 |
| | | | cuneus Lesioned | 157 | 3.8 | -16 | -76 | 42 |
| | | | x | | | | | |
| E | Pre>Post | MT | x | | | | | |
| | Pre<Post | CG | postcentral NonLesioned | 211 | 5.18 | -60 | -2 | 20 |
| | Pre>Post | | precentral NonLesioned | 252 | 5.22 | -60 | 2 | 34 |
| | | | postcentral NonLesioned | 65 | 4.08 | -44 | -20 | 54 |
| F | Pre<Post | CG | x | | | | | |
| | Pre>Post | | precuneus Lesioned | 301 | 4.1 | -22 | -76 | 40 |
| | | | postcentral Lesioned | 199 | 4.09 | -40 | -24 | 40 |
| | | | pariet sup NonLesioned | 270 | 3.92 | 26 | -72 | 44 |
| [Bimanual Hand Tapping] (masked[incl.] Bilateral_Motor&Sensory_BA1to7) | | | | | | | | |
| A | Pre<Post | MT | paracentral lobule Lesione | 1191 | 5.06 | -4 | 38 | 62 |
| | | | SMA NonLesioned | 189 | 4.84 | 12 | 16 | 62 |
| | | | precentral NonLesioned | 330 | 4.67 | 46 | 4 | 52 |
| | | | rolandic oper Lesioned | 71 | 4.35 | -56 | 2 | 6 |
| | | | occipital sup Lesioned | 175 | 4.24 | -14 | -80 | 30 |
| | | | frontal sup Lesioned | 190 | 3.81 | -18 | 10 | 62 |
| | | | precuneus Lesioned | 73 | 3.68 | -6 | -64 | 50 |
| | | | x | | | | | |
| B | Pre>Post | MT | x | | | | | |
| | Pre<Post | | precuneus NonLesioned | 628 | 4.89 | 2 | -66 | 44 |
| | Pre>Post | | precentral NonLesioned | 74 | 4.76 | -36 | 2 | 56 |
| | | | pariet inf Lesioned | 61 | 4.58 | 34 | -56 | 50 |
| C | Pre<Post | MT | postcentral NonLesioned | 523 | 4.98 | -54 | -22 | 38 |
| | | | occip sup NonLesioned | 129 | 4.72 | -30 | -78 | 44 |
| | | | precuneus NonLesioned | 307 | 4.13 | -2 | -56 | 36 |
| | | | SMA Lesioned | 248 | 4.47 | 6 | 2 | 70 |
| D | Pre>Post | MT | x | | | | | |
| | Pre<Post | | frontal sup NonLesioned | 564 | 5.72 | 12 | 12 | 54 |
| | Pre>Post | | postcentral NonLesioned | 256 | 5.1 | 56 | 0 | 44 |
| | | | frontal mid Lesioned | 291 | 4.92 | -30 | 4 | 54 |
| | | | postcentral Lesioned | 92 | 3.77 | -24 | -28 | 60 |
| | | | angular Lesioned | 105 | 3.66 | -32 | -58 | 50 |
| E | Pre<Post | CG | x | | | | | |
| | Pre>Post | | supp motor Lesioned | 159 | 4.68 | 8 | 24 | 62 |
| | | | lingual NonLesioned | 441 | 4.68 | -6 | -60 | 60 |
| | | | postcentral NonLesioned | 183 | 4.4 | -18 | -36 | 70 |
| | | | precentral Lesioned | 447 | 4.23 | 42 | -20 | 62 |
| | | | precentral NonLesioned | 167 | 4.17 | -48 | -2 | 48 |
| | | | postcentral Lesioned | 60 | 4.13 | 28 | -38 | 70 |
| | | | precuneus Lesioned | 98 | 3.97 | 14 | -46 | 56 |
| F | Pre<Post | CG | x | | | | | |
| | Pre>Post | | x | | | | | |
| At peak/cluster level p < .05 (cluster corrected), #voxels > 50. ; | | | | | | | | |
| Table 3. fMRI results per contrast following application of mask including BA1 to BA7 only | | | | | | | | |

Participant E: This CG participant had lesions located in white matter within the left central hemisphere (Figure 17 and 18). His ARAT performance, with the hemiparetic right upper limb, increased by 8 to 10 (a 20.0% improvement).

Voxel based analysis: Tapping with the intact hand (e.g. left hand) was associated with strong activation of the right CS and areas in the near vicinity (Figure 20). Tapping with the impaired hand was linked to BOLD activation in the postcentral, cingulate anterior and postcentral cortex of the non lesioned side of the brain and in the insula on the lesioned side (Table 4, Figure 25). However there were no areas of activation that survived FWE correction for a threshold of 100 voxels. As can be seen in Table 5 there was no significant change in the level of brain activation during the rehabilitation period for the healthy hand. Interestingly there was less activation pre- relative to post-rehab for the postcentral sulcus on the non lesioned side for tapping with the impaired hand but this activation was descriptively less (according to the magnitude of cluster activation) compared to the MG participants and also there was less activation post rehab period in the same task in areas of the pre- and postcentral gyrus that was larger in extent than the above increase. During the bimanual task there were also areas that activated less in the post-rehab scan and these areas were the SMA, precentral, postcentral and precuneus on the lesioned side and the lingual, postcentral and precentral gyrus on the non lesioned side.

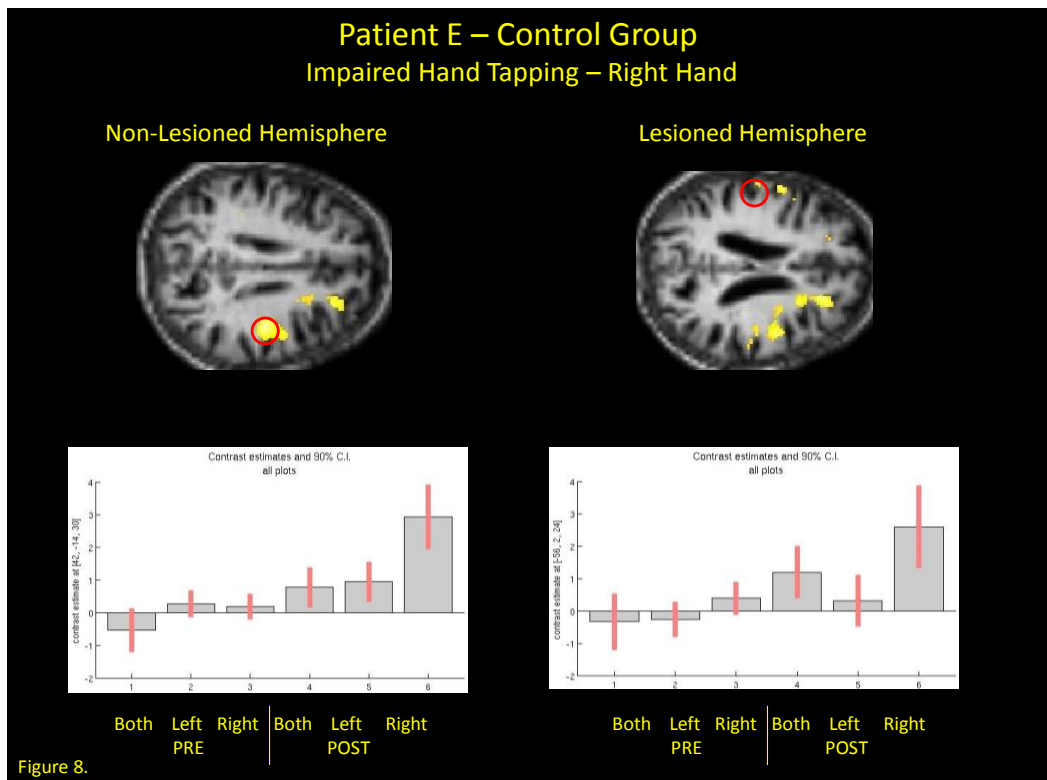


Figure 25: Patient E - Control Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

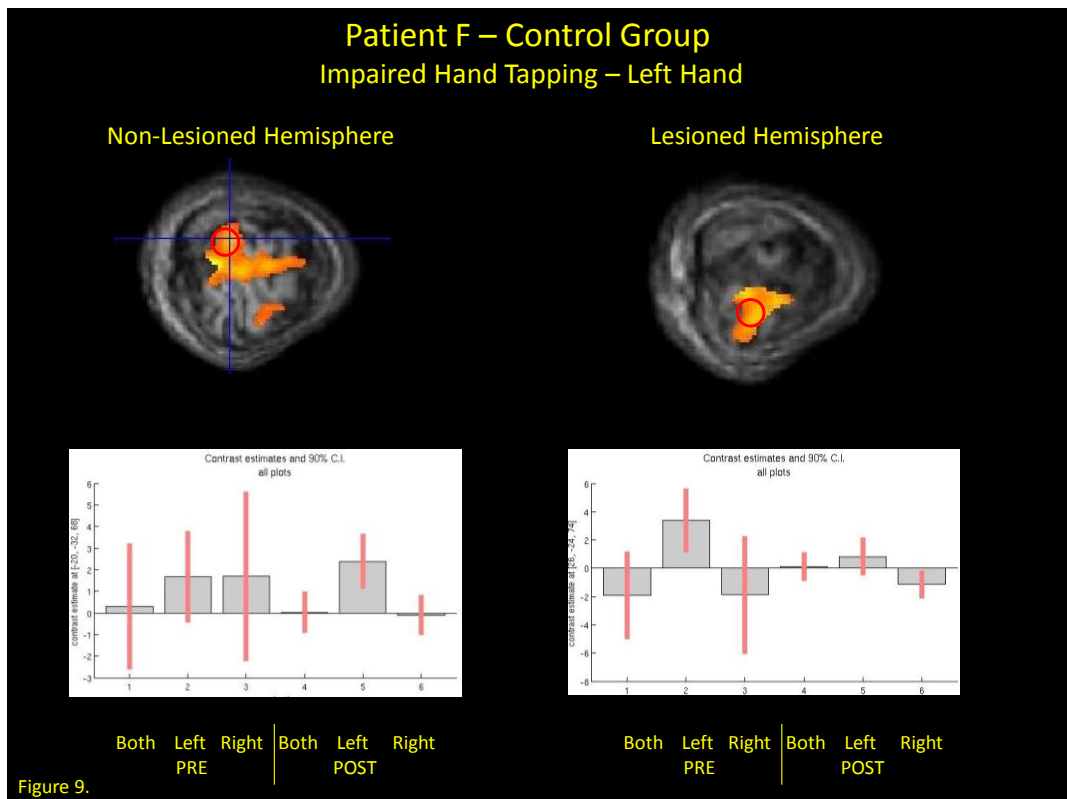


Figure 26: Patient F - Control Group - Impaired Hand Tapping Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant taps with the impaired hand both in the non-lesioned hemisphere (left bars) and in the lesioned hemisphere (right bars-graph)

Participant F: This CG participant had an extended lesion of the parietal and temporal areas of the right hemisphere (Figure 17 and 18). On the ARAT his performance with the hemiparetic right upper limb increased by 14 to 17 (an increase of 21.4% pre- compared to post-rehabilitation).

Voxel based analysis: When tapping with the healthy hand there was increased activation in regions of the left CS (Figure 20). Following the intervention period there was increased activation in the lesioned area and more specifically in postcentral, frontal supplementary and insula regions for tapping with the impaired hand. In the non lesioned hemisphere there were

activations in the frontal, lingual and occipital areas in the same task (Table 4). No areas survived the FWE correction for bimanual tapping. Following application of the mask we found the following changes for the healthy hand tapping: less activation in the precuneus of the non lesioned hemisphere and in the precentral gyrus of the lesioned hemisphere (Table 5). For tapping with the impaired hand there were no increases in motor related areas, but the precuneus and postcentral gyrus in the lesioned hemisphere and the parietal supplementary area of the non lesioned area were less activated in the post rehabilitation period scan. There were again no significant differences in activation relative to pre and post intervention scan in the bimanual tapping task.

Results presented above and in the Tables 2 and 3 showed that there was a general activation of the motor cortex in the healthy hemisphere during the tapping task with the impaired hand and this can be used as evidence that the fMRI task-experiment was actually followed by the participants during the scan. Because the number of patients that were scanned in this study is small (four participants in the MT group and two in the CG), this summary of the results can only identify possible mechanisms of activation but these patterns should not be generalized. In the tapping task with the impaired hand the results suggest that there was a takeover of performance by somatosensory cortex ipsilateral to the impaired hand following MT. This trend was followed in all participants with impaired motor cortex but the same effect did not take place in the control participants. In addition in patients where the motor cortex was intact the same take over has been noticed in the lesioned side. During tapping with the impaired hand it was noticed that the precentral area of the motor cortex, the premotor cortex and the SMA in the lesioned side of the

brain in all four participants all exhibited increased activation following MT intervention. A similar increase was not noticeable in the two control patients that were scanned.

4.4. DISCUSSION

The current results revealed that there were improvements in the functional ability of the hemiparetic hand following four weeks rehabilitation in early subacute stroke survivors. Notably an improvement was observed in the ARAT score, which assesses the participant's ability to perform daily functional tasks with the paretic upper limb. This was modulated when MT was applied on top of a rehabilitation regime. However, no differences were found on the Barthel score, which may reflect the relatively crude nature of this scale. In addition, there was no effect of the intervention on anxiety and depression, although both improved over time. These findings indicate that the effect on the ARAT was not modulated through a change in anxiety and depression.

We also assessed the neural basis of the effects using fMRI. Due to the small sample size these results are necessarily limited and focused on motor and somatosensory brain regions (BA's 1 to 7). For the healthy hand during unimanual tapping there were no large changes in brain activity. This finding is consistent with previous behavioural mirror therapy findings

showing no effect in the healthy side (i.e. Altschuler, 1999 etc). On the other hand, with regards to unimanual tapping with the impaired hand, increased brain activation (pre < post) was observed in the MG participants. Notably the hemisphere ipsilateral to the hemiparetic hand motor cortex and associated areas showed increased activation after MT. This finding is consistent with the results reported in Bhasin et al.'s (2012) study which revealed that there was more activation in BA4 and BA6 ipsilesional to the affected upper limb after MT intervention. Their findings for areas BA4 and BA6 match our data on motor cortex; premotor cortex and SMA are identical with areas that we found in this study. Moreover, in our study, in addition to increases of activation on the ipsilesional side, we also found increased activation of the lesioned side of the brain. The latter included motor associated areas in the lesioned hemisphere such as the rolandic operculum, the pre – and postcentral sulcus, the parietal supplementary area and the cuneus (basic visual processing). These results support Michielsen et al's (2012) findings which showed an increased activation on the lesioned side following MT intervention. Increased activation on the lesioned side found by Michielsen et al is a very interesting finding that is consistent with the results of our study, as all four participants in the MG followed this trend while the 2 participants in the CG did not.

During the bimanual task only one participant (A) of the MG showed increased activation (pre < post) in the lesioned hemisphere and, more specifically in the regions of the paracentral lobule, rolandic operculum, precuneus and frontal and occipital supplementary areas. Similarly, regions of the motor and somatosensory areas of interest from the non-lesioned side were activated, including the SMA in patient A, and the precuneus and postcentral gyrus in patient C. This is not apparent in the CG as there were no changes in brain activation in the bimanual task

pre- and post-intervention. This suggests that MT may play an important role in the balance of the two hemispheres following bimanual actions. It also indicates that MT (noticed in 3 out of 4 patients in the MG) led to a general decrease in activation for bimanual tapping (notably in the SMA, the postcentral gyrus, and the frontoparietal inferior lobules on the lesioned side). Similar trends were traced in two participants (B and D) for the non lesioned hemisphere (and more specifically in the central (pre and post) gyrus, the precuneus and the frontal supplementary areas).

4.5. CONCLUSIONS

Following a four-week application of MT, there were significant improvements in the behavioural outcome measure of ARAT and this improvement was larger in patients subject to MT when compared to the five controls. These behavioural improvements were associated with increased responses in motor associated regions both within the affected and intact hemispheres.

**CHAPTER 5: FUNCTIONAL ELECTRICAL STIMULATION
(FES) PROMOTES RECOVERY OF HAND FUNCTION AND
AMELIORATES SYMPTOMS OF VISUOMOTOR NEGLECT IN
STROKE – EVIDENCE OF CORTICAL REORGANIZATION**

ABSTRACT

Background and Purpose – We examined the effectiveness and neural pathways of functional electrical stimulation (FES) in promoting motor recovery of the upper limb and in ameliorating neglect symptoms after stroke.

Methods – Five subjects (mean 57.8 ± 6 years old and 26.8 ± 21 months post stroke) received 4 weeks of upper limb FES for 40 minutes, 4 days per week for 4 weeks. Outcome measurements included the Action Research Arm Test (ARAT), grip force, the apple cancellation test, tapping performance and fMRI acquisitions.

Results – After 4 weeks of treatment, there was a significant improvement in grip force and the ARAT, accompanied by an increase in tapping performance and an amelioration of neglect compared with the baseline measurements. These improvements remained significant at 6 months follow-up. These behavioural improvements were associated with increased responses in motor cortex within the affected hemisphere.

Conclusions – Four weeks of FES, applied to subjects with stroke, improved their motor and functional performance and ameliorated neglect-related impairments. These improvements are mediated by changes in the activation of the motor cortex in the lesioned hemisphere.

Key words: motor rehabilitation, neglect, stroke, functional electrical stimulation, functional magnetic resonance imaging, fMRI.

5.1. INTRODUCTION

Stroke is a major cause of functional disability (Ottenbacher, 1980) and occurs in approximately 150,000 patients per year in the UK (Stroke Care, 2004). Importantly, in as many as 50% of stroke survivors' upper paretic limb remains impaired with long term deficits. (Wade, 1989). In order to improve the functionality of the upper limb in stroke patients, a number of different techniques have been applied. In the United Kingdom the main rehabilitation procedures used include the Bobath method (Bobath, 1990) and the 'motor control theory approach' (Carr and Sephard, 1987) -coordinated movement of motor skill in various environments- , both of which may be enhanced through the use of splints (Basaran and Emre, 2012), exercise (Brazzelli and Saunders, 2012), plasters (Galea, 2012), biofeedback (Hsu and Lin, 2012), constraint induced therapy (Taub and Uswatte, 2012) and robotic rehabilitation (Zimmerli and Krewer, 2012). In rehabilitation settings a combination of these techniques is often applied with the aim of including a better outcome for the patient.

A somewhat different approach to the restoration of motor function following a stroke is Functional Electrical Stimulation (FES) (Powel et al., 1999). FES can be used to increase muscle strength on the applied area and it has been employed primarily in pain management (Ring and Rosenthal, 2005) and in attempts to reduce muscle atrophy following stroke (Lynch and Popovich, 2008). Functional electrical stimulation (FES), originally developed as a neuroprosthetic to replace function (Liebersen et al., 1961), has been used therapeutically to augment voluntary motor drive during motor rehabilitation (Merletti et al., 1975; Popovic et al., 2002, 2004). The external stimulation allows the patient to practise simple functional tasks with

the aim of developing the ability to perform the tasks through voluntary drive alone. Voluntary movements may become more effective due to a reduction in muscle tone and also due to increased flexibility provided by the application of FES on muscles which, post-stroke, are not normally connected to the cortical network controlling movement (Rushton, 2003). FES can effectively coordinate the activation of one or more muscles around a number of joints by varying the intensity of the stimulation applied to flexor and extensor muscles. This in turn can lead to active movement, which may be functional (e.g. a grasping action) when applied to the upper limb (Thrasher et al., 2008). Physiologically, FES results in the production of action potentials caused by short electrical pulses that travel along axons towards the periphery (muscles), which results in a contraction (Popovic et al., 2001). The application of FES is particularly effective when linked to the excitation of lower motor neurons and when the muscles and neuromuscular connections are intact, as previously observed in many stroke survivors (Peckham and Knutson, 2005). Overall, FES has been shown to be effective in increasing mobility and decreasing the risk of fall in stroke survivors (Taylor, Humphreys and Swain et al., 2013).

In a comprehensive review of the literature, Sheffler and Chae (2007) stated that, despite difficulties in clinical implementation of FES and costs, there is sufficient evidence for researchers to investigate FES in large, multicentre, randomized clinical trials in order to enlighten preliminary reports and initial evidence. Glinsky and Harvey (2007) reviewed the effects of electrical stimulation and suggested that there are clear benefits from electrical stimulation in stroke survivors when compared to conventional physiotherapy and sham electrical stimulation. However, the neural mechanisms underlying FES effects on movements still remain

poorly understood (Blickenstorfer and Lewis, 2009). Kimberley and Lewis (2004) found that activation increased in the ipsilateral somatosensory cortex post-FES, suggesting that neuromuscular electrical stimulation may stimulate the cortical sensory areas, which in turn lead to improved motor function. Iftime-Nielsen et al. (2012) further reported that, when neuromuscular stimulation was combined with voluntary movement, there was greater activation of the cerebellum and a decrease of activation in the secondary somatosensory cortex (contralesional), compared to FES applied alone. Thus, movement may be particularly facilitated when voluntary and electrical forces are joined, which may then also allow for better reorganization of the cortical areas that are responsible for movement. However, further investigation of neural routes by Christensen and Grey (2013) suggested that FES-related activation of S2 area mainly derives by sensory input. Interestingly Sasaki and Matsunaga (2012) argue that there might be two patterns of brain activation in stroke patients, based on FES. First, there may be bilaterally increased signals in the somatosensory cortices, which may then be followed by a second more localized pattern of activity in ipsilesional cortex.

Another noted effect of FES stimulation is the increase in awareness of the contralesional side in patients with post-stroke unilateral neglect (Harding and Riddoch, 2009). Unilateral neglect is mainly linked to right hemisphere lesions and is most commonly characterised by a failure to attend to contralesional stimuli (Kerhloff and Schenk, 2012). The dramatic effects of neglect following a stroke are associated with poor rehabilitative outcome and severe disability in daily functional activities (Punt and Riddoch, 2006). Harding and Riddoch (2009) applied a mild form of FES in four patients with unilateral visual neglect and found that three out of four participants benefited from it even 6 months after the intervention (4 weeks of daily FES

application). The authors suggested that FES may increase the proprioceptive excitation of the right parietal lobe, which in turn stimulates the interactions of the hemiplegic hand with the environment. Polanowska and Seniow (2009) contrasted the effects of FES combined with scanning training to the effects of scanning training alone in a randomised, double blind study of neglect patients. They found that patients who received the combined treatment on the contralesional hand had a greater alleviation of the symptoms of unilateral neglect relative to a group of patients who only received scanning training.

Nudo et al. (1996) suggested that motor rehabilitation can promote cortical reorganization in brain areas adjacent to the lesion site and that activation of these neighbourhood areas contributes to motor recovery. This has also been shown with the use of transcranial magnetic stimulation (TMS). For example, Liepert et al.'s (2001) findings of recovery was linked to increased motor excitability in the affected hemisphere. The authors suggested that there was greater engagement of cortical regions adjacent to the lesion site after a week of combined conventional physiotherapy and forced-use therapy in the subacute phase of stroke. In a similar study, Nelles et al. (2001) reported that, after task-oriented arm training in stroke patients, there was increased bilateral activation of the inferior parietal cortex (IPC) along with greater activity in the contralateral sensorimotor cortex (SMC). These findings provide evidence that successful rehabilitation can be associated with different changes of cerebral activity in ipsilesional as well as contralesional sensorimotor systems.

Interestingly, there is also growing evidence that recovery of function of the affected limb following stroke can be associated with changes in the engagement of motor cortex (e.g., Cramer and Bastings, 2000, Traversa et al., 2000, Johansen-Berg et al., 2002, Bosnell et al., 2011,

Rijntjes et al., 2011). For example, Traversa et al. (2000) used TMS to identify changes after neuro-rehabilitation intervention in twenty stroke participants over a period of four months. The authors reported that new cortical pathways leading to cortical reorganization could be traced in the lesioned hemisphere as long as eighty days post intervention. Johansen-Berg et al. (2002) linked brain plasticity, indexed by changes in the fMRI measures post- relative to pre-therapy, to motor rehabilitation therapy (constraint induced therapy combined with upper limb exercises for the affected upper limb). Although the magnitude of neuroplasticity varied across participants in the MRI task (when hand flexion-extension actions were made), the functional benefits of therapy were linked to increased MRI activity in the premotor cortex and secondary somatosensory cortex of the lesioned hemisphere. In a similar study conducted two weeks post-intervention, Bosnell et al. (2011) found that stroke participants showed significant improvements in regions of basal ganglia, inferior frontal gyrus, thalamus and superior temporal gyrus, while controls showed decreased activation in the same areas.

However, the pattern of neural recovery varies across studies. In some cases, higher activation has been noted in the ipsilesional to the moving hand hemisphere (Lu et al., 2012, Wieser et al., 2011, Honda et al., 1997). However, there are also studies showing widespread activation of around lesion areas (Liepert et al., 2000) or change of activation in a specific location of the brain (that was not activated prior to the intervention) (Pineiro, 2001, Calautti, 2003). In addition, Nelles et al. (2001) reported a correlation between motor recovery and changes in activation of the premotor and parietal cortex areas.

It has also been noted that cortical reorganization has been reported as more evident in the early stages of stroke recovery (acute and subacute phases) compared to the chronic cases

(Traversa et al., 2000). Although neuroplasticity changes are possible in chronic stroke survivors (Traversa et al., 2000), it is still unclear whether the neural basis of function recovery is the same for acute and subacute patients versus chronic survivors. In the current study, we examined the effects of FES on the functional and neural basis of motor performance in chronic stroke patients. More specifically, we investigated whether patients with chronic impairments in hand function and grasping following stroke would show (i) improvement in the functional ability of the upper limb following an intensive treatment with FES, and (ii) long-term improvement in visuospatial or motor neglect and in extinction 6 months after the intervention. In addition, we used functional MRI (fMRI) in order to examine possible changes in motor related areas of the brain, which might occur following the application of FES to the upper limb for a period of 4 weeks (4 days per week). During the fMRI assessment, patients performed a unilateral squeezing task. We used the fMRI responses while squeezing with the intact hand as a within-participant control condition, for the impaired hand. Given the heterogeneity of the patients we analysed individuals as single cases and focused on activation within the motor cortex and motor association regions. As we expected to observe changes in the activation of the motor cortex of the hemisphere ipsilesional to the impaired hand following FES training, our analysis focused on primary and secondary somatosensory regions.

5.2. METHODS

5.2.1. Study Design

The present study was approved by the University of Birmingham Ethical Review Committee and informed consent was obtained from all participants. Five participants undertook the intervention procedure, which involved 45 minutes of FES for 4 days per week, for 4 weeks. The following measurements were obtained 1 week prior to the start of the intervention (baseline) and 1 week after the end of the intervention period (post treatment): a) grip force, b) the apple cancellation test (Bickerton and Samson, 2011), c) the Action Research Arm Test (ARAT) (Hsieh and Hsueh, 1998), and d) tapping capacity (weekly measurements). The apple cancellation test, the ARAT and the tapping measures of performance were also obtained in the follow-up assessment 6 months after the end of the intervention period. During the intervention and the follow-up period the patients did not receive any other forms of upper limb rehabilitation. MRI scans (structural and functional) were obtained 1 week prior and 1 week after the end of the intervention.

5.2.2. Participants

Five first-stroke male participants (Table 6) with mild to moderate hemiparesis participated in the study. The average age of the participants was 57.8 +/-6 years. Three patients had right side lesions involving the parietal lobe and 2 patients had left hemispheric lesions where the parietal lobe was not affected. All patients met the following inclusion criteria: (1) had no history of prior stroke; (2) had stroke at least 6 months prior the start of the intervention; (3) were medically stable; (4) were not enrolled in any other rehabilitation programmes for the duration of the study and the 6 months follow-up period; (5) could perform simple functional movements with the hemiparetic upper limb; (6) had no prior experience of electrical stimulation for their upper limb; (7) were able to follow instructions and to understand the procedure of the intervention; (8) had no underlying neurological or musculoskeletal impairments that could affect the paretic upper limb. Patients who had a stroke more than 5 years before the study, as well as patients with severe pain of the upper limb that could be exacerbated following FES application, peripheral neuropathy, or an absence of proprioception or sensation in the hemiparetic upper limb, were excluded from the study. In addition, based on previous findings revealing that FES may be most effective in participants with mild to moderate impaired motor function (Chae and Yu, 2000), only patients who showed at least 5 degrees of active flexion and extension movement at wrist and metacarpophalangeal joints were included in the study. None of the patients had noted any improvement in arm function in the six months prior to the test. Moreover, 3 of the patients presented with unilateral neglect on the Apple cancellation task (see Results section). On the tests conducted six months prior to the rehabilitation procedure, there were no differences in

neglect (cancellation performance) compared with the pre-treatment baseline, in those patients presenting with the problem (70% cancellations six months prior vs. 71% pre-baseline, across the three patients).

Table 6a and 6b: Demographic Data - FES Participants

| Demographic | | | Months post |
|-------------|-----|-----|-------------|
| Subject | Sex | Age | stroke |
| 1 | M | 54 | 23 |
| 2 | M | 63 | 38 |
| 3 | M | 65 | 11 |
| 4 | M | 58 | 42 |
| 5 | M | 50 | 19 |

| Characteristics (n=5) | participants |
|---------------------------|--------------|
| Age (y) | 57.8 +/-6 |
| Men | 5 (100) |
| Stroke | |
| Infarct | 1 (20) |
| Hemorrhagic | 4 (80) |
| Impaired side | |
| Right | 3 (60) |
| Left | 2 (40) |
| Time post-stroke (months) | 26.8 +/-13 |
| FES treatment frequency | 4 pw |

5.2.3. Functional Electrical Stimulation Procedure

During the 4-week intervention period the participants received 45-min sessions of FES 4 times per week. A four-channel functional electrical stimulator (Compex Motion, Compex Medical SA, Zurich, Switzerland) and surface electrodes (Pals - platinum neurostimulation

electrodes, 1.25" diameter, Axelgaard A/S, Lystrup, Denmark) were used to stimulate the following actions: i) wrist extension (extensor carpi ulnaris and radialis longus and brevis), ii) wrist flexion (flexor carpi radialis and ulnaris), iii) thumb extension (extensor pollicis longus and brevis), iv) thumb flexion (flexor pollicis longus).

In order to find the most active points for the activation of the selected muscles a pen-form electrode was used prior to the intervention, and the areas that showed the highest forms of activation -identified by level of muscle contraction- for the same amount of electricity were marked on the skin surface using a permanent ink pen. The inactive electrode was placed on the dorsal surface of the forearm 3 cm distal to the wrist joint line. The device was programmed to generate a grasping action by starting muscle stimulation in wrist extensors (i.e., open the hand to get prepared for the grasp that will follow) and then the finger and wrist flexors so that they could grasp an object (cup), and there was then a release of grasp following stimulation of the extensors. The procedure was supervised by a qualified physiotherapist. The precise amount of stimulation was adjusted accordingly so that it would promote movement but would also be comfortable and under the pain threshold of the participant. Voluntary functional movement of the hand was promoted using the minimal amount of electrical stimulation to generate an action, with FES being used to amplify voluntary muscle activity but not to initiate movement. During the first session, the degree of stimulation was manipulated so as to allow an effective functional movement (sufficient to grasp and release a cup). If muscle tone increased during the procedure to a level where the fingers could not actively open, a short 3-minute break was given with passive stretching provided by the physiotherapist.

5.2.4. Outcome Measures

5.2.4.1. Grip Force

The maximum voluntary grip force of finger flexion was measured with a custom grip force device capable of measuring finger flexion and extension forces. These data were acquired and analysed with bespoke software (Center for Sensory-Motor Interaction (SMI), Aalborg University, <http://person.hst.aau.dk/knl/mk/introspec.html>) that indexed the peak force of each trial. The participants were instructed to perform five power grasp movements with maximum force possible as an indicator of changes in the flexors of the wrist and finger muscles. The ipsilesional hand was used as a control to compare performance with the contralesional hand.

5.2.4.2. Apple Cancellation Test

The Apple Cancellation Test² - Bickerton et al. (2011) constitutes an easily applicable outcome clinical measure of different forms of neglect that can be related to the functional outcome following a rehabilitation period. It consists of complete and incomplete apples and the participant is requested to cross only the full apples. Incomplete apples contain a gap on the right or on the left side. The test provides information about egocentric neglect (if targets are missed

² Appendix 1, Test 7

on one side of the page) and also allocentric neglect (if false positive responses are made to distractions with a gap on one side).

5.2.4.3. Action Research Arm Test (ARAT)

The Action Research Arm Test (Hsieh & Hsueh, 1998) was completed in specific tasks before and after the total period of the intervention and 6 months after the end of the intervention period. The Action Research Arm Test has been validated for stroke and consists of 4 different subscales. These subscales are related to grasping, gripping, pinching and gross movement ability. Different objects, such as various sized blocks of wood, a cricket ball, stone, jug and glass, tube, washer and bolt, ball bearing, and marbles were used. The test involved 19 movement tasks and the total score ranged from 0 to 57 (with each task graded from 0 to 3).

5.2.4.4. Tapping Performance

A custom electronic tapping counter device was specifically made for the study. The device consisted of two counters 15 cm apart mounted on a frame. Participants tapped the left counter with the left index finger and the right counter with the right index finger, either making unilateral or bilateral movements, over a period of 30 seconds, with the eyes opened. Patients were asked to make as many finger taps as they could under both the unilateral and bilateral

action conditions. For this test, baseline assessments were taken 1 week before the start of the intervention and 1 week after the end of the intervention period. Post-intervention measurements were also taken on a weekly basis during the full rehabilitation time course.

5.2.5. fMRI Scanning

All patients participated in two fMRI sessions (6 weeks apart). These two sessions were equal in time; the first one took place 1 week prior the start of the intervention and the second one took place one week after the end of the intervention. All individuals were scanned at the Birmingham University Imaging Centre (3T Achieva scanner; Philips, Eindhoven, The Netherlands). EPI and T1-weighted anatomical (1x1x1 mm) data were collected with an eight-channel SENSE head coil. For all fMRI measurements, gradient-echo EPI data were acquired from 34 axial slices with no gaps (repetition time = 2000ms, echo time = 35 ms, flip angle = 80°, 3x3x3 mm resolution). Three 170-second EPIs runs were performed for each hand. Patients followed visual instructions to squeeze an MRI compatible grip device (the grip force device manufactured at the University of Birmingham School of SportEx and consisted of a cylinder shaped grip force made of plastic. The cylindrical device had a 2cm gap in the centre that could be joined while the participant was squeezing the device so that the applied force could be measured in Newtons). An experimenter was present in the room to ensure patients complied with the task instructions. The sessions for each hand were randomized across participants with a short break in between. In each session there were three blocks of 30s during which patients

squeezed the grip device. Patients were instructed to squeeze at a pace of one squeeze every 3 seconds. Prior to each squeeze block, an instruction was presented for 20s to prepare the patients for the task ('get ready'). Following each block of squeeze trials a rest block took place for 10secs including a written instruction to the participants to relax. In addition, 10s fixation periods were added at the beginning and the end of each session. Patients practised the task prior to the scanning session.

5.2.6. Image Analysis

Image analysis was carried out using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, 2009) and was implemented in Matlab (2009) environment. To correct for movement and movement by distortion interactions, all volumes from the pre and the post- intervention scans were realigned to and unwrapped as proposed by Anderson's et al. (2001). To estimate the normalization parameters, the T1 scans were co-registered to the mean EPI image. The T1 scans were then wrapped to the normalized-MNI space by using the unified segmentation algorithm. This algorithm has been shown to be optimal proc for normalizing brain with large lesions (Crinion et al., 2007). The EPIs were then transformed to the MNI space by using the parameters obtained from the T1 normalization procedure and smoothed with a Gaussian of 8x8x8 FWHM, to accommodate the assumptions of random field theory (Worsley et al., 1996?).

We analysed the data in two ways: voxel-based analysis and region of interest analysis. Voxel based analysis was carried out separately for each patient, treating them as single cases. This was done due to there being considerable variability in each patient's lesion, the resulting behavioural pattern and the relatively small number of patients. For each patient we used the general linear framework to assess reliable changes in BOLD as a function of the conditions. The model included the following regressors of interest: the onsets of the right and left hand squeeze blocks separately for the pre- and post-intervention sessions. Regressors of no interests included the 'get ready' periods and the movement parameters for each session. For each patient and each hand we computed the following contrasts: 1) squeeze (pre + post) > rest; 2) squeeze pre > post; 3) squeeze pre < post. We focused on results that survive family wise error correction at the voxel level with a cluster size of 100 (apart from patient 5; see below). FWE-corrected results are plotted with a cluster size of zero.

In addition, we separately examined changes in the extent of motor cortex activation in each patient. We used the Brodmann's areas (Brodmann, 1909) to localize these regions of interest. The areas focused on were: primary somatosensory cortex (BA 3, 1 & 2), primary motor cortex (BA 4), somatosensory association cortex (BA5), premotor cortex (BA6), somatosensory association cortex (BA7) and all the above areas together (BA 1-7). By using the `wfu_pickatlas` (<http://fmri.wfubmc.edu/software/PickAtlas>), we generated a mask for each of these BAs and we counted how many voxels responded above threshold ($p < .05$ uncorrected) during the squeeze versus the rest blocks in each of the four conditions. We then computed whether there was an increase or decrease in activity between the pre and post sessions.

5.3. RESULTS

5.3.1. Evaluation of Grip Force

Maximum voluntary grip force for the impaired hand in all 5 participants increased 1 week post intervention when compared to the baseline results, $t(4) = -3.391$, $p = 0.028$. The healthy hand was used as a control before and after the intervention and for this hand, there were non-significant effects ($p > 0.05$) for the post-intervention vs. Baseline comparison ($t(4) = 1.190$, $p = 0.3$) (Figures 27a and 27b).

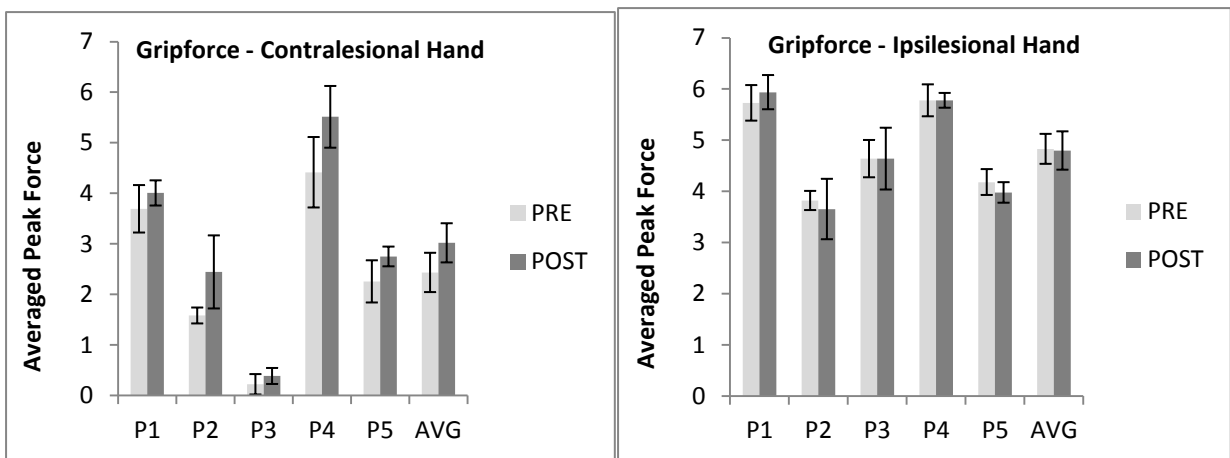


Figure 27a and 27b: Pre and Post FES grip force performance per patient (in terms of peak applied force N for a) Contralesional and b) Ipsilesional Hand. Error bars depict 1 SE on each side of the mean

5.3.2. Assessment of Apple Cancellation – Neglect

The Apple cancellation test was carried out by participants 1 week before the start of the intervention (pre), one week after the end of the intervention (post) and in the 6 months follow-up assessment. Of the participants included in the study, 3 had right hemisphere lesions and showed impairments related to visual and motor neglect. The other 2 left hemisphere participants did not show signs of neglect. In order to assess the possible effect of FES in neglect we performed an analysis of the apple cancellation test neglect and non-neglect patients. Statistical analysis of the 3 participants who performed below the cut off (<48/50) in the apple cancellation test was conducted using a hierarchical three-way log-linear analysis with the factors being participant, time (pre vs. Post) and accuracy (number target apples missed vs. Correctly cancelled). This produced a final model with two 2-way interactions between accuracy and patient and between accuracy and time. The likelihood ratio of this model was $\chi^2 (4) = 1.946$; $p = 0.746$. The interaction between patient and accuracy ($\chi^2 (2) = 8.066$; $p = 0.019$) was due to some patients performing overall better than others (see Figure 28a and 28b). The interaction between time and accuracy ($\chi^2 (1) = 15.001$; $p < 0.001$) was due to neglect reducing in the post-intervention test compared with the pre-intervention test (cancellations increased from 71% correct to 89% correct).

A further analysis compared performance at the 6 months follow up with that in the pre and immediately post treatment sessions. When the 6 months post intervention performance was compared the pre intervention level, there was a final log-linear model with two 2-way interactions between accuracy and patient and between accuracy and time, $\chi^2 (4) = 1.139$; $p =$

0.888. Again some patients were performed functionally superior than others ($\chi^2 (2) = 8.288$; $p = 0.016$), for the 2-way interaction). The time by accuracy interaction ($\chi^2 (1) = 10.390$; $p=0.001$) reflected an improvement in measures of neglect at 6 months post rehabilitation (from 71% correct cancellations to 86% across participants).

Patients with no signs of neglect did not show any statistically significant difference before and after the intervention (Figure 28b) ($\chi^2 < 1.0$ for each patient).

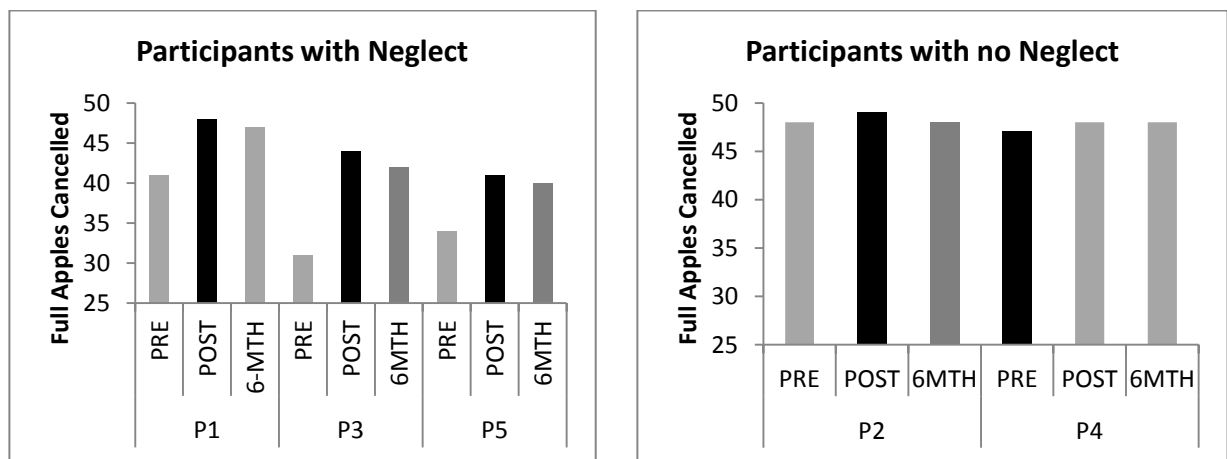


Figure 28a and 28b: Pre and Post FES apple cancellation test performance per patient a) participants with Neglect, b) participants with no signs of neglect.

5.3.3. Action Research Arm Test (ARAT)

Data from the action research arm test were analyzed by comparing the scores of the baseline assessment relevant to performance at the end of the intervention period. Figure 29

shows the averaged improvement across all 5 patients and Figure 30 the pre- and post-training scores in the ARAT per patient. There was a statistically significant improvement across the patients post vs. pre-therapy, $t(4) = -5.573$, $p = 0.005$. Moreover this improvement was maintained on the 6 months follow up assessment when compared both with the pre- training session, $t(4) = -5.245$, $p = 0.006$ and with the immediate post-training session, $t(4) = 5.880$, $p = 0.004$. The increase in performance in the left hemisphere (non-neglect) patients was at least as large as that in the right hemisphere (neglect) patients (the mean increase for the immediate post therapy performance for the right and left hemisphere patients was 8 and 7 respectively; the improvement at the following up relative to pre-therapy was 5.6 and 5 respectively).

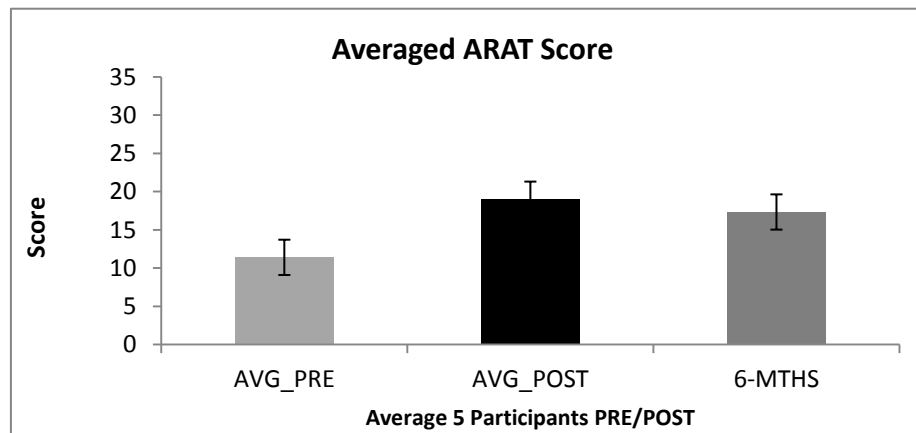


Figure 29: Pre, Post and 6mths follow up ARAT Performance averaged for all participants. Error bars depict 1 SE on each side of the mean

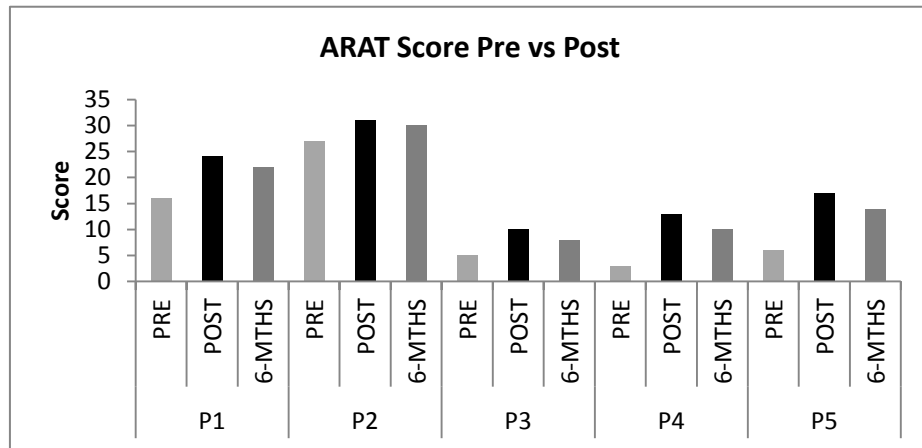


Figure 30: ARAT performance before (pre), after (post) and follow up (6 months) of FES intervention per participant

5.3.4. Tapping Performance – Motor Extinction

The outcomes of the intervention were initially tested in the baseline assessments taken prior to and after the completion of the functional electrical stimulation period (Figure 31). A 2x2x2 ANOVA (time: before – after, hand: ipsilesional – contralesional, task: unilateral – bilateral) returned significant main effects of all factors: time ($F(1, 4) = 9.310$; $p=0.038$), hand ($F(1, 4) = 522.196$; $p<0.001$) and task ($F(1, 4) = 17.440$; $p=0.014$). Also there was a significant interaction between hand and task ($F(1, 4) = 25.946$; $p=0.007$). Since there were no interactions involving time (pre – post), further analyses were conducted averaging over this factor. Separate t-tests (contrasting between unimanual and bimanual actions by analyzing the data for each session as a separate subject), one for each hand, returned significant results for the contralesional hand ($t(4) = 2.902$, $p = 0.044$) and no significant results for the ipsilesional hand ($t<1.0$). Overall there were more taps made on unimanual compared to bimanual trial, and this effect was stronger

on the impaired rather than the intact side. There was an overall improvement on post vs. pre-training trials, but this did not differ across the hands or the bi vs. unimanual tasks.

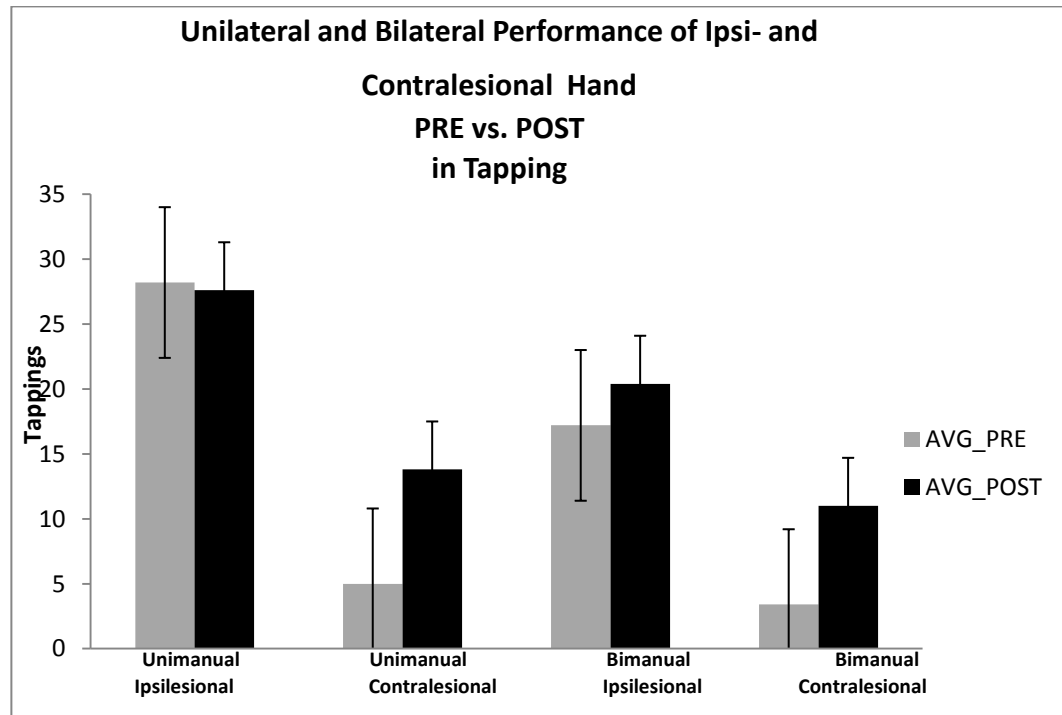


Figure 31: Pre and Post FES tapping performance (in terms of N(Taps) for experimental participants in unimanual – bimanual task of ipsilesional and contralesional hand. Error bars depict 1 SE on each side of the mean

We also assessed performance on the tapping task across the weeks as training took place. Here performance was assessed as a function of: time (week 1-4), task (bimanual – unimanual) and hand (ipsilesional - contralesional). The main effects of time ($F(3, 12) = 14.020$; $p < 0.001$) and hand ($F(1, 4) = 775.208$; $p < 0.001$) were significant. Also, there was a significant interaction between time and hand ($F(3, 12) = 16.727$; $p < 0.001$). There were no interactions with task (unimanual vs. bimanual). There was no effect of time on the ipsilesional hand ($F(3, 12) = 0.721$; $p = 0.558$), but there was on the contralesional hand ($F(3, 12) = 30.661$; $p < 0.001$). There was a

reliable linear effect of time related to the contralesional hand, $F(1, 4) = 36.756$; $p = 0.004$, (see Figures 32a and 32b where the data are averaged across the unimanual and bimanual conditions).

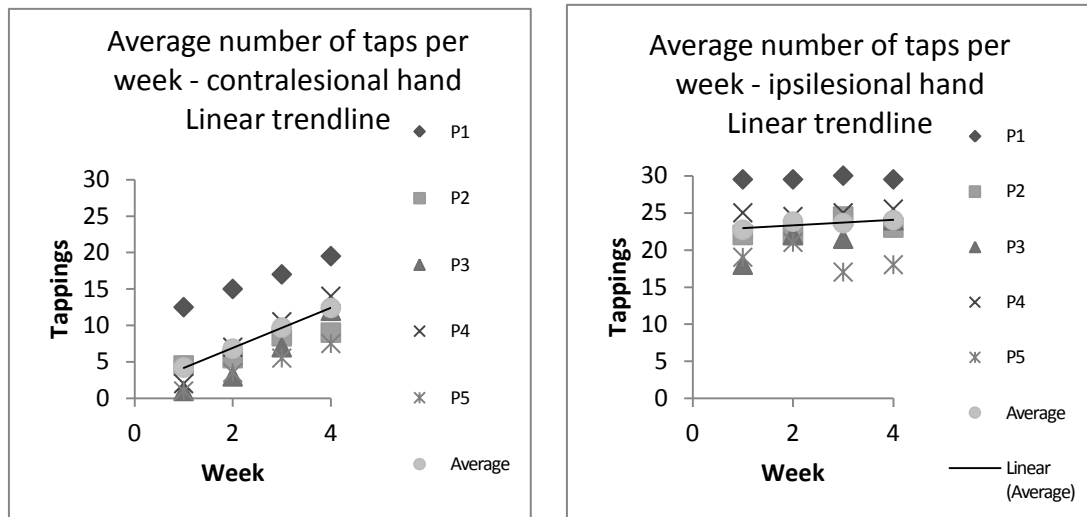


Figure 32a and 32b: Weekly tapping Performance:

Figure 32a (left). Average tapping performance obtained on a weekly basis (intervention period), for the contralesional hand, with linear trend line based on data averaged across 5 patients. Figure 32b (right). Average tapping performance obtained on a weekly basis (intervention period), for the ipsilesional hand, with linear trend line based on data averaged across 5 patients.

5.3.5. Effect of Therapy as Assessed by fMRI

Each patient was analysed as a single case, given disparity across their lesion sites. We reported results from the first level analysis focusing on the four contrasts of interests: 1) healthy hand squeeze (pre + post); 2) impaired hand squeeze (pre + post); 3) healthy hand squeeze pre vs.

post; and 4) impaired hand squeeze pre vs. post. We examined both increases and decreases in the BOLD response following treatment for both hands. The results are summarized in Tables 7 and 8. We next described the findings for each patient separately. Topographic lesions of participants' can be seen in Figure 33.

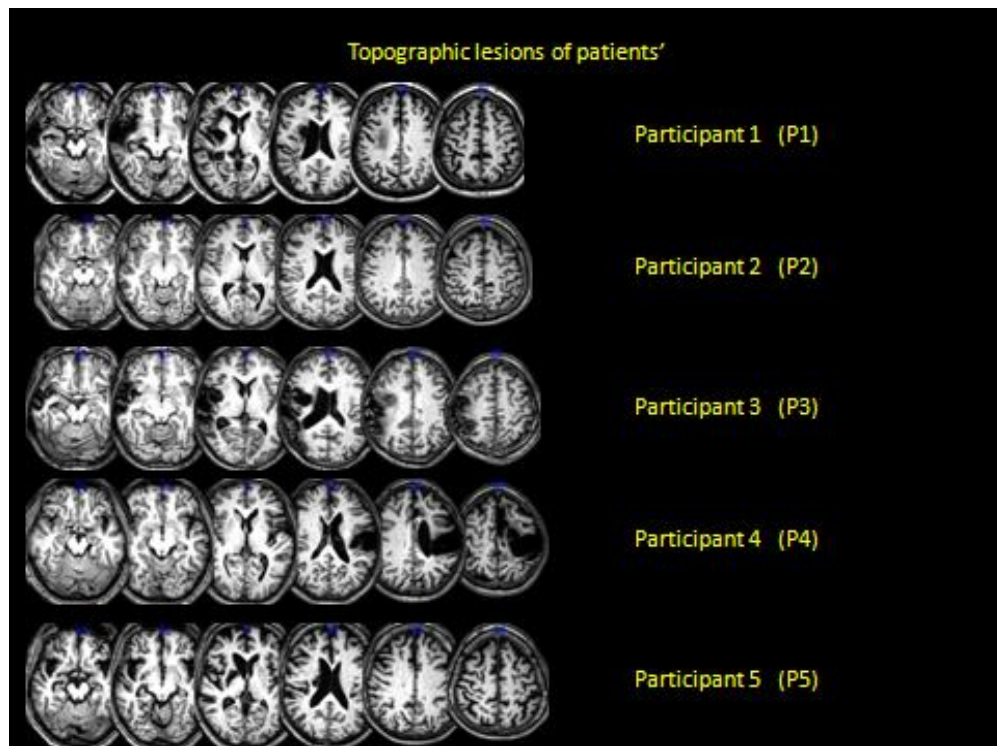


Figure 33: Topographic Lesions of Patients' Left refers to anatomical Left brain.

Table 7: MNI Areas and Broadmann areas of activation for Healthy Hand

| Subject | Region | BA | Cluster size | Peak-Z | MNI Coordinates | | |
|---|-------------------------|-----|--------------|--------|-----------------|-----|----|
| | | | | | x | y | z |
| <i>[Healthy Hand Squeeze]</i> | | | | | | | |
| P1 | Primary Motor Ctx & SMA | 4,6 | 6394 | Inf | -34 | -24 | 56 |
| | Temporal Sup R | 42 | 362 | 7.21 | 64 | -28 | 18 |
| | PostCentral R | 3 | 411 | 6.98 | 54 | -20 | 50 |
| | Temporal Mid L | 37 | 112 | 6.08 | -52 | -66 | 8 |
| P2 | Primary Motor Ctx | 4 | 574 | 7.5 | 38 | -18 | 54 |
| P3 | SMA | 6 | 827 | Inf | -34 | -16 | 62 |
| P4 | Primary Motor Ctx & SMA | 4,6 | 289 | Inf | 38 | -22 | 58 |
| <i>[Healthy Hand Squeeze Pre<Post]</i> | | | | | | | |
| P1 | Primary Motor Ctx | 4 | 297 | 6.49 | -42 | -22 | 62 |
| <i>[Healthy Hand Squeeze Pre>Post]</i> | | | | | | | |
| P1 | Cuneus R | 19 | 542 | 6.32 | 16 | -82 | 28 |
| | Precuneus L | 7 | 183 | 5.64 | -6 | -70 | 56 |

At peak/cluster level $p < .05$ (FWE corrected), #voxels > 100. ;
 BA = Brodmann's area; SMA = supplementary motor area.

Table 8: MNI Areas and Broadmann areas of activation for Impaired Hand

| Subject | Region | BA | Cluster size | Peak-Z | MNI Coordinates | | |
|--|---------------------|----|--------------|--------|-----------------|-----|----|
| | | | | | x | y | z |
| <i>[Impaired Hand Squeeze]</i> | | | | | | | |
| P1 | Primary Motor Ctx | 4 | 140 | 6.07 | 26 | -20 | 46 |
| P2 | Primary Motor Ctx | 4 | 4155 | Inf | -42 | -18 | 60 |
| | Rolandic Oper L | 48 | 354 | Inf | -48 | -16 | 12 |
| | SMA | 6 | 173 | 7.42 | 58 | 12 | 20 |
| | Frontal Mid R | 45 | 106 | 6.03 | 42 | 44 | 2 |
| P3 | Primary Motor Ctx | 4 | 1494 | Inf | 20 | -14 | 82 |
| | Occipital Sup R | 19 | 2297 | Inf | 24 | -76 | 30 |
| | Precuneus L | 18 | 1366 | 7.04 | 0 | -48 | 14 |
| | Postcentral L | 48 | 1276 | 7.01 | -52 | -20 | 26 |
| | SMA | 6 | 401 | 6.47 | -52 | -8 | 52 |
| | Lingual L | 19 | 162 | 6.08 | -18 | -50 | -4 |
| P4 | Precentral R | 6 | 24 | 5.6 | 44 | -10 | 54 |
| P5 | Temporal Superior R | 22 | 138 | 6.32 | 66 | -30 | 12 |
| | Temporal Superior R | 41 | 170 | 5.95 | 42 | -38 | 18 |
| <i>[Impaired Hand Squeeze Pre<Post]</i> | | | | | | | |
| P1 | Primary Motor Ctx | 4 | 425 | 6.83 | 8 | -24 | 72 |
| | Precuneus R | 5 | 159 | 5.95 | 14 | -50 | 60 |
| | Precuneus L | 5 | 216 | 5.91 | -12 | -44 | 64 |
| | Occipital Mid L | 37 | 174 | 5.86 | -42 | -68 | 4 |
| | Thalamus L | 20 | 119 | 5.44 | -20 | -26 | 4 |
| | Temporal Sup L | 48 | 183 | 5.39 | -64 | -32 | 22 |
| | Calcarine R | 18 | 240 | 5.3 | 12 | -74 | 8 |
| P3 | Temporal Mid R | 37 | 106 | 5.77 | 42 | -66 | 16 |

At peak/cluster level $p < .05$ (FWE corrected), #voxels > 100. ;
 BA = Brodmann's area; SMA = supplementary motor area.

Patient 1: Extended lesions on the right parietal lobe and an intact motor cortex (see figure 33).

Voxel based analysis: Squeezing with the healthy hand (e.g. right hand) was associated with strong activation in his left central sulcus (CS) and regions in the surrounding region (figure 34a). In the post session, patient 1 showed a reliable decrease in response of the left CS (Table 7). Note that the apparent increases from pre to post, seen in figure 34a, were not reliable. More interestingly, squeezing with the impaired hand (e.g. left hand) was associated with increase response of the right primary motor cortex (i.e. CS), a response that was magnified after training (Figure 34b). The stimulation intervention also led to increase responses in additional regions that were not active initially. These included left thalamus, left superior temporal and bi-lateral posterior occipital (Table 8). No area showed decrease of response for impaired hand squeezing following treatment.

ROI analysis: We next examine the extent of response (i.e. number of above threshold voxels) in each motor associated Broadman area (BA). As expected, for the healthy hand, we did not observe any change in the extent of activation between the pre to the post session in any of the BA tested. However, when comparing activation of the impaired hand pre vs. post, all somatosensory cortex (i.e. BA 1-7) tested showed a larger response during the post -treatment phase relative to the pre-treatment phase. This was true both for contra- and ipsi-lesional hemispheres (Table 9).

Table 9: Brodmann areas of activation for Healthy and Impaired Hand

| Side/BA | Hemisphere | | | | | | | | | | | |
|--|------------|---|---|---|---|--------|----------|---|---|---|---|--------|
| | Healthy | | | | | | Impaired | | | | | |
| | 1,2,3 | 4 | 5 | 6 | 7 | 1 to 7 | 1,2,3 | 4 | 5 | 6 | 7 | 1 to 7 |
| Healthy | | | | | | | | | | | | |
| pre<post | | | | | | | | | | | | |
| P1 to P5 no changes | | | | | | | | | | | | |
| pre>post | | | | | | | | | | | | |
| P1, P4 and P5 no changes | | | | | | | | | | | | |
| P2 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| P3 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| Impaired | | | | | | | | | | | | |
| pre<post | | | | | | | | | | | | |
| P2, P3 and P4 no changes | | | | | | | | | | | | |
| P1 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| P5 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| pre>post | | | | | | | | | | | | |
| P1 and P5 no changes | | | | | | | | | | | | |
| P2 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| P3 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| P4 | | | | | | | | | | | | |
| + | | | | | | | | | | | | |
| Broadmann's Areas as per change in activation pre and post intervention according to motor areas; BA: Brodmann Area; Areas 1,2,3: Primary Somatosensory Ctx, Area 4: Primary Motor Ctx; Area 5: Somatosensory Association Cortex; Area 6: Premotor Ctx and Supplementary Motor Area (SMA); Area 7: Somatosensory Association Ctx | | | | | | | | | | | | |

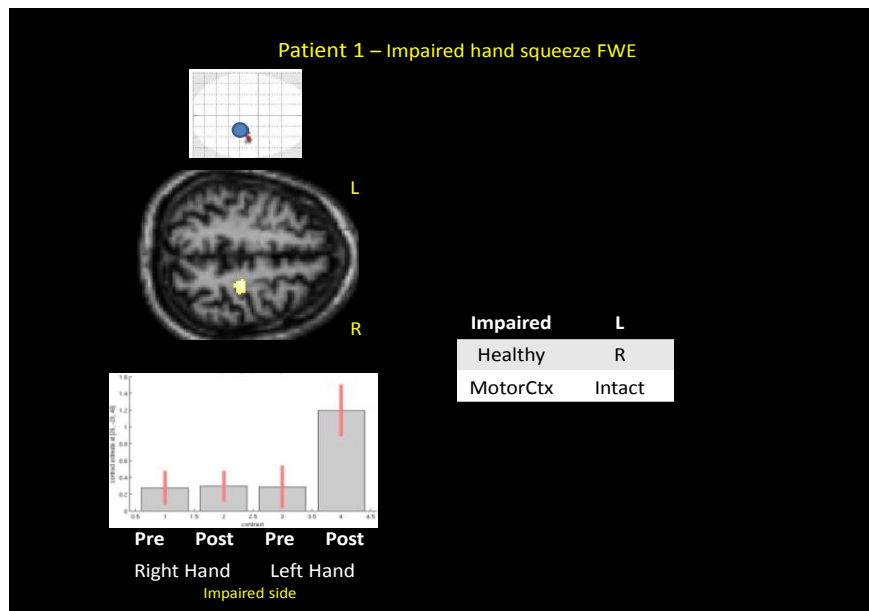
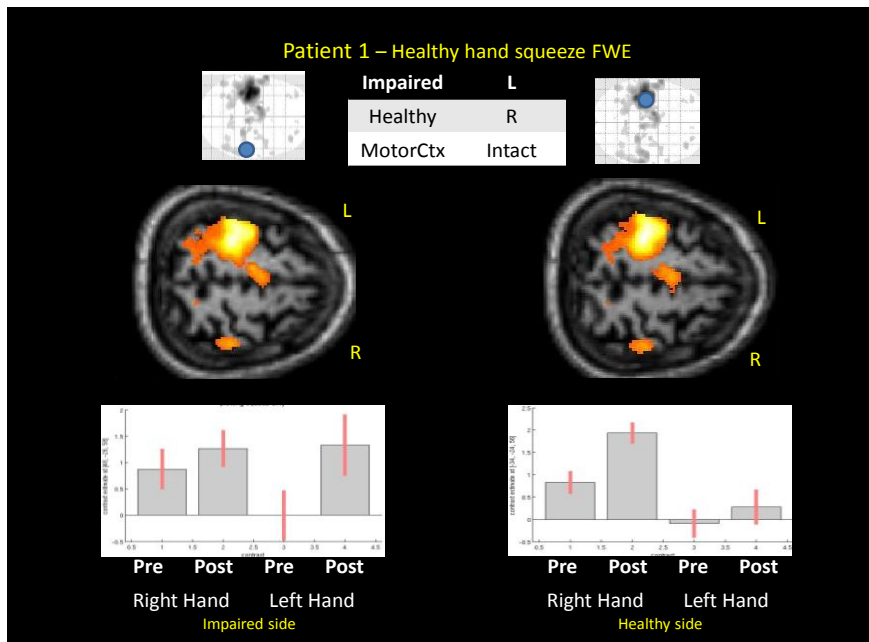


Figure 34a and 34b: Participant 1. a) Healthy Hand Squeezing, b) Impaired Hand Squeezing. Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant squeezes with the a) healthy hand – bar-graphs refer to impaired side and to healthy side accordingly to where the blue circle depicts the area of interest and b) impaired hand. FWE

Patient 2: Sub-cortical lesions within the frontal lobe along with an intact motor cortex (see figure 33).

Voxel based analysis: Squeezing with the intact hand (e.g. left hand) was associated with high activation of the right CS and neighbourhood areas (figure 35a). During the post session, patient 2 showed less activation in response of the CS bilateral when making the same response. When squeezing with his impaired hand (i.e., his right hand) there was an increase of activation in the impaired left lesioned area and more specifically in the left M1 (primary motor cortex and supplementary motor areas) (figure 35b). Also there were parallel activations in areas of the rolandic operatory left and middle right frontal areas.

ROI analysis: For the healthy hand we found less activation pre vs. post intervention in the impaired hemisphere in areas BA4 and BA6. During the impaired hand squeezing task there was less activation of BAs 1-3, 4 and 6 within the spared hemisphere (Table 9).

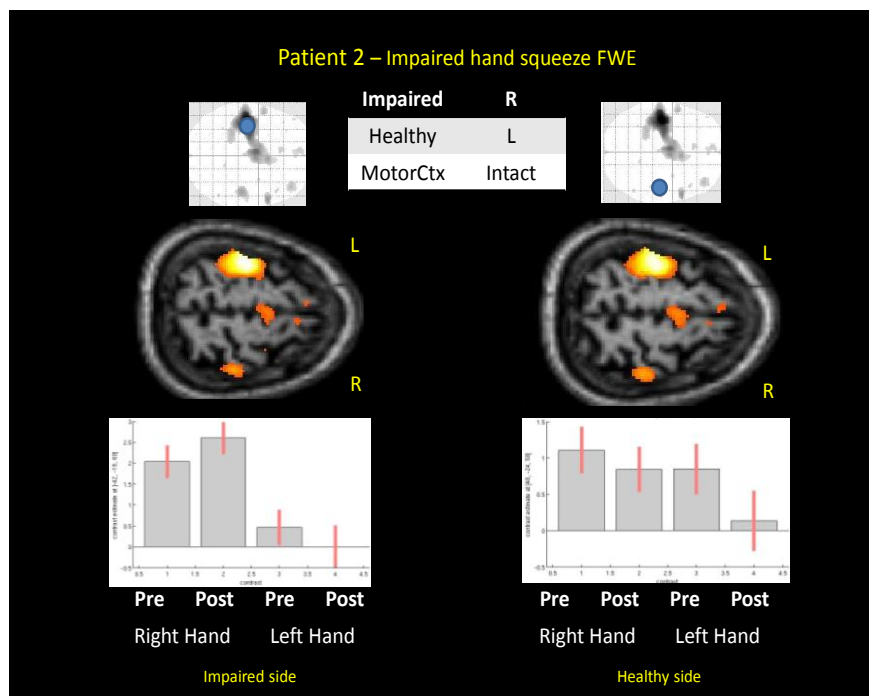
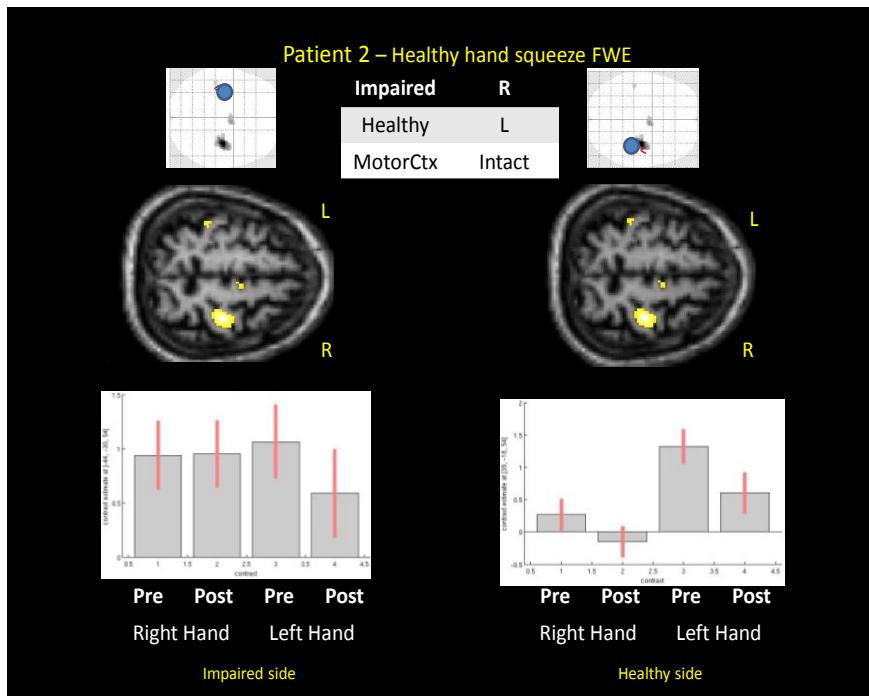


Figure 35a and 35b: Participant 2. a) Healthy Hand Squeezing, b) Impaired Hand Squeezing. Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant squeezes with the a) healthy hand – bar-graphs refer to impaired side and to healthy side accordingly to where the blue circle depicts the area of interest and b) impaired hand. FWE

Patient 3: Extended lesions on the right frontal lobe and parietal lobes that had severely affected motor cortex (see figure 33).

Voxel based analysis: During the squeezing task with his healthy hand (right hand) there was extended activity in the left motor cortex and surrounding areas (figure 36a). In the impaired hand squeezing task (left hand) the participant activated areas of the right motor cortex and also areas of the right occipital and left (ipsilesional) post-central cortices and the precuneus (figure 36b). More interestingly there was increased activation pre vs. post intervention for the temporal middle areas (Table 6).

ROI analysis: There was less activation for the healthy side in BA6 during the intact hand squeezing and also less activation for the healthy side when the impaired hand was used post- vs. pre-treatment (BA5 and BA7). Also there was less activation in Bas 6 and7 in the lesioned hemisphere in the post-treatment phase (Table 9).

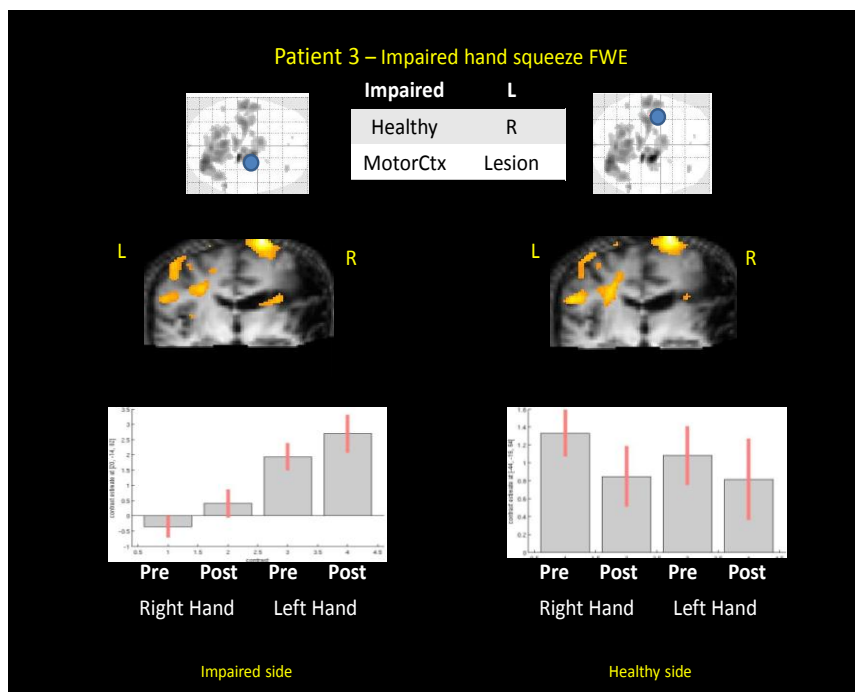
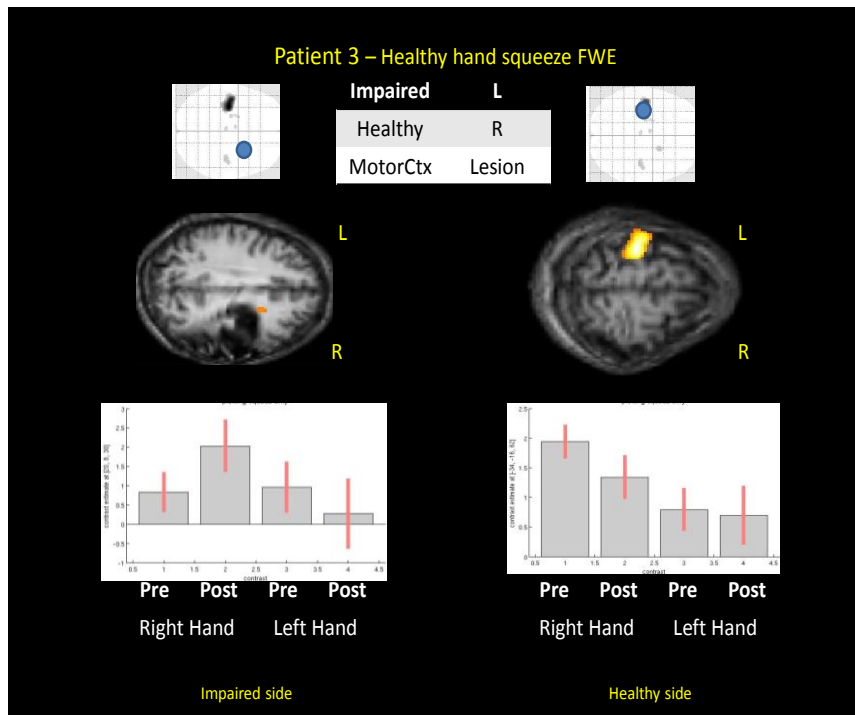


Figure 36a and 36b: Participant 3. a) Healthy Hand Squeezing, b) Impaired Hand Squeezing. Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant squeezes with the a) healthy hand – bar-graphs refer to impaired side and to healthy side accordingly to where the blue circle depicts the area of interest and b) impaired hand. FWE

Patient 4: Extended lesions of the left frontal and parietal lobes including the motor cortex (see figure 33).

Voxel based analysis: As expected and following the trend of all participants during the intact upper limb (left hand) squeezing task there was extended activation of the primary motor cortex and supplementary motor areas (figure 37a). For the impaired hand (right hand) there was ipsilateral activation of the right precentral gyrus (Table 6) and adjacent motor areas and some activation in areas surrounding the lesion motor cortex. Perhaps due to the almost absent motor cortex in the lesioned hemisphere it seemed that activation of the impaired hand took place through the intact motor areas of the healthy hemisphere (figure 37b).

ROI analysis: There were no changes pre- vs. post-treatment for the intact hand but there was a decrease in activation within the impaired hemisphere pre- vs. post-intervention for the primary somatosensory cortex (BA123), premotor cortex and SMA (BA6) and somatosensory association cortex (BA7) in the lesioned hemisphere, when actions were made with impaired hand (Table 9).

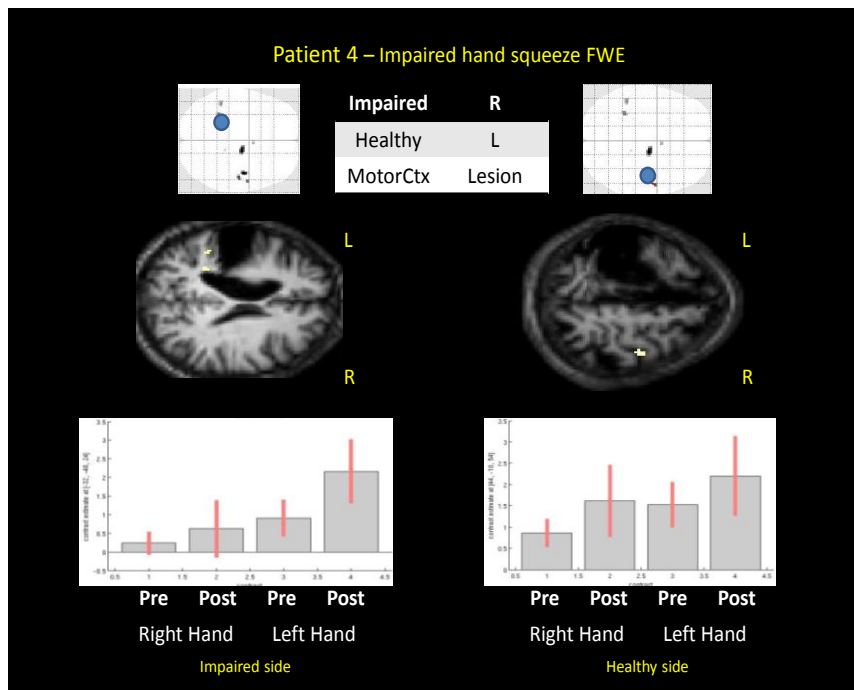
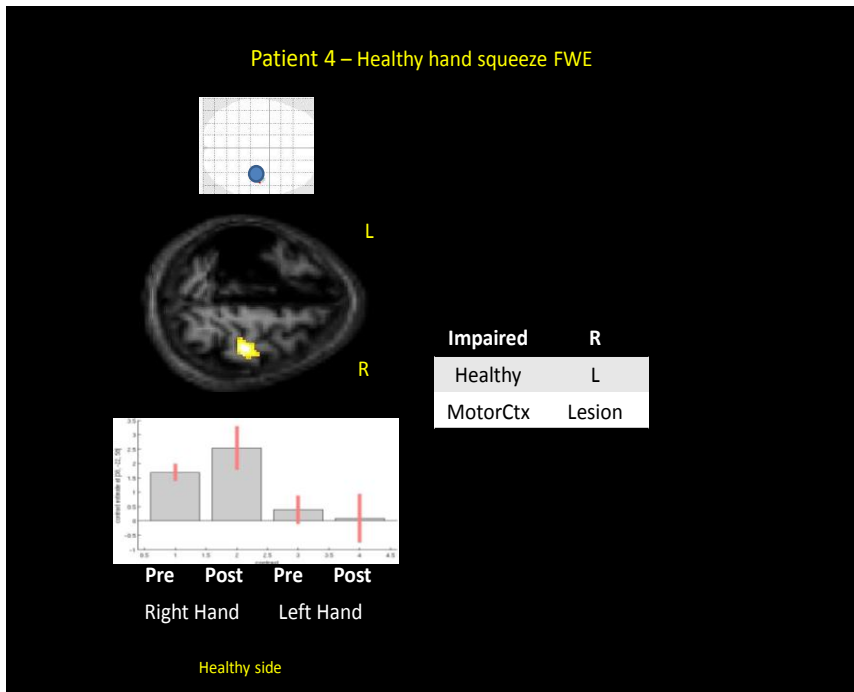


Figure 37a and 37b: Participant 4. a) Healthy Hand Squeezing, b) Impaired Hand Squeezing. Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant squeezes with the a) healthy hand – bar-graphs refer to impaired side and to healthy side accordingly to where the blue circle depicts the area of interest and b) impaired hand. FWE

Patient 5: Extended lesions of the right parietal lobe along with intact motor cortex (see figure 33).

Voxel based: Squeezing with the healthy hand (i.e., the right upper limb) was associated with low activation of motor cortex but this was not reliable in the FWE analysis (figure 38a) though there was reliable activation in bilateral frontotemporal cortex (FWE corrected). For actions with the impaired hand (left hand) there were significant activations of the impaired temporal supplementary area (figure 38b and Table 8).

ROI analysis: There was significantly higher activation pre- and post-intervention actions for the impaired hand in the premotor cortex, SMA (BA6) and the somatosensory association cortex (BA7) in the lesioned hemisphere (Table 9).

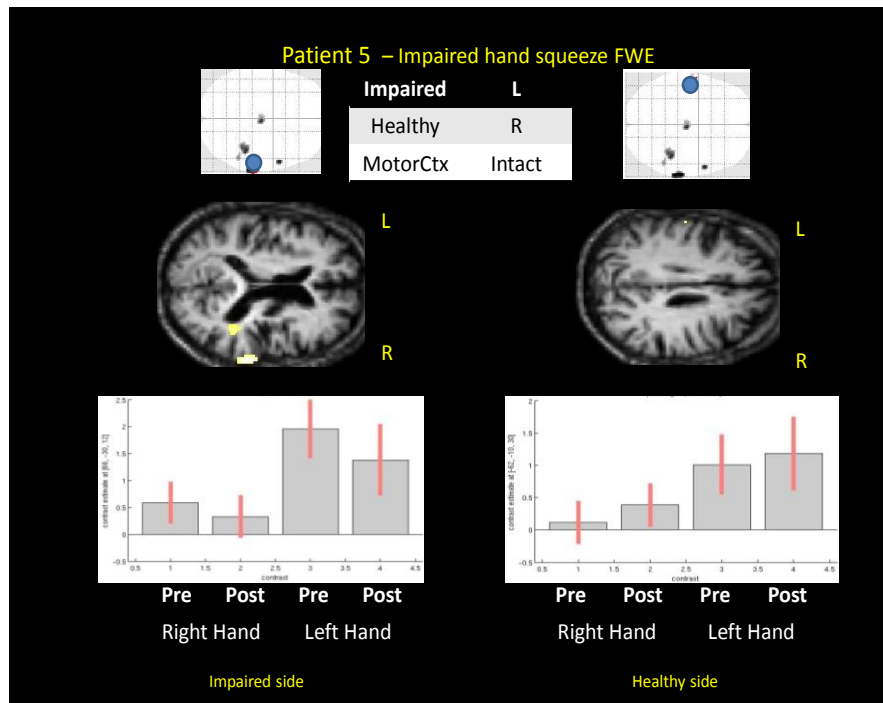
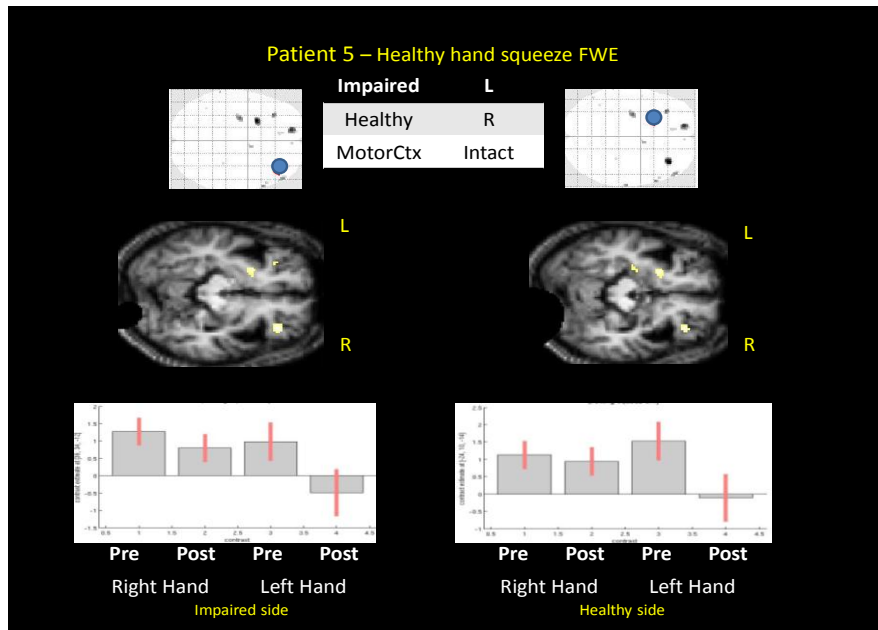


Figure 38a and 38b: Participant 5. a) Healthy Hand Squeezing, b) Impaired Hand Squeezing. Right refers to anatomical Right hemisphere. Graphs depict activation of areas related to the motor cortex while participant squeezes with the a) healthy hand – bar-graphs refer to impaired side and to healthy side accordingly to where the blue circle depicts the area of interest and b) impaired hand. FWE

fMRI analysis revealed changes in brain activation pre and post FES intervention in all five participants of this study. The functional task chosen was followed by all participants and evidence of this can be seen in Table 7 where the level of activation in the motor cortex during squeezing with the healthy hand is presented. In addition, in the next functional task during the scanning participants were requested to squeeze with the impaired hand. It was found that during squeezing with the impaired hand the level of activation in the motor cortex increased on the lesioned side in three out of five participants. These were the participants where the primary motor cortex had not been affected by the stroke and therefore there was evidence of neuroplasticity and increase of engagement of the hemisphere contralateral to the paretic upper limb. Similarly increased activation was shown in the same patients in the SMA, precuneus and precentral areas of the lesioned hemisphere. In all these three patients smaller increases were noticed in the healthy hemisphere and more specifically in the precuneus area. In the other two participants where the motor cortex was severely impaired following the brain injury it was found that there was increased activation in the motor and temporal areas of the ipsilesional side during the impaired hand squeezing task. This reveals that there was a shift in the activation in favour of the healthy hemisphere. It needs to be mentioned that because the number of participants in this study is small (n=5) generalization of the MRI results needs to be evaluated by larger trials although an effort to explain these results will take place in the discussion section based on previous findings.

5.4. DISCUSSION

Rehabilitation of stroke and brain injury-related disabilities is often successful, but there is a large variety of outcome measures used and a lack of solid evidence for the correlation between improved function and alterations in brain activity (Kwakkel, Kollen and Lindeman, 2004). The aim of the present study was to examine whether therapeutic functional electrical stimulation applied to the upper paretic limb would increase functional muscle activation and unilateral neglect in participants at a chronic stage post-stroke. Five patients, with stable motor function and stable neglect (when present) were recruited for a 4 - week FES intervention. In addition, functional MRI was performed pre- and post- FES treatment in order to identify neural changes correlating with behavioural motor functional improvements. Patients were scanned while performing a squeeze – release hand movement. The results confirmed positive functional and clinical outcomes for motor function in the post-intervention period, and this was found across two different measures of motor performance: the ARAT and a tapping task. The improvement was maintained at the time of the 6-month follow-up assessment. In addition, there was evidence of effects of FES on unilateral neglect, and again some indications of long-term carry-over.

The type of FES used in this study was more advanced compared to FES devices that have been used in similar research protocols (Powell and Radian, 1999, Harding and Riddoch, 2009). The 4-channel device that we used could stimulate wrist flexors-extensors and thumb flexors-extensors following a sequence that facilitated patients in the functional movement of grasping following the intervention. In all 5 participants the disability level of the hemiplegic

upper limb as observed in the ARAT was found to decrease, and improved function was maintained at 6 months after training. The grade of muscle activation as assessed by using the grip force dynamometer confirmed the positive results of FES application, and contradicted previous findings of Powell and Radyan (1999), revealing that reduced upper limb disability scores in ARAT initially observed in hemiparetic participants after FES intervention were not maintained. The difference between our results and those of Powell and Radyan (1999) could reflect differences in the samples used (sub-acute stroke vs. chronic stroke survivors) and the fact that their control group was participating in a standard rehabilitation programme. Other studies (Chae and Bethous, 1998) have also failed to find beneficial improvement of FES on disability, possibly due to differences in the outcome measures used. For example, the Functional Independence Measure (FIM) may not be sensitive enough to depict functional changes in upper limb after FES intervention, especially compared to the more objective and sensitive outcome measures of this study. In addition to improving functional movements in the ARAT test, there were also significant effects on the tapping task. Overall, there was an improvement on the post- vs. the pre therapy session, but this did not vary across the bimanual vs. the unimanual condition. There was generally decreased performance under bimanual action conditions and this may reflect either the extra difficulty of coordinating actions and/or increased attentional demands when bimanual actions occur. In sum, there was no evidence here for FES selectively reducing any co-ordination difficulty or effects of attentional demand on action. Instead, there was a general improvement in functional movement in the contralesional limb, which affected unimanual and bimanual actions alike.

As well as examining motor function, we also tested whether FES on the affected side improved neglect. Three out of five participants showed evidence of chronic neglect prior to the intervention. Interestingly, neglect decreased after FES on the apple cancellation task, and although the number of participants was small, it would be important to replicate the current findings in a larger sample in a randomised clinical trial. Performance improved immediately at the end of each trial, but also across sessions in the pre-training assessment. This improvement was maintained over 6 months, although the benefit at 6 months was not found to be maintained to the extent that found immediately post session. As Hardling and Riddoch (2009) suggested, the use of FES may boost both visual and sensory input on the body schema within the brain. In a similar way to prism therapy (Rossetti and Rode, 1998), FES may reduce neglect by changing the cortical maps of visual and body space representations, thus increasing patients' awareness of the contralesional side. It is important that these effects were observed in patients with chronic neglect, indicating that FES can be effective even in these cases (Punt and Riddoch, 2006).

The improvement in motor and attentional function may stem from a combination of effects. First of all FES may directly reduce muscle tone and increase muscle strength and motor control (Dewald and Given, 1994). It could be the case that FES and repetition movements during the intervention period promote learning (Rushton, 2003), which could promote the reorganization of the brain connections and result in a better and permanent functional outcome in motor performance. This is suggested by Joa and Han (2012), who found that neuromuscular stimulation combined with voluntary movements resulted in activation of more and larger areas of the brain. In the current study all patients had good sensory awareness of the affected upper limb and it may be possible that FES therapy may lead to functional benefit through these

sensory components. This notion was supported by Gritsenko and Prochazka et al. (2012) findings, which revealed that cerebral blood flow in the sensory motor cortex area in the lesional hemisphere increased during FES with voluntary interaction, when compared to simple electrical stimulation. Although the level of improvement varied across patients, therapy-related benefits in motor function were identified in all five participants. These improvements of behavioural motor function were used as a principle that would promote changes in brain activity as depicted by fMRI. Due to the small sample size of this study a case analysis of brain imaging results was performed and different routes of brain recovery were identified relative to each patient's lesions.

The results showed that improved functional ability of paretic upper limb's function as shown in ARAT and tapping performance were associated with changes in fMRI activity in the primary motor cortex and supplementary motor area in most of the participants (particularly BAs 4 and 6). It is, however, important to note that stronger activation in the contralesional – intact side of the brain post-treatment, and especially in the motor cortex and neighbouring areas, as well as in the peri-lesional regions of the affected hemisphere were observed in patients whose motor cortex was partially or almost entirely damaged. This might reflect neural plasticity in regions surrounding a lesion in order to substitute the loss of the motor cortex, as well as recruitment of homolog areas in the spared hemisphere.

The current results support previous findings by Johansen-Berg et al. (2002), who reported increases in fMRI activity in the premotor cortex and secondary somatosensory cortex contralateral to the affected hand following exercise intervention. The authors also reported increased fMRI activity in superior posterior regions of the cerebellum bilaterally (note that the cerebellum was excluded in our data collection).

In previous imaging studies of the effects of brain lesion on motor rehabilitation (Johansen-Berg, 2002, Liepert 2000 and 2001), participants with infarcts of the primary motor cortex are often not included. In contrast, two out of five participants in our study had extended lesions that affected motor cortex or surrounding areas. Liepert et al. (2000, 2001) reported that patients that participated in their study showed increased excitability and a shift in centre of the motor-related cortex areas in the lesioned hemisphere, which supports the present results.

5.5. CONCLUSIONS

In sum, therapeutic FES, i.e. functional electrical stimulation, combined with volitional movement led to improved functional outcomes in our chronic stroke population. The current study provides evidence for positive results of FES stimulation on neglect and motor performance. Following a four-week application of FES, all five patients showed significant improvements in behavioural outcome measures of grip force, ARAT and tapping performance. These behavioural improvements were associated with increased responses in motor associated regions within the affected hemisphere. These increases were observed in the primary motor cortex or in regions adjacent to it (if the later was lesioned) or even in the healthy motor cortex in cases of patients that presented with severely impaired motor cortex.

**CHAPTER 6: REDUCING COGNITIVE DEFICITS AFTER
STROKE THROUGH COMPUTERIZED PROGRESSIVE
ATTENTIONAL TRAINING (CPAT) – A PILOT STUDY**

ABSTRACT

Background and Purpose – Cognitive deficits following stroke are associated with poor rehabilitation outcome. Computerized Progressive Attentional Training (CPAT) has been tested and found effective in children with Attention Deficit/Hyperactivity Disorder (ADHD) and there is evidence also for similar training effects on healthy older adults (Anguera et al., 2013). This pilot trial explored the effectiveness of CPAT for improving cognition in stroke survivors with cognitive deficits within 2 months of their stroke.

Methods – Eight subacute stroke participants were recruited. Participants had cognitive deficits identified by using the Birmingham Cognitive Screen (BCoS). Aged-matched controls were also recruited in order to assess intervention effects in a healthy population, and a further control population of subacute stroke patients provided baseline (no treatment data) to evaluate effects of time and repeat testing. Participants in the experimental arm underwent 10 hours of CPAT intervention over a period of two weeks. Outcome measures used computerized tests of attention and the BCoS test battery and were scored blind to group assignment.

Results – CPAT intervention improved cognitive outcomes compared to the improvements in both healthy control and neuropsychological control patients.

Conclusion – CPAT is an effective and valuable instrument that can be applied to help ameliorate attentional deficits following stroke.

Key words: attention, stroke, rehabilitation, neuropsychology

6.1. INTRODUCTION

Stroke is recognized worldwide as one of the major causes of disability (Zhang et al., 2012). Cognitive deficits following stroke are common and may lead to long term disability with significant impact on daily activities and independence of stroke survivors (Cumming et al., 2013). Negative consequences of attention post stroke may even have a dramatic impact on functional recovery and are responsible for poor attendance during rehabilitation process (Heruti et al., 2002). Cognitive and attentional problems in stroke often have often impact on behaviour and can lead to chronic depression (Hackett et al., 2005).

Given the high prevalence of stroke and its impact on cognitive and attentional aspects of daily living and functioning, extensive work has been obtained in the development of various interventions that could ameliorate the impact (Lincoln et al., 2000). Previous studies into the effects of attentional training have returned positive results not only on attention but also on other domains of cognition (speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, and reasoning and problem solving – Nuechterlein et al., 2005) and on everyday functional skills (Sohlberg and Mateer, 1987, Ben-Yishay, 1978, Gray, 1992). For example, Ben –Yishay (1978) investigated the positive outcomes of a computer intervention in focusing and in sustaining attention tested on 40 adults with brain injury. Positive outcome was not only returned on the attention domain but also to all attentional domains that were maintained 6 months following the intervention.

Stimulated by research showing that playing action video games can improve perceptual and attentional performance in young normal participants (e.g., Green et al., 2010; Green &

Bavelier, 2003), a substantial number of attempts have now been made to use computer-based training to improve cognition in individuals showing some aspects of cognitive decline. This has included research on normal healthy ageing populations (e.g., Owen et al., 2010), patients with mild cognitive impairment (Gagnon et al., 2012), Alzheimer's patients (Gaitan et al., 2013), individuals with multiple sclerosis (Cerasa et al., 2013), acquired brain injury (Johansson & Tommalm, 2012) and stroke survivors (Prokopenko et al., 2013). The results are mixed. In many of the studies training has produced benefits on the trained cognitive functions (e.g., improvements in working memory after working memory training; Johansson & Tornmalm, 2012; Owen et al., 2010), but very often there have been failures to generalise improvements to non-trained functions (Owen et al., 2010; Anguera et al., 2013). In a recent Cochrane review of cognitive training of patients following stroke or other non-progressive forms of acquired brain damage, Chung et al. (2013) concluded that there was insufficient high quality evidence for training having a benefit. Few studies used training tasks specifically designed to stress critical cognitive processes, and few were designed with appropriate controls to measure effects of repeat testing and time. The authors highlight the need for high quality research which provides a fine-grained test of whether targeted cognitive training can improve cognition in neurological populations, whether training generalizes, and whether training effects supersede improvements produced by recovery through time and engagement in other ongoing activities.

In the present paper we sought to improve cognitive function in sub-acute stroke patients with impairments in cognition. We identified executive functions (task switching and inhibiting irrelevant stimuli and responses) and sustained attention as being problems that are both common in occurrence after stroke (Bickerton et al., in press; Humphreys et al., 2012) and potentially

critical to a number of other cognitive domains (e.g., if there is poor sustained attention then patients may show increased visual neglect and increased problems in language; Fillingham, Sage & Lambon Ralph, 2005; Robertson et al., 2001). Thus the targeting of executive functions and sustained attention may be beneficial to induce generalized improvements after training. However, rather than target only one of these domain-general abilities, we elected to take a pragmatic approach and to create a suite of programs which tackle all of the identified functions, in order to produce gains across a range of patients. We had patients carry out 3 training tasks. In one, patients were required to detect low frequency targets occurring in a stream of items presented at irregular time intervals, challenging the ability to sustain attention over time. In a second task, patients had to attend selectively to targets in increasingly complex displays and as the targets increased in similarity to distractors. In a third, the task was to select local or global elements and to suppress distraction at the other level (e.g., see Mevorach et al., 2006). Importantly, all of these tasks had progressive levels of difficulty which could be tuned to the abilities of individual patients, all used engaging ‘game-like’ displays (see Figure 39), and all generated easy-to-understand graphical feedback to help motivate patients (see also Shalev et al., 2007, for a similar approach to cognitive training in individuals with ADHD). Performance was measured on the CPAT tasks, on other computerised tasks assessing visual attention and on the BCoS test battery which examines a number of different aspects of cognition.



Figure 39: Example of CPAT training screen

Figure 39. Example displays from our training of selective attention, executive functions and sustained attention. **Left:** Selective Attention. In this task the participant has to decide whether the display includes a target (which is an orange quidditch on a broom with open arms). Since this is a high level of difficulties the visual load is high (many items presented on a noisy background) which poses a high demand of selective attention. **Middle:** the task is to detect occasional targets in 1 of 2 boxes, Sustained Attention. In this task the participant has to respond only when the target – a red car – appears in one of the two target locations (within one of the squares). Target trials are infrequent (30% or less). At this level of frequency (which is one of the higher levels) many distractors may appear not only in the target locations but also in other locations. Note that in this case the red car is presented outside of the squares which means it is a distractor and the participant has to ignore it. **Right:** the task is to discrimination the local shapes as being faces or hearts (conflict condition, Executive Attention. In this task the participants are ask to decide whether the global configuration of the hierarchical figure forms a smiley face (level 1). As the level of difficulty increases elements of working memory and task switching are inserted to the task which make the task extremely challenging tapping different aspects of executive functions.

6.2. METHOD

6.2.1. Participants

Eight first stroke participants, mean age 56.3 years (SD 7.5), four with right-side lesions and four with left-side lesions, six males and two females, were recruited from the National Health System (NHS) in United Kingdom. All participants provided informed consent under ethics approved by the NHS REC. Time post stroke for the experimental group was twenty one days post stroke (+/- 7days). Ethics were obtained from the IRAS scheme. An additional six aged and gender matched participants were recruited as a neuropsychological control group. Both the controls and the stroke participants were either at home or they were hospitalised at the time of the intervention, when a standard rehabilitation regime was applied consisting of physiotherapy, occupational therapy and speech and language therapy. The patient control group (mean age 54 (SD 6.0)) was used to assess the effects of time and general participation in cognitive research on functional recovery. These control patients took part in weekly cognitive experiments in Birmingham University for the same length of time as the experimental group underwent intervention. The patient control group were then compared against the experimental patient group for their performance on the BCoS test battery. The healthy age-matched control participants underwent the same pre- and post-intervention tests as the experimental patient group but they did not have the intervention. This group then served to provide measures of normal levels of performance on the computer-based attention tasks. Demographic data of participants are presented in Table 10.

| Group | Participant | Age | Hand | Side | Stroke | Type | Main deficits | Sex |
|-----------------------------|-------------|-----|------|------|--------|---------|---------------|-----|
| CPAT Experimental | 1 | 52 | R | L | | Infarct | Attention | M |
| | 2 | 58 | R | L | | Haemor | Neglect | M |
| | 3 | 46 | L | L | | Haemor | Neglect | M |
| | 4 | 67 | L | R | | Haemor | Attention | M |
| | 5 | 62 | R | L | | Infarct | Attention | F |
| | 6 | 53 | R | R | | Infarct | Attention | F |
| | 7 | 54 | R | R | | Infarct | Attention | M |
| | 8 | 62 | L | R | | Haemor | Attention | M |
| CPAT Controls Healthy | A | 52 | R | – | | – | – | M |
| | B | 61 | L | – | | – | – | M |
| | C | 58 | L | – | | – | – | F |
| | D | 49 | L | – | | – | – | M |
| | E | 53 | R | – | | – | – | F |
| | F | 60 | R | – | | – | – | F |
| BCoS Participants | I | 64 | R | L | | Haemor | Attention | M |
| | II | 57 | L | L | | Haemor | Neglect | F |
| | III | 72 | L | R | | Infarct | Neglect | F |
| | IV | 54 | R | R | | Infarct | Attention | M |
| | V | 56 | R | R | | Haemor | Attention | M |
| | VI | 65 | R | L | | Infarct | Attention | M |
| | VII | 60 | L | L | | Infarct | Attention | F |
| | VIII | 68 | R | R | | Haemor | Attention | F |

Table 10: Demographic data of participants. Chapter 6

6.2.2. Training. The Computerized Progressive Attention Training (CPAT) program (Shalev, Tsal, & Mevorach, 2007)

The three comprehensive training tasks are based on expansions and modifications of various tasks that have extensively been investigated in the attention literature and are known to uniquely reflect the various attention functions. The three training tasks included the Computerized Continuous Performance Task (CCPT; based on Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), which was designed to improve the function of Sustained

Attention, the Conjunctive Search Task (based on Treisman & Gelade, 1980), which was designed to improve the function of Selective Attention and the task switching Stroop-like Task (based on Navon, 1977), which was designed to improve the function of Executive Attention in particular and the Executive Functions in general. Snapshots of the training tasks are presented below (Figure 39).

Each attention training session should include approximately nine blocks from different training tasks. Numbers of blocks will vary across participants primarily due to age differences and severity of symptoms (minimum 8, maximum 12 similar to the procedure followed in Shalev, Tsal and Mevorach (2007) in children with ADHD). Every block contains 40 trials, except for blocks in the CCPT (which train sustained attention) that consist of either 80 or 60 trials depending on the level of difficulty. Participants will advance in levels of difficulty according to prespecified criteria based on fixed-accuracy and individually adjusted reaction time (RT). Participants will receive an auditory feedback (beep) when an error will be committed and on-line positive visual feedbacks on RT performance. These feedbacks are translated into points that are presented on the screen at the end of each block.

The training program carried out over a period of two weeks consisting ten one-hour sessions. Each participant supervised by a skilled research assistant during the entire session. During each session participants performed a selection of tasks and within each task participants advanced in the levels of difficulty according to their personal gradual progress, expressed in accuracy and speed performance.

After completing the training program the assessment tools administered again along with behavioural cognitive assessment (pre-training).

6.2.3. Assessment tools

A PC with a graphic display controlled stimulus presentation and data collection (Figure 39). All stimuli were presented against a dark background. Viewing distance was set at about 50cm so that 1cm represented about 1.15 deg of visual angle. Each task was preceded by practice trials during which auditory feedback was given on accuracy. Practice trials were repeated if the rate of errors exceeded 10%. No feedback was provided during the experimental blocks. Reaction times (RT) were recorded from the onset of the stimulus to the nearest msec. In each task, participants were required to respond as fast and as accurately as possible. Different measures were derived from mean accuracy and mean RTs for correct responses, as described below.

In order to form a detailed assessment of attention functioning we used four attention tasks that were developed along with the four functions of attention model proposed by Tsai, Shalev and Mevorach (2005) in the context of ADHD. The theoretical framework of this model is derived from Posner and Petersen's (1990) influential theory of attention networks. The four functions of attention model refers to four distinct functions within the attention regime: (a) sustained attention - the ability to allocate attentional resources to a non-attractive task over time while maintaining a constant level of performance; (b) selective (spatial) attention - the ability to focus attention on a relevant target while ignoring adjacent distracters; (c) orienting of attention - the ability to direct attention over the visual or auditory field according to sensory input, and to disengage and reorient efficiently; (d) executive attention - the ability to resolve conflicts of information and/or responses.

6.2.3.1. Description of the assessment tasks

We implemented the four proposed attentional functions of attention by using four computerized neuropsychological tasks. All four tasks were established by Tsal, Shalev and Mevorach (2005), where they were used to assess attention functioning in children with ADHD and without ADHD. Each attention test starts with a short practice block and the test lasts approximately 12 minutes. When many breaks are needed the overall duration will be longer, accordingly.

The task that assesses sustained attention was always administered in a continuous mode (no possible breaks!) and always as the first task. The other three attention tasks were administered in blocks (that is, 4 series of 40 trials).

6.2.3.2. Sustained Attention

A Conjunctive Continuous Performance Test (CCPT) was used to assess sustained attention. Participants were presented with a sequence of color drawings of geometric shapes appearing in the centre of the screen. The size of each stimulus ranged from 2.5 to 2.7cm in height and from 2.6 to 3.0cm in width. There were 16 possible stimuli resulting from the factorial combinations of square, circle, triangle, or star appearing in red, blue, green or yellow. Participants were instructed to respond, by pressing the space bar with their preferred index finger, as soon as a target (red square) appears and to withhold responses to all other stimuli. The

target appeared on 30% of the trials. Using a low rate of target stimuli (30%) and varying the inter-stimulus interval (ISI), this task maintains a high demand on sustained attention but minimizes the involvement of other cognitive factors (Shalev, Ben-Simon, Mevorach, Cohen & Tsal, 2011; Stern & Shalev, 2013). On 17.5% of the trials a differently coloured square appeared, on 17.5% of the trials a red non-square geometric shape appeared, and on 35% of the trials a non-target shape appeared, that shared neither identity nor colour with the target. Each stimulus was presented for 100msec and was separated from the next by an interval of 1000, 1500, 2000, or 2500msec. The various stimulus types and inter-stimulus intervals were randomly intermixed. The task consisted of a single block of 320 trials preceded by 15 practice trials and lasted approximately 12 minutes. Figure 40.

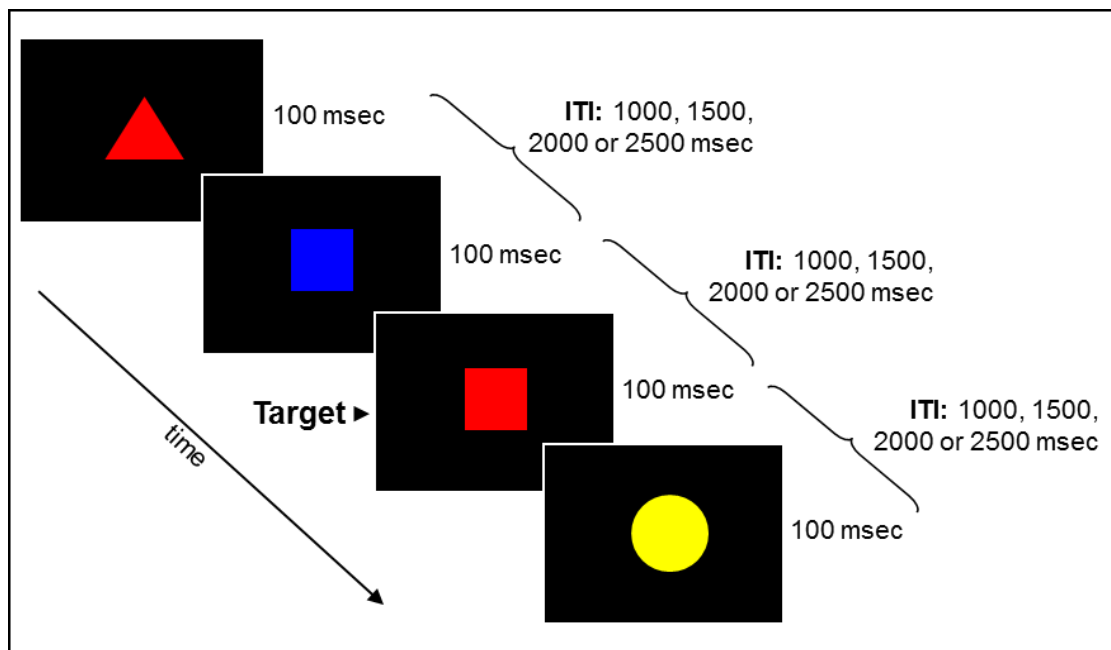


Figure 40: Sustained Attention - Assessment

6.2.3.3. Selective Attention

For the assessment of selective attention, a Conjunctive Visual Search task (Treisman & Gelade, 1980) was used. Participants were required to search for a target defined as a specific conjunction of colour and shape. The target was a blue square (1.1cm in width and height) appearing among an equal number of red squares (1.1cm in width and height) and blue circles (1.1cm in diameter). There were four display sizes of 4, 8, 16 or 32 items, which were equally frequent and randomly intermixed within a block. The items were randomly positioned within a 7 x 6 matrix subtending 9.5cm in width and 8cm in height. 50% of the displays contained a target. Each trial began with the presentation of a small white central cross (0.6cm in width and height) for 1000msec which was immediately followed by the onset of the search display which remained on until response. The Inter-trial interval (ITI), from response to the presentation of the fixation point, was 500 msec. Participants were required to respond with their right index finger to the presence of the target and with their left index finger to its absence. There were four 40-trial blocks, preceded by 10 practice trials. Figure 41.

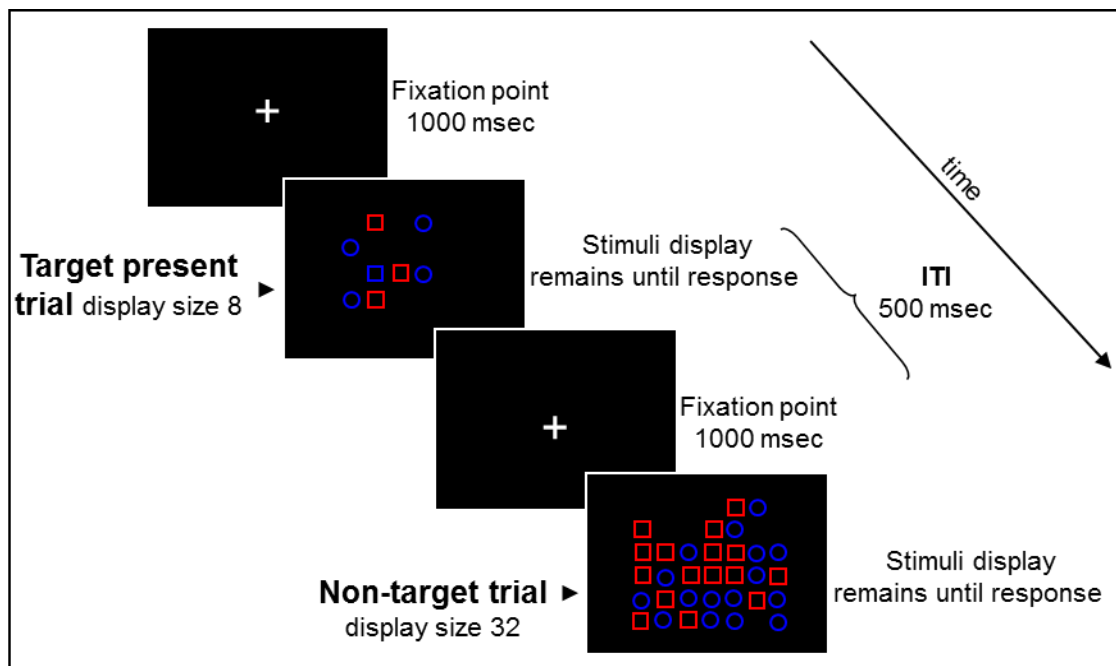


Figure 41: Selective Attention - Assessment

6.2.3.4. Orienting Attention

A peripheral cueing paradigm with exogenous cues - A visual cueing paradigm (Posner, Snyder, & Davidson, 1980) with an exogenous cue (Jonides, 1981) was used to assess orienting of attention. Participants were instructed to respond to the identity of a stimulus (circle or triangle), which appeared in a cued or an un-cued location. A discrimination task in which participants had to decide whether the target was a circle or triangle was used. The fixation display consisted of a white cross at the center of the screen (0.6cm in width and height) and two white rectangles, subtending 4cm in width and 3cm in height, and centered at 6 cm to the right and to the left of fixation. The cueing display was identical to the fixation display except that one of the rectangles

brightened briefly. The target display consisted of either a white-perimeter circle (subtending 1.4cm in diameter) or a white-perimeter triangle (subtending 1.4cm in length and in height) superimposed on the fixation display and centered inside one of the two rectangles. On each trial, the fixation display appeared for 1000msec, followed by the cueing display that appeared for 100 msec. The fixation display then appeared again for a 100msec following which the target was displayed for 100 msec. The time for response was unlimited. The ITI was 1500 msec. 80% of trials were valid trials (in which the target appeared at the same location as the bright rectangle) and 20% were invalid trials (in which the target appeared at the location of the other rectangle), randomly intermixed within a block. Participants were instructed to respond with their right index finger to the circle and with their left index finger to the triangle. The task consisted of three blocks of 60 trials each, preceded by 10 practice trials. (Figure 42).

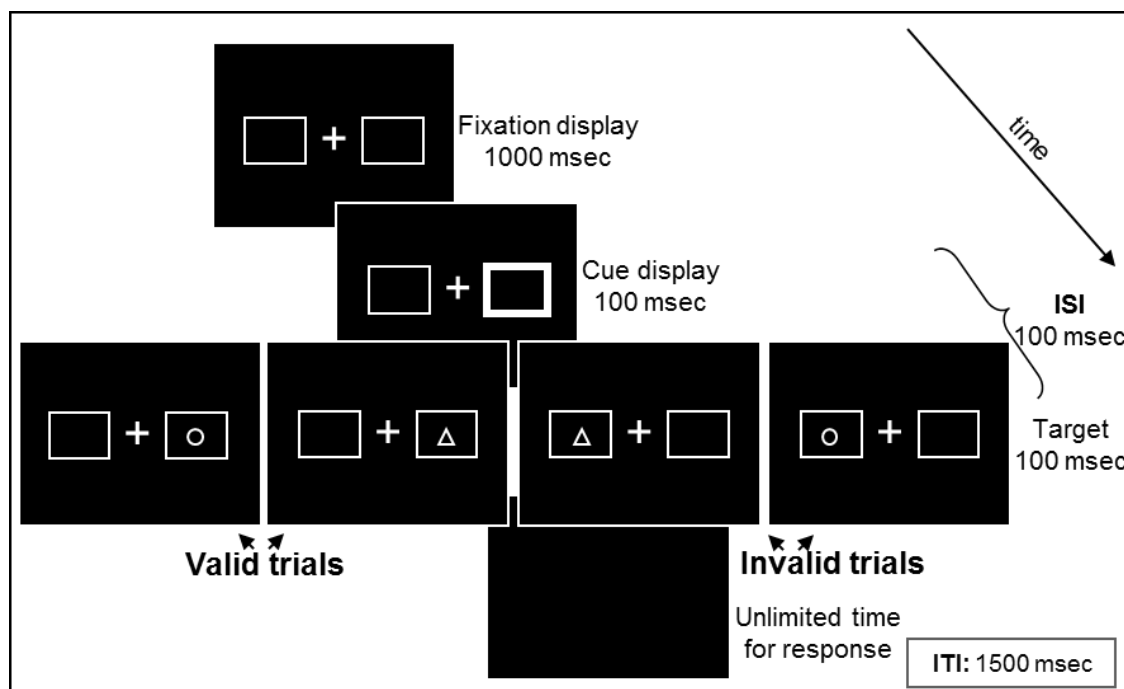


Figure 42: Orienting Attention - Assessment

6.2.3.5. Executive Attention

A Direction-Location Stroop-like task (or Flanker task) was used to assess executive attention (Stroop, 1935). Participants were presented with a single stimulus varying along two dimensions which could elicit conflicting responses. A white arrow subtending 1.5cm in height and 0.6cm in width, pointing either up or down, appeared either 1.2cm above or below fixation along the vertical meridian. Participants responded “up” with their right index finger and “down” with their left index finger. The task was composed of two subtasks: Location judgments and direction judgments. In the location subtask participants were required to respond “up” or “down” to the location of the arrow (above or below fixation) ignoring its direction. In the direction subtask participants were required to respond “up” or “down” to the direction which the arrow is pointing to ignoring its location. 50% of the trials within each block were congruent (e.g., an arrow above fixation pointing upward) and 50% were incongruent (e.g., an arrow above fixation pointing downward). These two types of trials were randomly intermixed within each block. Each display was preceded by a 1000msec white central fixation cross. The stimulus was presented for 150msec. The time for response was unlimited. The ITI was 1500msec. Participants were presented with two 40-trials "location" blocks followed by two 40-trials "direction" blocks. Each subtask was preceded by 10 practice trials. Figure 43 illustrates the displays.

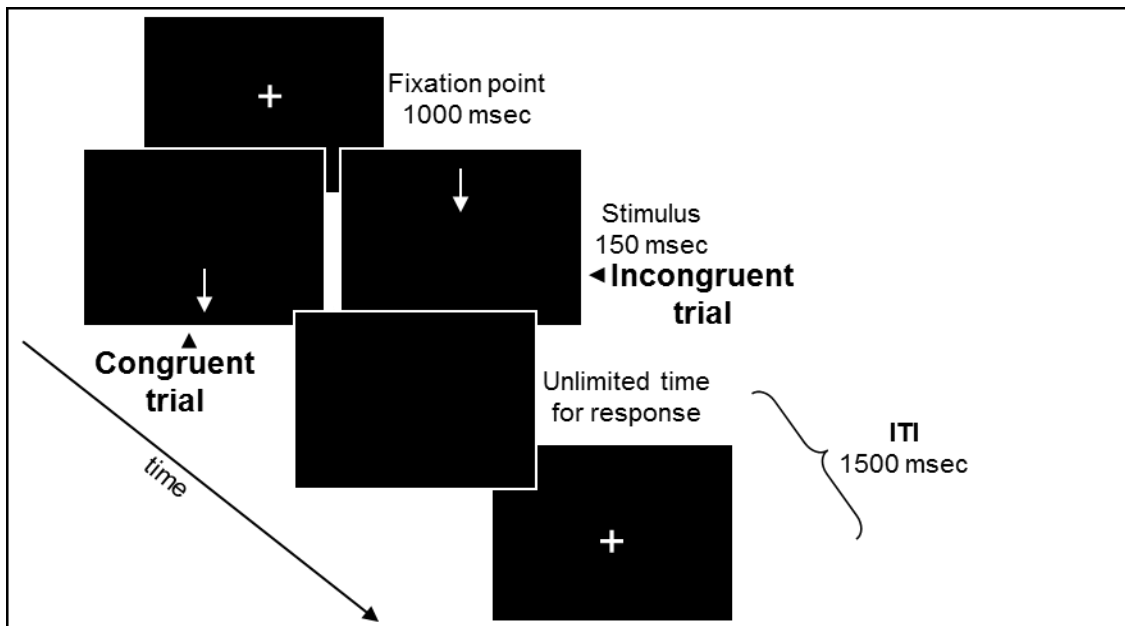


Figure 43: Executive Attention - Assessment

6.2.4. Procedure

One week before the start of the intervention period, the BCoS test³ (Humphreys et al., 2012) was administered to all stroke participants (duration approximately one hour). The BCoS instrument has been developed to enable comprehensive and efficient screening of post stroke cognitive function and maximises inclusion for stroke survivors by being ‘aphasia and neglect friendly (i.e. tests are designed not to be contaminated by aphasia or neglect) and time efficient

³ Appendix 1

(to minimise testing time). It assesses five primary domains of cognition: attention and executive function, language (spoken and written), memory (orientation in time and place, longer term verbal recall and recognition, and task recognition), number skills (reading, writing and calculations) and praxis and action (visuo-spatial construction, everyday multiple task construction, gesture production – recognition – imitation).

Also one week before the intervention a computerized assessment was conducted. The following scales were also obtained: Barthel Index (Mahoney and Barthel, 1965), MoCA (Montreal Cognitive Assessment) (Cumming, 2011), NIHSS (National Institute Health Stroke Scale) and HADS (Hospital Anxiety Depression Scale) (Zigmond, 1983). One week post intervention all the above were re-measured.

The experimental patient group was compared with the healthy normal controls for their performance on computer-based attentional tasks pre- and post-intervention. Here we ask whether the patients not only showed improvement but also whether they improved to a normal level after the intervention. The patient controls were invited in for regular cognitive assessments (but not training) in the period between the initial assessment and the follow-up, controlling for general engagement with therapists during the intervention period. These control patients were compared with the experimental patient group on the BCoS test battery, to assess if the intervention selectively boosted performance in the experimental group.

Table 11: Participant groups and testing schedule

| Participant groups and schedule | | |
|---|--|---|
| Sub-acute stroke survivors (experimental group) | Control group of stroke survivors (age matched) | Control Group of healthy individuals (age matched) |
| 1 week prior to intervention: computer assessment and behavioural tests 10 days of intervention 1 week post intervention: computer assessment and behavioural tests | BCoS (behavioural) test twice to assess natural recovery | Computer assessment twice (3 weeks apart) |

6.3. RESULTS

6.3.1. General Outcome Measures

Table 12 presents data on the Barthel Index, MoCA NIHSS and HADS assessments, pre- and post-intervention for the experimental patient group.

| Outcome Measure | Mean Pre (std) | Mean Post (std) |
|------------------------|---------------------------|----------------------------|
| Barthel Index | <i>14.8 (1.6)</i> | <i>15.6 (1.4)</i> |
| MOCA | <i>21.6 (4.1)</i> | <i>24.7 (1.7)</i> |
| NIHSS | <i>23.6 (1.8)</i> | <i>24.5 (1.7)</i> |
| HADS depression | <i>4.0 (1.7)</i> | <i>3.9 (1.6)</i> |
| HADS anxiety | <i>5.6 (1.5)</i> | <i>5.2 (1.6)</i> |

Table 12: Pre and Post intervention General Outcome Measures

Statistical analysis was performed on the general outcome measures (pre and post) and returned significant improvements for the Barthel Index ($t(7) = -2.393$, $p = 0.048$), the MoCA ($t(7) = -2.818$, $p = 0.026$), and the NIHSS ($t(7) = -2.497$, $p = 0.041$). There was no significant change for the HADS scale and this might be due to the scores being in a range of ‘normal’ values.

6.3.2. Tests on training tasks: Computer Assessment.

For the selection, orienting and executive attention tasks mean accuracy rates were calculated for the different conditions in each task (i.e. each display size in the selective attention task, valid and invalid trials in the orienting attention task, etc.). In order to eliminate trials in which exceptionally long latencies were obtained mean Reaction Times (RTs) for correct responses were calculated for each condition after excluding (a) trials in which the RT exceeded 4000 ms; (b) trials in which the RT deviated more than 2 STDs from the participant's mean RT. In the sustained attention task, variability of the responses represents the theoretical construct measured (i.e., the ability to sustain attention over time).

6.3.2.1. CCPT (Sustained attention – Conjunctive Continuous Performance Test)

Performance of the experimental patients on the CCPT assessment task was compared with the performance of the healthy control group that underwent the pre and post assessment only, using the RT's and the STD values for the 2x2 ANOVA. There was no main effect in the RT analysis for the pre and post intervention ($F(1, 14) = 2.390, p=0.144$) or for the interaction between pre and post intervention and group ($F(1, 14) = 2.914, p=0.11$) but there was a significant effect for group ($F(1, 14) = 7.869, p=0.013$). The patients were slower than the healthy controls. However, for the analysis for the standard deviation of RT's returned both significant main effects of pre post intervention ($F(1, 14) = 8.719, p=0.01$) and group ($F(1, 14) = 12.262, p=0.004$) and a significant interaction of pre-post intervention and group ($F(1, 14) = 17.291, p=0.001$). To break down this interaction separate ANOVAs were run for each group. For the experimental group there was a significant effect of time (pre vs. post) of $F(1, 7) = 21.974, p = 0.002$. For the control group no significant effect was found. Figures 44a and 44b present the data. At both the pre- and post-intervention tests the experimental patient group was more variable than the non-lesioned controls (pre: experimental: mean=254.5 STD=106.8, control: mean=67.7, STD=26.37, post: experimental: mean=134.5, STD=53.2, control: mean=88.1, STD=85.7) (paired samples t-test between groups pre: $t(7) = 5.094, p=0.001$ and post: $t(7) = 1.543, p=0.167$), but the interaction indicates that this effect was larger pre- than post-intervention.

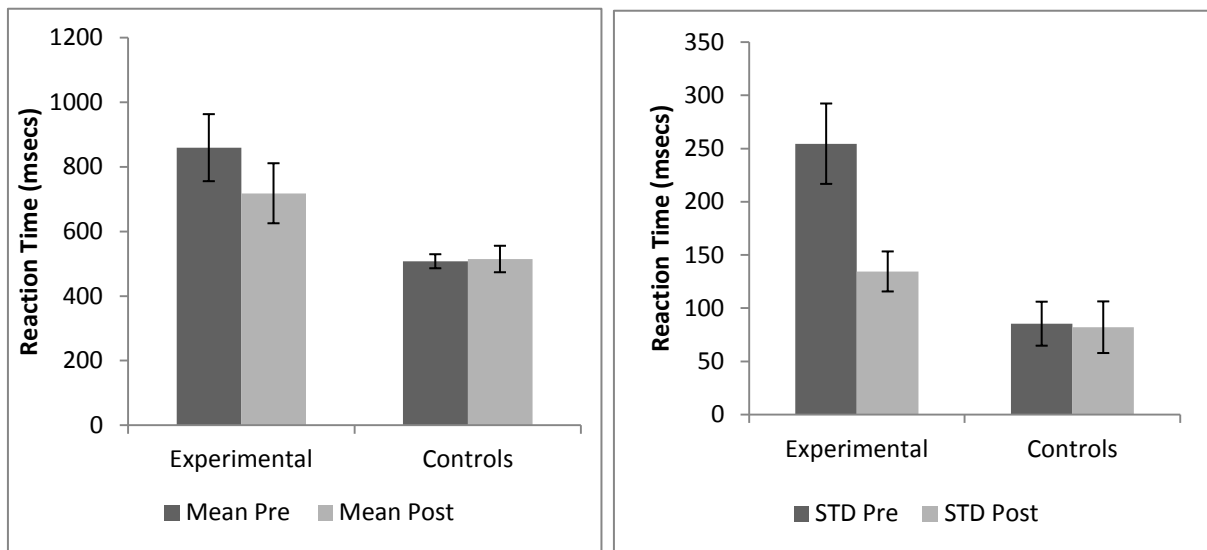


Figure 44: Pre and Post CCPT task performance for experimental and control participants in a) Reaction Times and b) Standard deviations. Error bars depict 1 SE on each side of the mean

6.3.2.2. Conjunction search (Selective Attention)

The data were assessed in a 2x2x5 factor ANOVA with the factors being pre- vs. post-intervention, display size (the number of distractors present: 4, 8, 16, 32 and average) and group (patient vs. the healthy control group). For the mean RTs there was a reliable main effect of group ($F(1, 14) = 21.506$, $p < 0.001$), of pre- vs. post-intervention ($F(1, 14) = 17.908$, $p = 0.001$) and display size ($F(4, 56) = 16.377$, $p < 0.001$). There were also interactions between pre/post and group ($F(1, 14) = 7.350$, $p = 0.017$), pre/post and the display size ($F(4, 56) = 28.871$, $p < 0.001$) and between pre/post, display size and group ($F(4, 56) = 20.097$, $p < 0.001$).

The interaction was broken down by running separate ANOVAs for the experimental and control groups. For the experimental group there was no main effect of pre-post RT's ($F(1, 7) = 0.705$, $p = 0.429$) but there was a significant effect of displayed objects ($F(4, 28) = 3.135$,

$p=0.03$) and a significant interaction of pre-post and displayed objects ($F(4, 28) = 23.689$, $p<0.001$). For the control group there were not a significant main effect of pre-post testing ($F(1, 7) = 1.943$, $p<0.206$) but only a reliable main effect of for displayed objects ($F(4, 28) = 52.125$, $p<0.001$). Also, there was no significant interaction of pre-post and displayed objects ($F(4, 28) = 0.301$, $p<0.875$). Figures 45a and 45b illustrate the results. The experimental patient group improved in overall RT's and also showed reduced effects of the number of displayed objects across the pre and post-training sessions. The healthy controls showed no effect of repeated testing (pre vs. post) and the effects of the number of displayed objects remained.

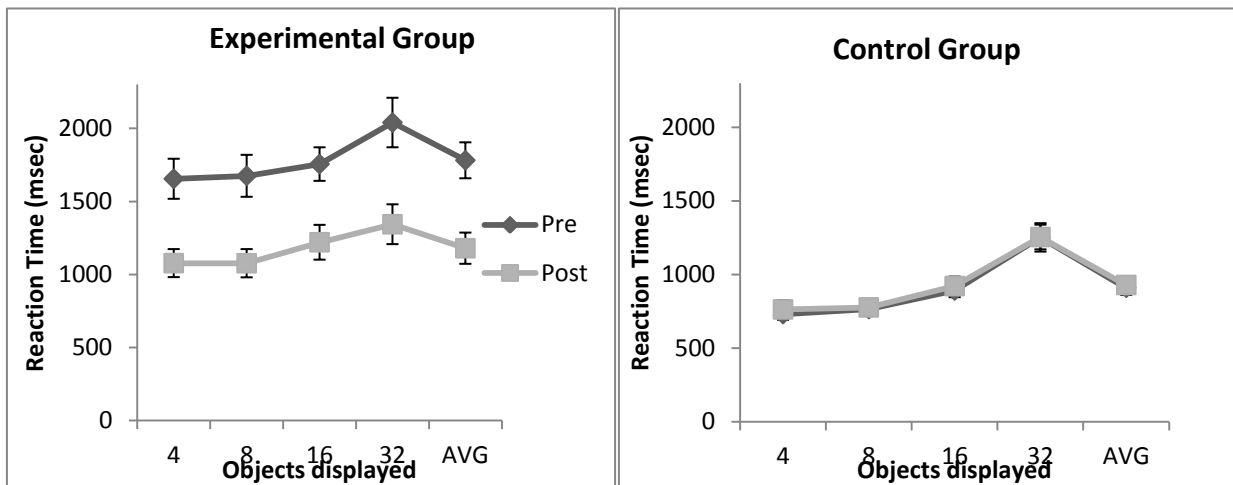


Figure 45a and 45b: Pre and Post CPAT performance in Selective attention's task for a) experimental and b) control participants. Error bars depict 1 SE on each side of the mean

For search accuracy significant results were returned for: pre/post ($F(1, 4) = 12.273$, $p = 0.004$), display size ($F(4, 56) = 3.617$, $p = 0.011$). There was no significant main effect of group ($F(1, 4) = 2.095$, $p=0.17$) and no interactions. Figures 46a and 46b.

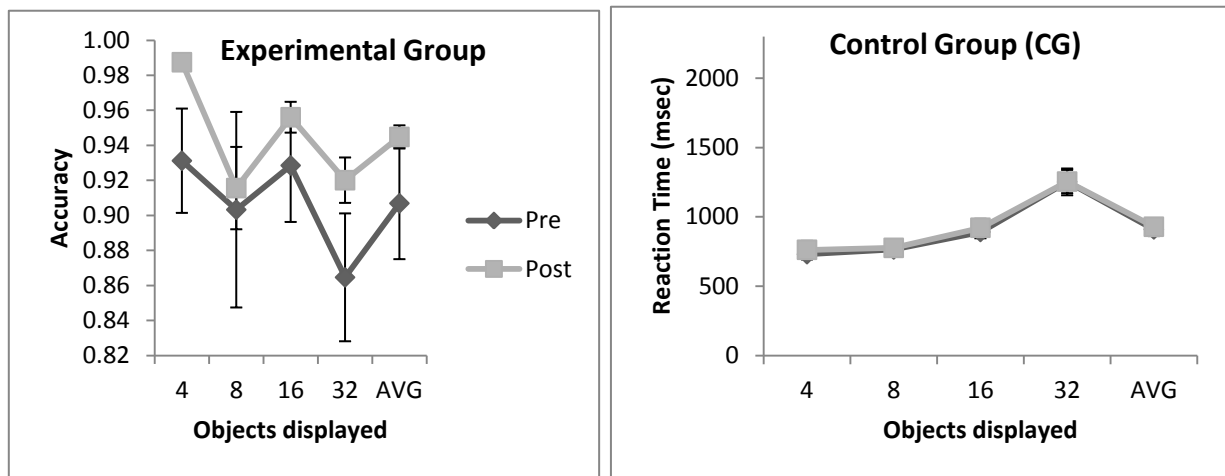


Figure 46a and 46b: Pre and Post CPAT task performance for a) experimental and b) control participants in accuracy search tasks. Error bars depict 1 SE on each side of the mean

6.3.2.3. Attentional Orienting (Posner Task)

The third task was the Attentional Orienting (Posner) Task. Cue validity, pre/post and group were factors. For the RT data there were significant main effects of group ($F(1, 14) = 20.306, p < 0.001$), pre/post ($F(1, 4) = 28.362, p < 0.001$) and cue validity ($F(1, 4) = 10.700, p = 0.006$). There was a reliable interaction between cue validity and group ($F(1, 14) = 14.558, p = 0.002$). No other interactions were significant. The experimental patient group showed a larger effect of cue validity than the controls, and this remained presented across the pre and post-training intervals. RT's improved across time. The data are shown in Figures 47a and 47b.

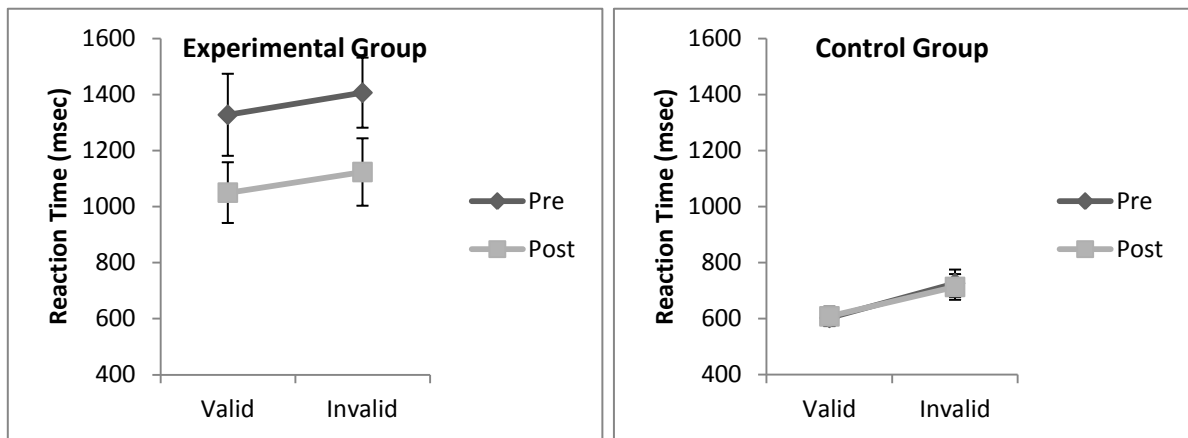


Figure 47a and 47b: Pre and Post CPAT task performance for a) experimental and b) control participants in attention orienting tasks. Error bars depict 1 SE on each side of the mean

For the same task the accuracy analysis returned a significant main effect of group ($F(1, 14) = 6.830, p = 0.02$) and no other significant main effects or interactions. Although the patients improved their overall RTs they continued to show larger validity effects than the controls.

6.3.2.4. Executive Attention Task

The fourth task was the executive attention task (Direction – Location Stroop-like – Flanker task). A mixed design ANOVA was conducted with the factors target-distractor congruency, target level (location – direction), pre/post training and group. For the RT data there were reliable main effects of group ($F(1, 14) = 14.998, p = 0.002$), target-distractor congruency ($F(1, 14) = 50.950, p < 0.001$) and pre/post ($F(1, 14) = 11.401, p = 0.005$). There was an interaction between time and group ($F(1, 14) = 11.989, p = 0.004$). For the experimental group

there was a significant effect of time ($t(7) = 3.607, p = 0.009$). No significant effects were found for the control group ($t < 1.0$). No other significant interactions were returned. Figures 48a and 48b

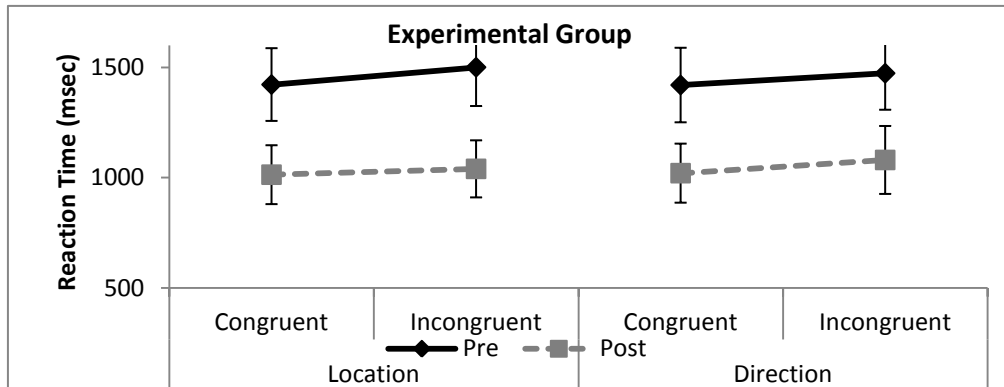
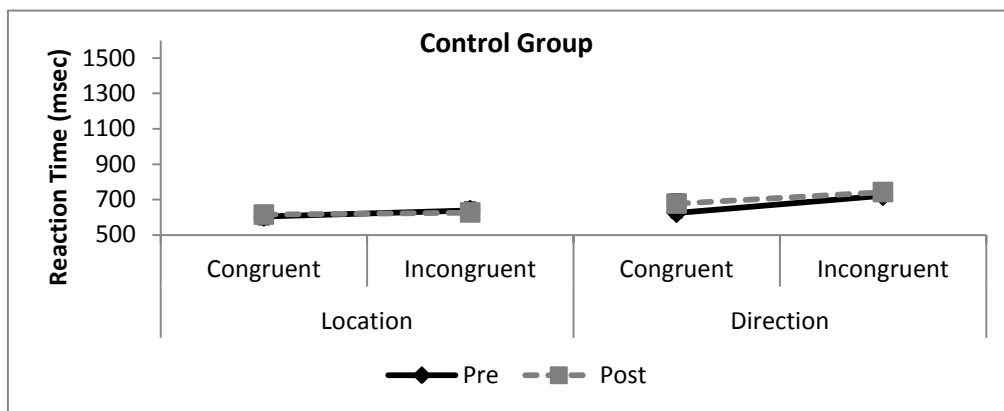


Figure 48a and 48b: Pre and Post CPAT task performance for a) experimental and b) control participants in reaction times of executive attention task. Error bars depict 1 SE on each side of the mean



For the accuracy data there were significant main effects of group ($F(1, 14) = 14.193, p = 0.002$), target-distractor congruency ($F(1, 14) = 12.471, p = 0.003$) and pre/post ($F(1, 14) = 13.186, p = 0.003$). No further interactions were returned. The results are shown in Figures 49a and 49b. The patients alone showed a significant improvement in RT's over time, but there was no difference in the magnitude of flanker interference for the patients and the controls and interference effects did not change over time.

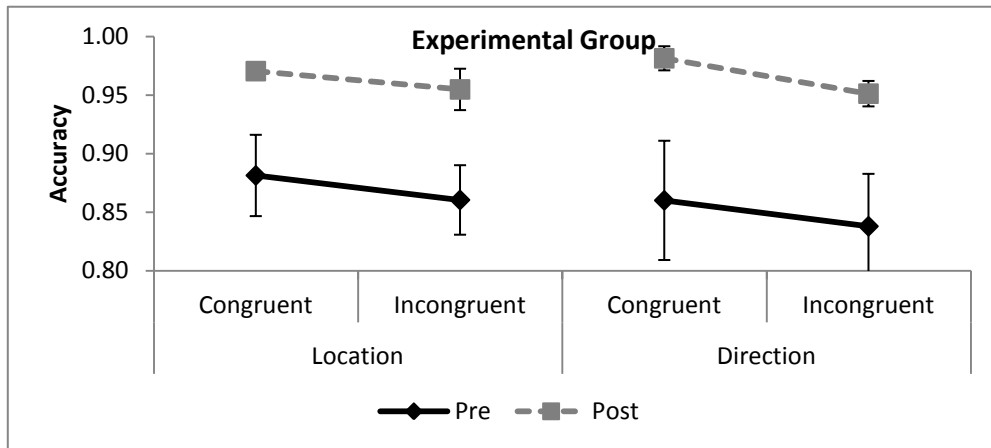
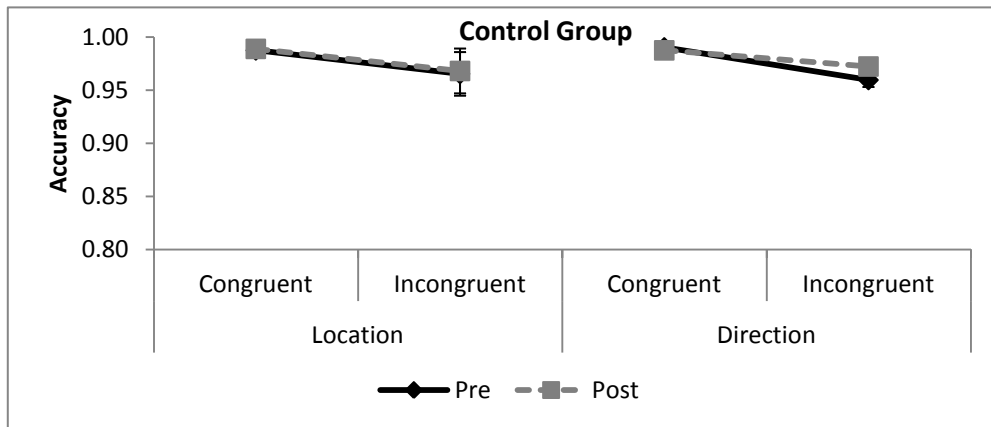


Figure 49a and 49b: Pre and Post CPAT task performance for a) experimental and b) control participants in accuracy executive attention task. Error bars depict 1 SE on each side of the mean



6.3.3. Behavioural assessment – BCoS battery test.

Scores on the BCoS battery were simplified by averaging performance across the subtests within each domain (attention and executive function, language, memory, number processing and praxis). This was done by calculating a z score for each test for each patient, based on the mean and standard deviation of performance for the normal control participants reported by Humphreys et al. (2012) BCoS ($z = (\text{patients score} - \text{mean of controls}) / \text{standard}$

deviation of controls). The z scores for the tests within each domain were then averaged to create a single z score per domain (see the Appendix for a list of the individual tests). Results from BCoS for the experimental group were compared with data derived from 8 matched neurologically damaged individuals who had attended regularly to take part in experiments at Birmingham University during the intervention period but who did not take part in the intervention.

Normalised data from the five domains (attention, language, memory, number skills and praxis) of BCoS were analysed using a repeated measure analysis (5x2x2 ANOVA) with the factors of group (experimental – controls), time (pre-post) and domain. There were no significant main effects of group (experimental vs. control), domain or pre/post intervention. There were significant interactions of pre-post and domain ($F(4, 56) = 4.784, p = 0.02$) and of pre-post, domain and group ($F(4, 56) = 3.621, p = 0.011$). To break down the three-way interaction we ran two separate ANOVAs, one for each group. For the experimental group there was a significant interaction of time by domain ($F(4, 28) = 9.341, p < 0.001$) and no significant main effects. For the control group the same ANOVA returned no significant effects or interactions. Thus there was no effect of the re-test of the BCoS on the control group but there was on the experimental patient group. The interaction of domain and time, for the experimental group, was due to the improvements with time varying across the domains, with the effect being somewhat smaller for the domain of praxis relative to the other domains. However the effect of time was significant for each domain for the experimental group (for attention and executive function: $t(7) = -3.229, p = 0.014$, language: $t(7) = -4.540, p = 0.003$, memory: $t(7) = -3.439, p = 0.011$, number skills: $t(7) = -4.881, p = 0.002$, and praxis: $t(7) = -4.279, p = 0.004$). Figures 50a - 50e present the results.

Interestingly post-training the experimental patient group fell within 0.5 SD of the normal controls for their age, taken from BCoS (Humphreys et al., 2012).

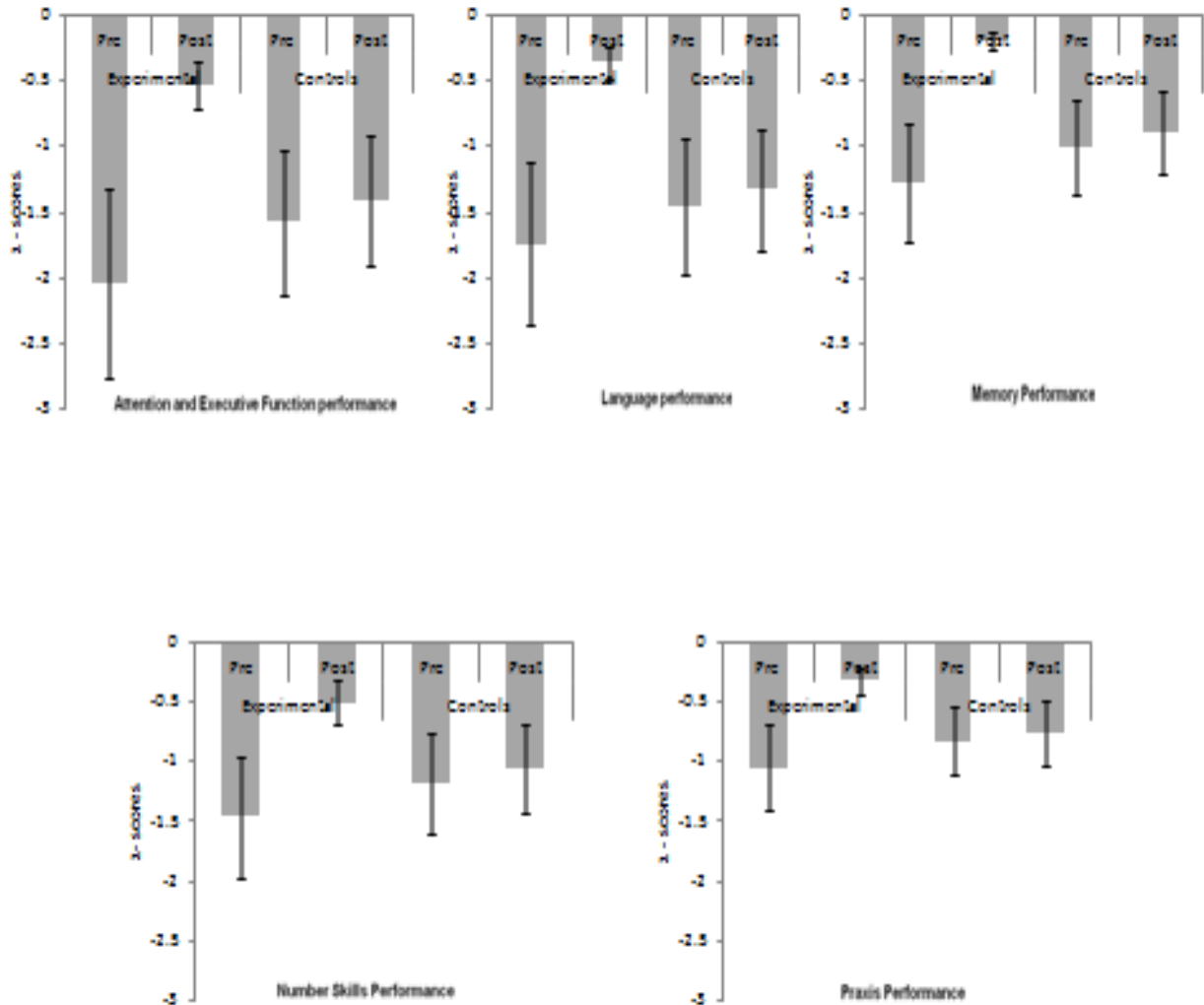


Figure 50: BCoS Performance per Task per GroupBCoS. The data across Figures 50a-50e are plotted as Z scores relative to the performance of age-matched controls reported by Humphreys et al. (2012). A negative score indicates a case where the patients are worse than the age-matched controls. A z score of 0 conforms to the mean of the age-matched controls.

The control data shown in the Figures are provided by the control group of stroke survivors who did not undergo attentional training.

6.4. DISCUSSION

We report highly positive results from ten sessions of computerised progressive attentional training (CPAT) on cognitive performance after stroke. As has previously been shown in studies of computer-based ‘brain training’ (e.g, Owens et al., 2012) the patients improved on the tests they were trained on. This was not merely an effect of being tested twice, since there were typically minimal improvements for the healthy control participants. The training did not simply speed overall performance but they also reduced patient variability on the test of sustained attention and they reduced the effects of the display load in the conjunction search task. The result for sustained attention suggests that patients become better able to maintain their concentration on the target detection task following practice. The result for the conjunction search task indicates either that those patients improved at guiding their search to targets and/or at rejecting distractors that were attended – either would reduce the effects of the distractors on performance.

The results for the other computer-based assessments, which were not practiced, were less clear. The patients improved their overall reaction times on the test of orienting attention and the flanker task, but the effects of cue validity and of flanker interference did not change. The results of the flanker task should be viewed with caution since the patients did not show a larger interference from the flanker than the healthy controls even prior to training, so it is not clear that there was a major deficit in inhibitory components of executive function in the first place (Friedman and Miyake, 2004). However in the attentional orienting task the patients did show a larger effect of cue validity and this remained after training even though overall RT’s improved for the patients. This indicates that the costs from attentional disengagement were not strongly

modified by the training. It may be that a disengagement problem remains as a residual impairment, even when other aspects of performance improve.

Although there was not clear evidence for generalisation of training on the attentional cueing and flanker experiments, there was evidence for generalized effects of training on the BCoS. We divided the BCoS into its 5 main domains and assessed if there was general improvement across each domain in the experimental patient group relative to a patient group who underwent other cognitive tests across the training time period. Here there was good evidence for improvements in 4 domains that were not the subject of specific training in the CPAT procedure: language, memory, number skills and praxis (though the gains were less in the praxis domain, they nevertheless remained significant). Moreover, the gains are not merely statistical; the experimental patient group improved so that they fell within 0.5 SD of the mean for healthy aged matched controls while the control patients were over 1 SD away on average. This suggests that there was a real gain in aspects of cognitive processing. This is also supported by the improved scores the patients showed in the MoCA and the NIHSS – with the latter in particular pointing to a functional gain from the training.

What were the critical factors underlying these effects? This is difficult to conclude from the present data as the training programs were established to include several different aspects of attention in order to increase the likelihood of some training effect emerging. A key issue for future research will be to try and refine the training procedure so that only the critical aspects of performance are focused on. However one of the noteworthy results here is in the memory domain where the mean performance of the experimental patient group was initially 1.74 SDs from the norm and this improved to be just 0.35 SDs away. The memory tests in the BCoS require relatively few additional processes (e.g., visual scanning, selection of local vs. global

shapes) beyond holding and consolidating items in memory. The data suggest that cognitive training enhanced these processes.

One way to conceptualise these results is that the training tasks facilitated some domain-general processes which can be applied to a range of different input and output modalities - such as the ability to sustain attention, to stay focused on the task by holding targets in memory, and the ability to switch between stimuli. Improvements in such domain general processes should support the better maintenance of items in memory, the processing of sentences, simple calculations and so forth. Hence there can be generalization into more domain-specific processes in language, memory, number skills and praxis.

The major limitation of the present research is that it involved only a small number of patients and the full impact of the training can only be judged by a larger-scale randomised trial with a control group randomised into a procedure where therapist's attention is matched but the demands on the attentional processing of the patient is reduced. It would also be useful to give the functional measures of performance to patients allocated to the experimental and control groups so that we can match for training-specific effects on aspects of everyday life, Despite these limitations though the present results hold promise that attention-training of stroke patients can lead to functional benefits in cognition and everyday life.

CHAPTER 7: GENERAL DISCUSSION

7.1. DISCUSSION

This thesis has reported four empirical chapters examining effects of mirror therapy (MT) and functional electrical stimulation (FES) on motor and attentional recovery in patients.

In the first experimental chapter (Chapter 2) the effects of MT on hand function and motor extinction in chronic stroke population were investigated. In this research project experimental participants attended weekly MT sessions over a prolonged period of six months. Previous studies of MT in stroke survivors have investigated effects following MT courses of up to eight weeks of application. However, given that MT can be used in home environment and that many patients will receive little prolonged hospital treatment, it is important to develop therapies that can be self-applied over the long-term. MT is a prime candidate for this.

Here MT intervention was applied for six months with chronic stroke patients. The results showed an improvement in functional ability as depicted by the ARAT outcome measure. Participants in the experimental group were able to perform better in reaching and grasping tasks following MT intervention compared to chronic stroke survivors in the control group. In addition, patients that were more impaired in the start of the intervention's protocol period improved more compared to the more functional participants. A second positive result in this study was that patients who underwent a prolonged period of MT performed better than controls in a unimanual tapping task with the impaired hand but this did not extend to the use of the hemiparetic arm during bimanual finger tapping. This result suggests that motor extinction, underutilization of the

impaired hand during bimanual conditions, cannot be altered by MT. It may be that attentional constraints on action continue to operate even in the presence of improved unimanual motor function in patients.

In the next chapter (Chapter 3) the effects of home based MT were examined. This time MT was applied daily for over a period of four weeks in the home. There was in addition weekly monitoring of practice at a clinical setting. As in Chapter 2, there were functional improvements measured using the ARAT in favour of the experimental group. Again performance was examined in both uni- and bimanual conditions. Although both sets of actions improved, the ratio of unimanual to bimanual tapping did not vary – i.e., there was no differential improvement in motor extinction. The data consolidate the argument that MT has an effect on motor function which cannot be generalised to improvement in the allocation to the affected limb under bimanual conditions (as there should then be differential improvement for bimanual actions).

In Chapter 4 I examined the neural basis of MT effects. The aim was to identify any evidence for the recruitment of new neural routes/areas before and after a six weeks course of intensive (5 days a week) application of MT on top of the standard NHS regime. Early subacute stroke survivors were examined because neural plasticity is likely to be larger in this population compared to chronic stroke survivors (Barbro, 2000). Again the ARAT score improved differentially after MT though changes were not observed on the more general Barthel Index or mood (i.e. anxiety and depression in HADS scale). fMRI imaging of the patients before and after MT intervention revealed changes in both the intact and affected hemispheres of the brain. Bhasin et al. (2012) have also reported changes in the ipsilateral, non-lesioned hemisphere. I found changes primarily in motor related areas: the SMA and postcentral sulcus, although there

were also changes in the calcarine gyrus and the precuneus. Similarly, Hamzei et al (2012) found that following a short MT course the participants of the mirror group increased activation of the ipsilateral (contralesional) to the moving (impaired) hand in regions of the primary sensorimotor cortex. The authors explained these results by naming MT as a tool to connect both hands across the two hemispheres. In addition to this, I found increased activation in the impaired hemisphere and more specifically in regions of the rolandic operculum, pre and postcentral sulcus, cuneus and parietal supplementary areas. These changes in the lesioned hemisphere are directly related to research conducted by Michielsen et al. (2012) who also identified increased activation in the impaired hemisphere following MT. The areas reported in both cases involved motor and somatosensory regions.

Another specific result in Chapter 4 concerned bimanual tapping. It was noticed that, during the bimanual tasks following MT there was a decrease of activation in the lesioned areas of SMA, postcentral gyrus and frontal and inferior parietal cortex. This decrease in activation might reflect some relative benefit in using the affected limb under bimanual conditions – though behaviourally any differential effects on behaviour were difficult to observe (see Chapters 2 and 3).

Chapter 5 switched from MT to examine the effects of functional electrical stimulation (FES). Chronic stroke participants underwent a four week intervention protocol of FES four times per week, which helped the participant perform functional tasks of reaching and grasping – releasing objects. Effects on movement and on visual attention (visual neglect) were examined, as previous work indicates that attention in patients can be modified by FES (Harding & Riddoch, 2009). A wide variety of outcome measures were used: ARAT, tapping task, grip force,

apple cancellation (neglect assessment) and fMRI. Improvements on the ARAT and on apple cancellation (as a measure of neglect) were obtained not only pre and immediately after the end of the intervention but also at six months follow up. This provides strong evidence for long-term functional benefits in both motor and attentional functions. As for MT, however, there was not strong evidence for differential improvement on bimanual action. Limitations on motor attention remained. Harding and Riddoch (2009) suggested that the internal body schema might be boosted following a course of FES and these cortical changes may lead to new visual and body space representations. This might ameliorate neglect but not necessarily bimanual action.

The above behavioural changes were linked to changes in brain activity as depicted by fMRI. Participants were asked to squeeze an MRI friendly device with their impaired or intact hand as their brains were scanned. There was a trend across participants towards a larger activation of regions BA4 and BA6 (primary motor cortex) and the supplementary motor area (SMA) in the lesioned side of the brain. Interestingly patients with impaired motor cortex tended to recruit more the contralesional (intact) motor cortex along with peri-lesional regions of the affected hemisphere. In contrast, patients with spared motor cortex showed increased activation of the lesioned primary motor cortex. In a similar study by Johansen-Berg et al. (2002) participants without damage to motor cortex underwent an exercise rehabilitation regime after which it was reported that there was changed activation in the premotor and secondary somatosensory cortex on the affected side.

The last experiment in this thesis (Chapter 6) describes the application of a computer intervention paradigm previously used in children with ADHD in early subacute stroke survivors. This project took place at a community NHS hospital for ten sessions over a period of 2 weeks

and the aim was to identify improvements on cognitive performance. The computerised progressive attentional training (CPAT) was used and patients were tested not only on the trained tasks (Owens et al., 2012) but also on a range of other tests (e.g., the Birmingham Cognitive Screen (BCoS)). CPAT was found to be beneficial for tasks measuring sustained attention (maintain concentration) and conjunction search (searching for targets – rejecting non targets, distracters), which were part of the training set. In addition, though, there was a generalised improvement following CPAT training across different tests of BCoS. Clear improvements were found in: language, memory, number skills and praxis (with the least significant effect on praxis). Indeed, the performance of the trained patients post intervention fell within 0.5 SD of the mean for healthy aged matched controls when, at the same time, control patients (not given training) remained over 1 SD away from the controls. Our general outcome measure, the BCoS, proved to be sensitive to generalised improvements following the intervention. These benefits could be used during the rehabilitation period to improve a patient's participation in therapy sessions. For example the improvement found in sustained attention may make a stroke survivor better able to concentrate for longer periods of time to a specific task and this may be of general benefit to therapy.

The work presented in this thesis would be incomplete if the importance of combining different interventions were not emphasized. What is important both for clinicians and researchers is to improve stroke survivor's potential to return to pre stroke activities of daily living. The need to understand what types and intensities of rehabilitation therapies result in optimal and cost-effective outcomes has always been a driving force behind research. According to the results of this study and as a recommendation for future directions it is important to

rehabilitate stroke survivor in a holistic way. Therefore a combination of the suggested interventions (MT, FES and CPAT) on top of patients' rehabilitation regime may potentially improve the functional outcome and succeed better results for patients' benefit.

In order to identify the importance of the findings of this thesis an effect size calculation took place across the different studies. More specifically an effort to compare size effects from tapping performance and ARAT test have been made for the following studies: a) MT in chronic stroke population in a low frequency (weekly sessions) over a six months period of intervention (Chapter 2), b) MT in chronic stroke population in a high frequency (five sessions per week) over a short period of four weeks (Chapter 3), c) MT in acute stroke survivors on a daily basis (five sessions per week) over a short period of four weeks trial (Chapter 4) and d) FES in chronic stroke survivors four days a week over a period of four weeks. Using the standardised measurements of the ARAT task and the tapping performance it was possible to compare the effect sizes between the different studies although different scales of measurements (i.e. time of tapping) were used across the studies. The effect size was calculated as: the value of Cohen's 'd' using the means and standard deviations of the two groups (treatment and control):

$$\text{Cohen's } d = M_1 - M_2 / \sigma_{\text{pooled}}$$
$$\text{where } \sigma_{\text{pooled}} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$$

Tapping performance in the above studies returned the following effect sizes shown in Table 13 for the impaired hand pre and post intervention

| | | | | |
|-------------|--|--|--|---|
| Experiment | a)MT chronic weekly sessions over six months | b) MT chronic daily sessions over four weeks | c) MT acute daily sessions over four weeks | d) FES chronic daily sessions over four weeks |
| Cohen's 'd' | -0.89 | -0.59 | No data collected | -2.91 |

Table 13: Effect size per study for Tapping Performance

From the above results and using absolute values the greatest effect size in tapping performance can be noticed in the FES study followed by the MT over a long period of application and smaller effect size was associated with MT over a short period of time. No tapping data were collected for the MT in acute stroke survivors.

ARAT performance in the above studies returned the following size effects for the impaired hand pre and post intervention

| | | | | |
|-------------|--|--|--|---|
| Experiment | a)MT chronic weekly sessions over six months | b) MT chronic daily sessions over four weeks | c) MT acute daily sessions over four weeks | d) FES chronic daily sessions over four weeks |
| Cohen's 'd' | -1.23 | -1.07 | -1.13 | -1.82 |

Table 14: Effect size per study for ARAT

From the above results and using absolute values the greatest effect in ARAT performance can be identified again in the FES study followed relatively closely by the MT intervention protocols with a slight greater effect in the acute population. Again in the chronic population it seems that it is more important to apply a treatment for longer rather than with higher frequency. Although the above size effects provide useful directions for future research in order to be validated randomized controlled trials in a larger scale are required.

7.1.1. Limitations

This thesis has limitations that will be discussed below in relation to each experimental chapter. In Chapter 2 the prolonged course of MT was applied to just a small number of participants ($n = 7$) and this constrains generalization of the findings. Also, the intervention involved (prolonged application of MT but only once a week) may not be suitable for the majority of patients. This limitation was overcome in Chapter 3 where MT was applied for a short course of four weeks in the patient's home. Again, though, the number of the experimental participants in the study ($n = 8$) was small and this limits generalization of the positive outcomes. Chapter 4 involved the application of FES. Here there was a lack of control participants to

exclude natural recovery – although the fact that FES was applied to stable, chronic stroke survivors makes natural recovery unlikely. In addition, the number of participants was small (n = 5). It also has to be mentioned that in the experimental chapters 2, 3 and 5 and during the tapping task only participants allocated to the experimental group were performing the weekly tapping sessions where controls only performed the pre and post intervention period tapping sessions. It needs therefore to be acknowledged as a potential confound with the treatment of interest that participants in the experimental group may have improved their tapping performance due to learning – practicing effect. Although this unlikely in the future the control condition needs to be improved by adding the tapping weekly sessions in all participants. This work may best be considered as providing pilot data for a larger scale research study. Finally in Chapter 6 the computer based intervention was given to just a small number (n = 8) of patients. Though the results were promising, the procedure requires a larger-scale randomised control trial before a more complete judgement can be made. Despite these limitations though the reported effects indicate how it is possible to generate evidence base for the rehabilitation of motor and attentional problems after stroke, applicable both to the subacute and chronic stages of the disability.

7.1.2. Pragmatism in rehabilitation

Stroke is one of the most serious causes of long term disability. It is well known between clinicians that a one size fits all approach cannot be applied in the rehabilitation of stroke and that

each patient needs to be approached through personalised strategies. Although both MT and FES did not significantly change the impairment of using both hands simultaneously, both interventions improved functional performance in patients. ARAT improvement, as observed here, can be translated to better functional reaching and grasping which in turn is one of the most important goals for the paretic upper limb throughout the rehabilitation period. MT (Chapters 2-4) is a generally well received intervention and there were no adverse reactions during all the above experiments. Patients could be included as long as they had the ability to concentrate and they were able to perform movements in front of the mirror. Feedback received from patients was unanimously positive even from the first session.

The positive outcomes observed in motor strength and ARAT performance after FES indicate that it too can be a useful tool for rehabilitation that can even have generalised effects on attention (visuomotor neglect). Unlike MT, FES will require more input from clinicians, however, to ensure that stimulation is appropriately applied.

It is important for the clinician to take into account not only motor and attentional performance but also other cognitive impairments that can impact on recovery after stroke. In Chapter 6 CPAT, a computerised intervention was found to be helpful in improving different aspects of cognition. This may be usefully employed alongside more conventional therapy techniques in order to boost how receptive a patient may be to other forms of intervention.

7.1.3. Concluding remarks and future directions

This thesis has focused on motor and cognitive impairments that follow a stroke. The aim of this thesis was to provide novel evidence of possible ways to promote positive rehabilitative outcome. Prior to this work mirror therapy, functional electrical stimulation and computer based interventions have been used with stroke survivors so the novel aspects of the interventions here concern the particular protocols used, the application in both subacute and chronic stroke, and the tests of bimanual as well as unimanual action. The work is promising but now needs to be assessed through larger-scale RCTs. The thesis also points to the involvement of both ipsilesional and contralesional cortices in the neural recovery of function. How much this depends on the nature of the stroke (e.g., cortical vs. subcortical) remains a question for future research.

REFERENCES

Alon, G. (2013). Functional Electrical Stimulation (FES): Transforming Clinical Trials to Neuro-Rehabilitation Clinical Practice-A Forward Perspective. *J Nov Physiother*, 3(176), 2.

Altschuler, E. L., & Hu, J. (2008). Mirror therapy in a patient with a fractured wrist and no active wrist extension. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, 42(2), 110-111.

Altschuler, E. L., Wisdom, S. B., Stone, L., Foster, C., Galasko, D., Llewellyn, D. M. E., & Ramachandran, V. S. (1999). Rehabilitation of hemiparesis after stroke with a mirror. *The Lancet*, 353(9169), 2035-2036.

Andersson JL, Hutton C, Ashburner J, Turner R, Friston K. Modeling geometric deformations in EPI time series. *Neuroimage*. 2001;13:903–119.

Anguera, J. A., et al. "Video game training enhances cognitive control in older adults." *Nature* 501.7465 (2013): 97-101.

Aziz-Zadeh, L., Maeda, F., Zaidel, E., Mazziotta, J., & Iacoboni, M. (2002). Lateralization in motor facilitation during action observation: a TMS study. *Experimental Brain Research*, 144(1), 127-131.

Barbro B. Johansson (2000). *Brain Plasticity and Stroke Rehabilitation. The Willis Lecture. Special Report. Stroke*. 31:223-230.

Barsi, G. I., Popovic, D. B., Tarkka, I. M., Sinkjær, T., & Grey, M. J. (2008). Cortical excitability changes following grasping exercise augmented with electrical stimulation. *Experimental brain research*, 191(1), 57-66.

Basaran A, Emre U, Karadavut, KI, Balbaloglu O and Bulmus N. Hand Splinting for Poststroke Spasticity: A Randomized Controlled Trial. *Topics in Stroke Rehabilitation*. 2012; 4:329-337.

Ben-Yishay, Y., Diller, L., & Rattok, J. (1978). A modular approach to optimizing orientation, psychomotor alertness and purposive behaviour in severe head trauma patients. *Rehabilitation Monograph*, 59, 63-67.

Bhasin, A., Padma Srivastava, M. V., Kumaran, S. S., Bhatia, R., & Mohanty, S. (2012). Neural interface of mirror therapy in chronic stroke patients: A functional magnetic resonance imaging study. *Neurology India*, 60(6), 570.

Bickerton, W., L., Samson D. Separating Forms of Neglect Using the Apples Test: Validation and Functional Prediction in Chronic and Acute Stroke. *Neuropsychology*. 2011; 5:567-580.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research*, 52(2), 69-77.

Blickenstorfer A, Kleise R. Cortical and Subcortical Correlates of Functional Electrical Stimulation of Wrist Extensor and Flexor Muscles Revealed by fMRI. *Human Brain Mapping*. 2009; 30:963-975.

Bobath B. *Adult Hemiplegia: Evaluation and Treatment*. London, UK: Butterworth Heinemann Medical Books; 1990.

Bosnell, R. A., Kincses, T., Stagg, C. J., Tomassini, V., Kischka, U., Jbabdi, S., Woolrich, M. W., Andersson, J., Matthews, P., M., & Johansen-Berg, H. (2011). Motor practice promotes increased activity in brain regions structurally disconnected after subcortical stroke. *Neurorehabilitation and neural repair*, 25(7), 607-616.

Brazzelli M, Saunders D. Physical Fitness Training for Patients Eith Stroke. Updated Review. *Stroke*. 2012; 43:39-40.

Brodmann K. Vergleichende Lokalisationslehre der Grosshirnrinde. Leipzig : Johann Ambrosius Bart, 1909

Cacchio, A., De Blasis, E., De Blasis, V., Santilli, V., & Spacca, G. (2009). Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabilitation and neural repair*, 23(8), 792-799.

Calautti, C., & Baron, J. C. (2003). Functional neuroimaging studies of motor recovery after stroke in adults a review. *Stroke*, 34(6), 1553-1566.

Carey, L. M., Seitz, R. J., Parsons, M., Levi, C., Farquharson, S., Tournier, J. D., ... & Connelly, A. (2013). Beyond the lesion: neuroimaging foundations for post-stroke recovery. *Future Neurology*, 8(5), 507-527.

Carr JH, Shephard RB. *A Motor Relearning Program for Stroke*. 2nd ed. London, UK: Heinemann Medical Books; 1987.

Carson, R. G. (2005). Neural pathways mediating bilateral interactions between the upper limbs. *Brain Research Reviews*, 49, 641-662.

Cerasa, A., Gioia, M. C., Valentino, P., Nisticò, R., Chiriaco, C., Pirritano, D., ... & Quattrone, A. (2013). Computer-Assisted Cognitive Rehabilitation of Attention Deficits for Multiple Sclerosis A Randomized Trial With fMRI Correlates. *Neurorehabilitation and neural repair*, 27(4), 284-295.

Cha, Y. J., & Kim, H. (2013). Effect of computer-based cognitive rehabilitation (CBCR) for people with stroke: A systematic review and meta-analysis. *NeuroRehabilitation*, 32(2), 359-368.

Chae J, Bethous F. Neuromuscular Stimulation for Upper Extremity Motor and Functional Recovery in Acute Hemiplegia. *Stroke*. 1998; 29:975-979.

Chae J., Yu D. (2000). A Critical Review of Neuromuscular Electrical Stimulation for Treatment of Motor Dysfunction in Hemiplegia. *Assistive Technology*. 2000; 12:33-49.

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., Pasquina, P. F., ... & Tsao, J. W. (2007). Mirror therapy for phantom limb pain. *New England Journal of Medicine*, 357(21), 2206-2207.

Christensen, M. S., & Grey, M. J. (2013). Modulation of proprioceptive feedback during functional electrical stimulation: an fMRI study. *European Journal of Neuroscience*.

Chung, C. S. Y., Pollock, A., Campbell, T., Durward, B. R., & Hagen, S. (2012). Cognitive rehabilitation for executive function problems after brain injury. *Health*.

Cozens, J. E., Punt, T. D., Nuttall C., Henley, C. E., Riddoch, M. J. What is it that pushes neglect? *Physiotherapy Congress*, 2003.

Cramer, S. C., & Bastings, E. P. (2000). Mapping clinically relevant plasticity after stroke. *Neuropharmacology*, 39(5), 842-851.

Crinion, J., Ashburner, J., Leff, A., Brett, M., Price, C., & Friston, K. (2007). Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. *Neuroimage*, 37(3), 866-875.

Cumming, T. B., Bernhardt, J., & Linden, T. (2011). The Montreal Cognitive Assessment Short Cognitive Evaluation in a Large Stroke Trial. *Stroke*, 42(9), 2642-2644.

Cumming, T. B., Marshall, R. S., & Lazar, R. M. (2013). Stroke, cognitive deficits, and rehabilitation: still an incomplete picture. *International Journal of Stroke*, 8(1), 38-45.

Darnall, B. D. (2009). Self-delivered home-based mirror therapy for lower limb phantom pain. *American Journal of Physical Medicine & Rehabilitation*, 88(1), 78-81.

Dewald JPA, Given JD. Electrical Stimulation and Spasticity Reduction: Fact or Fiction. *Physical Medicine and Rehabilitation. State of the Art Reviews*. 1994; 8:507-522.

Dohle, C., Püllen, J., Nakaten, A., Küst, J., Rietz, C., & Karbe, H. (2009). Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. *Neurorehabilitation and neural repair*, 23(3), 209-217.

Duncan, P., Studenski, S., Richards, L., Gollub, S., Lai, S.M., Reker, D., Perera, S., Yates, J., Koch, V., Rigler, S., Johnson, D. (2003). Randomized clinical trial of therapeutic exercise in subacute stroke. *Stroke*, 34, 2173–2180.

Edwards, M. G., & Humphreys, G. W. (2002). Visual selection and action in Balint's syndrome. *Cognitive neuropsychology*, 19(5), 445-462.

Ezendam, D., Bongers, R. M., & Jannink, M. J. (2009). Systematic review of the effectiveness of mirror therapy in upper extremity function. *Disability & Rehabilitation*, 31(26), 2135-2149.

Fillingham, J., Sage, K., & Lambon Ralph, M. (2005). Further explorations and an overview of errorless and errorful therapy for aphasic word-finding difficulties: The number of naming attempts during therapy affects outcome. *Aphasiology*, 19(7), 597-614.

Forouzanfar, T., Köke, A. J., Kleef, M., & Weber, W. E. (2002). Treatment of complex regional pain syndrome type I. *European Journal of Pain*, 6(2), 105-122.

Freysteinson, W. M. (2009). Therapeutic Mirror Interventions An Integrated Review of the Literature. *Journal of Holistic Nursing*, 27(4), 241-252.

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of Experimental Psychology: General*, 133(1), 101.

Fukumura, K., Sugawara, K., Tanabe, S., Ushiba, J., & Tomita, Y. (2007). Influence of mirror therapy on human motor cortex. *International Journal of Neuroscience*, 117(7), 1039-1048.

Funase, K., Tabira, T., Higashi, T., Liang, N., & Kasai, T. (2007). Increased corticospinal excitability during direct observation of self-movement and indirect observation with a mirror box. *Neuroscience letters*, 419(2), 108-112.

Gagnon, L. G., & Belleville, S. (2012). Training of attentional control in mild cognitive impairment with executive deficits: Results from a double-blind randomised controlled study. *Neuropsychological rehabilitation*, 22(6), 809-835.

Gaitán, A., Garolera, M., Cerulla, N., Chico, G., Rodriguez-Querol, M., & Canela-Soler, J. (2013). Efficacy of an adjunctive computer-based cognitive training program in amnesic mild cognitive impairment and Alzheimer's disease: a single-blind, randomized clinical trial. *International journal of geriatric psychiatry*, 28(1), 91-99.

Galea MP. Physical Modalities in the Treatment of Neurological Dysfunction. *Clinical Neurology and Neurosurgery*. 2012 114; 5:483-488.

Garry, M. I., Loftus, A., & Summers, J. J. (2005). Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Experimental brain research*, 163(1), 118-122.

Glanz, M., Klawansky, S., Stason, W., Berkey, C., & Chalmers, T. C. (1996). Functional electrostimulation in poststroke rehabilitation: a meta-analysis of the randomized controlled trials. *Archives of Physical Medicine and Rehabilitation*, 77(6), 549-553.

Glinsky J, Harvey L. (2007). Efficacy of Electrical Stimulation to Increase Muscle Strength in People with Neurological Conditions: A Systematic Review. *Physiotherapy Research International*, 12:175-194.

Gontkovsky, S. T., McDonald, N. B., Clark, P. G., & Ruwe, W. D. (2002). Current directions in computer-assisted cognitive rehabilitation. *NeuroRehabilitation*, 17(3), 195-199.

Gray JM, Robertson I, Pentland B, Anderson S. Microcomputer-based attentional retraining after brain damage: a randomised group controlled trial. *Neuropsychological Rehabilitation* 1992; 2:97-115.

Green, C. S., & Bavelier, D. (2003). Action video game modifies visual selective attention. *Nature*, 423(6939), 534-537.

Green, C. S., Pouget, A., & Bavelier, D. (2010). Improved probabilistic inference as a general learning mechanism with action video games. *Current Biology*, 20(17), 1573-1579.

Grezes, J., & Decety, J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. *Human brain mapping*, 12(1), 1-19.

Gritsenko V, Prochazka A. A Functional Electric Stimulation Assisted Exercise Therapy System for Hemiplegic Hand Function. *Archives of Physical Medicine and Rehabilitation*. 2004; 85:881-885.

Grotta, J.C., Noser, E.A., Ro, T., Boake, C., Levin, H., Aronowski, J., and Schallert, T. (2004). Constraint induced movement therapy. *Stroke*, 35, 2699–701.

Grünert-Plüss, N., Hufschmid, U., Santschi, L., & Grünert, J. (2008). Mirror therapy in hand rehabilitation: a review of the literature, the St Gallen protocol for mirror therapy and evaluation of a case series of 52 patients. *The British Journal of Hand Therapy*, 13(1), 4-11.

Gygax, M. J., Schneider, P., & Newman, C. J. (2011). Mirror therapy in children with hemiplegia: a pilot study. *Developmental Medicine & Child Neurology*, 53(5), 473-476.

Hackett, M. L., & Anderson, C. S. (2005). Predictors of depression after stroke a systematic review of observational studies. *Stroke*, 36(10), 2296-2301.

Halligan, P., Wilson, B., & Cockburn, J. (1990). A short screening test for visual neglect in stroke patients. *Disability & Rehabilitation*, 12(3), 95-99.

Hamzei, F., Lämpchen, C. H., Glauche, V., Mader, I., Rijntjes, M., & Weiller, C. (2012). Functional Plasticity Induced by Mirror Training The Mirror as the Element Connecting Both Hands to One Hemisphere. *Neurorehabilitation and neural repair*, 26(5), 484-496.

Hankey, G. J., Jamrozik, K., Broadhurst, R. J., Forbes, S., Burvill, P. W., Anderson, C. S., & Stewart-Wynne, E. G. (2000). Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke*, 31(9), 2080-2086.

Hanling, S. R., Wallace, S. C., Hollenbeck, K. J., Belnap, B. D., & Tulis, M. R. (2010). Preamputation mirror therapy may prevent development of phantom limb pain: a case series. *Anesthesia & Analgesia*, 110(2), 611-614.

Harding P, Riddoch MJ. Functional Electrical Stimulation (FES) of the Upper Limb Alleviates Unilateral Neglect: A Case Series Analysis. *Neuropsychological Rehabilitation*. 2009; 19:41-63.

Harris, A. J. (1999). Cortical origin of pathological pain. *The Lancet*, 354(9188), 1464-1466.

Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Annals of neurology*, 5(2), 166-170.

Hendricks, H. T., van Limbeek, J., Geurts, A. C., & Zwarts, M. J. (2002). Motor recovery after stroke: a systematic review of the literature. *Archives of physical medicine and rehabilitation*, 83(11), 1629-1637.

Heruti, R. J., Lusky, A., Dankner, R., Ring, H., Dolgopiat, M., Barell, V., ... & Adunsky, A. (2002). Rehabilitation outcome of elderly patients after a first stroke: effect of cognitive status at admission on the functional outcome. *Archives of physical medicine and rehabilitation*, 83(6), 742-749.

Honda, M., Nagamine, T., Fukuyama, H., Yonekura, Y., Kimura, J., & Shibasaki, H. (1997). Movement-related cortical potentials and regional cerebral blood flow change in patients with stroke after motor recovery. *Journal of the neurological sciences*, 146(2), 117-126.

Hsieh, C. L., Hsueh, I. P., Chiang, F. M., & Lin, P. H. (1998). Inter-rater reliability and validity of the action research arm test in stroke patients. *Age and ageing*, 27, 107-113.

Hsu HY, Lin CF, Su FC, Kuo HT, Chiu HY and Kuo LC (2012). Clinical Application of Computerized Evaluation and Re-education Biofeedback Prototype Sensorimotor Control of the Hand in Stroke Patients. *Journal of NeuroEngineering and Rehabilitation* 2012, 9:26.

Humphreys, G.W., Bickerton, W., Samson, D. & Riddoch, M.J. (2012) BCoS: Cognitive profiling after brain injury. London: Psychology Press.

Ietswaart, M., Johnston, M., Dijkerman, H. C., Joice, S., Scott, C. L., MacWalter, R. S., & Hamilton, S. J. (2011). Mental practice with motor imagery in stroke recovery: randomized controlled trial of efficacy. *Brain*, 134(5), 1373-1386.

Iftime-Nielsen SD, Schram Christensen M. Interaction of Electrical Stimulation and Voluntary Hand Movement in SII and the Cerebellum during Simulated Therapeutic Functional Electrical Stimulation in Healthy Adults. *Human Brain Mapping*. 2012; 1:40-49.

Joa KL, Han YH. Evaluation of the Brain Activation Induced by Functional Electrical Stimulation and Voluntary Contraction Using Functional Magnetic Resonance Imaging. *Journal of Neuro Engineering and Rehabilitation*. 2012; 9 48-57.

Joa, K. L., Han, Y. H., Mun, C. W., Son, B. K., Lee, C. H., Shin, Y. B., ... & Shin, Y. I. (2012). Evaluation of the brain activation induced by functional electrical stimulation and voluntary contraction using functional magnetic resonance imaging. *Journal of neuroengineering and rehabilitation*, 9(1), 1-10.

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S. M., Wade, D. T., & Matthews, P. M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, 125(12), 2731-2742.

Johansson, B., & Tornmalm, M. (2012). Working memory training for patients with acquired brain injury: effects in daily life. *Scandinavian Journal of Occupational Therapy*, 19(2), 176-183.

Jongbloed, L. (1986). Prediction of function after stroke: a critical review. *Stroke*, 17, 765-76.

Jonides, J., Voluntary versus automatic control over the mind's eye's movement. In J. B. Long & A. D. Baddeley (Eds.), *Attention and Performance IX*. Hillsdale, N. J. : Erlbaum, 1981.

Jørgensen, H. S., Nakayama, H., Raaschou, H. O., Vive-Larsen, J., Støier, M., & Olsen, T. S. (1995). Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Archives of physical medicine and rehabilitation*, 76(5), 406-412.

Kasai, T., Kawai, S., Kawanishi, M., & Yahagi, S. (1997). Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery. *Brain research*, 744(1), 147-150.

Kerkhoff G, Schenk T. Rehabilitation of Neglect: An Update. *Neuropsychologia*. 2012; 6:1072-1079.

Kim, H. J., & Kramer, J. F. (1997). Effectiveness of visual feedback during isokinetic exercise. *The Journal of Orthopaedic and Sports Physical Therapy*, 26, 318.

Kim, H., Lee, GH., Song, CH. (2013). Effect of Functional Electrical Stimulation with Mirror Therapy on Upper Extremity Motor Function in Poststroke Patients. *Journal of stroke and cerebrovascular disease*, pp 1-7.

Kimberley TJ, Lewis ML. Electrical Stimulation Driving Functional Improvements and Cortical Changes in Subjects with Stroke. *Experimental Brain Research*. 2004; 154:450-460.

Kinsbourne, M. (1987). Mechanisms of unilateral neglect. *Neurophysiological and neuropsychological aspects of spatial neglect*, 45, 69-86.

Knutson, J. S., Hisel, T. Z., Harley, M. Y., & Chae, J. (2009). A novel functional electrical stimulation treatment for recovery of hand function in hemiplegia: 12-week pilot study. *Neurorehabilitation and neural repair*, 23(1), 17-25.

Kuys, S. S., Edwards, T., & Morris, N. R. (2012). Effects and Adherence of Mirror Therapy in People with Chronic Upper Limb Hemiparesis: A Preliminary Study. *ISRN Rehabilitation*, 2012.

Kwakkel, G., Kollen, B., & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke: facts and theories. *Restorative neurology and neuroscience*, 22(3), 281-299.

Laepchen, C. H., Ringer, T., Blessin, J., Seidel, G., Grieshammer, S., Lange, R., & Hamzei, F. (2012). Optical illusion alters M1 excitability after mirror therapy: a TMS study. *Journal of Neurophysiology*, 108(10), 2857-2861.

Lai SM, Studenski S, Duncan PW, Perera S. Persisting consequences of stroke measured by the Stroke Impact Scale. *Stroke*. 2002; 33:1840-1844.

Laplane, D., & Degos, J. D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery & Psychiatry*, 46, 152-158.

Laver, K., George, S., Thomas, S., Deutsch, J. E., & Crotty, M. (2012). Virtual reality for stroke rehabilitation. *Stroke*, 43(2), e20-e21.

Legh-Smith, J., Wade, D. T., and Hewer, R. L. (1986). Driving after a stroke. *Journal of the Royal Society of Medicine*, 79, 200–3.

Liberson WT, & Holmquest HJ. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Archives of physical medicine and rehabilitation*, 42, 101-105.

Liepert, J., Bauder, H., Miltner, W. H., Taub, E., & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke*, 31(6), 1210-1216.

Liepert, J., Uhde, I., Gräf, S., Leidner, O., & Weiller, C. (2001). Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. *Journal of neurology*, 248(4), 315-321.

Lin, K. C., Chen, Y. T., Huang, P. C., Wu, C. Y., Huang, W. L., Yang, H. W., ... & Lu, H. J. (2012). Effect of mirror therapy combined with somatosensory stimulation on motor recovery and daily function in stroke patients: A pilot study. *Journal of the Formosan Medical Association*.

Lincoln, N. B., Majid, M. J., & Weyman, N. (2000). Cognitive rehabilitation for attention deficits following stroke. *Cochrane Database Syst Rev*, 4.

Loetscher, T., & Lincoln, N. B. (2013). Cognitive rehabilitation for attention deficits following stroke. *The Cochrane Library*.

Lu, M. K., Arai, N., Tsai, C. H., & Ziemann, U. (2012). Movement related cortical potentials of cued versus self-initiated movements: Double dissociated modulation by dorsal premotor cortex versus supplementary motor area rTMS. *Human brain mapping*, 33(4), 824-839.

Lynch C, Popovic MR. Functional Electrical Stimulation. *IEEE Controls Systems Magazine*. 2008.

Lynch, B. (2002). Historical review of computer-assisted cognitive retraining. *The Journal of head trauma rehabilitation*, 17(5), 446-457.

Maeda, F., Kleiner-Fisman, G., & Pascual-Leone, A. (2002). Motor facilitation while observing hand actions: specificity of the effect and role of observer's orientation. *Journal of Neurophysiology*, 87(3), 1329-1335.

Mahoney Fl, Barthel DW:Functional evaluation: the Barthel Index. *Md State Med J* 14:2, 1965

Mant, J., Wade, D., & Winner, S. (2004). Health care needs assessment: stroke. *Health care needs assessment: the epidemiologically based needs assessment reviews*, 2.

Maria Galeazzi, G., Monzani, D., Gherpelli, C., Covezzi, R., & Guaraldi, G. P. (2006). Posturographic stabilisation of healthy subjects exposed to full-length mirror image is inversely related to body-image preoccupations. *Neuroscience letters*, 410(1), 71-75.

Masiero, S., Celia, A., Rosati, G., Armani, M. (2007). Robotic assisted rehabilitation of the upper limb after acute stroke. *Archives of Physical Medicine and Rehabilitation*, 88, 142-9.

Matsuo, A., Tezuka, Y., Morioka, S., Hiyamiza, M., & Seki, M. (2008). Mirror therapy accelerates recovery of upper limb movement after stroke: a randomized cross-over trial. In *Sixth World Stroke Conference*, Vienna, Austria.

Matthys, K., Smits, M., Van der Geest, J. N., Van der Lugt, A., Seurinck, R., Stam, H. J., & Selles, R. W. (2009). Mirror-induced visual illusion of hand movements: a functional magnetic resonance imaging study. *Archives of physical medicine and rehabilitation*, 90(4), 675-681.

Mazzaro, N., Spaich, E. G., Andersen, O. K., Grey, M. J., Popovic, D., & Sinkjaer, T. (2006). Electrical stimulation augmented rehabilitation of hemiparetic gait. *28th IEEE EMBS*, New York.

McCabe, C. S., Haigh, R. C., & Blake, D. R. (2008). Mirror visual feedback for the treatment of complex regional pain syndrome (type 1). *Current pain and headache reports*, 12(2), 103-107.

Mercier, C., & Sirigu, A. (2009). Training with virtual visual feedback to alleviate phantom limb pain. *Neurorehabilitation and Neural Repair*, 23(6), 587-594.

Merletti, R., Acimovic, R., Grobelnik, S., & Cvilak, G. (1975). Electrophysiological orthosis for the upper extremity in hemiplegia: feasibility study. *Archives of physical medicine and rehabilitation*, 56(12), 507.

Mevorach, C., Humphreys, G. W., & Shalev, L. (2006). Opposite biases in salience-based selection for the left and right posterior parietal cortex. *Nature neuroscience*, 9(6), 740-742.

Michielsen, M. E., Selles, R. W., van der Geest, J. N., Eckhardt, M., Yavuzer, G., Stam, H. J., Smiths, M., Ribbers, G. M., & Bussmann, J. B. (2011). Motor Recovery and Cortical Reorganization After Mirror Therapy in Chronic Stroke Patients A Phase II Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, 25(3), 223-233.

Mohan, K. M., Wolfe, C. D., Rudd, A. G., Heuschmann, P. U., Kolominsky-Rabas, P. L., & Grieve, A. P. (2011). Risk and Cumulative Risk of Stroke Recurrence A Systematic Review and Meta-Analysis. *Stroke*, 42(5), 1489-1494.

Moseley, G. L. (2004). Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain*, 108(1), 192-198.

Moseley, G. L., Gallace, A., & Spence, C. (2008). Is mirror therapy all it is cracked up to be? Current evidence and future directions. *Pain*, 138(1), 7-10.

Nakayama, H., Jørgensen, H. K. S., Raaschou, H. O., & Olsen, T. S. (1994). Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Age (SD)*, 74, 11-2.

National Audit Office. Progress in Improving Stroke Care. 2004.

National Stroke association UK home page. Available at: <http://www.stroke.org/site/PageServer?pagename=hemiparesis>. Accessed April 21, 2011.

Navon, D. (1977). Forest before trees: The precedence of global features in visual perception. *Cognitive psychology*, 9(3), 353-383.

Nelles, G., Jentzen, W., Jueptner, M., Müller, S., & Diener, H. C. (2001). Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *Neuroimage*, 13(6), 1146-1154.

Nelles, G., Spiekermann, G., Jueptner, M., Leonhardt, G., Müller, S., Gerhard, H., & Diener, H. C. (1999). Reorganization of Sensory and Motor Systems in Hemiplegic Stroke Patients A Positron Emission Tomography Study. *Stroke*, 30, 1510-1516.

Nojima, I., Mima, T., Koganemaru, S., Thabit, M. N., Fukuyama, H., & Kawamata, T. (2012). Human motor plasticity induced by mirror visual feedback. *The Journal of Neuroscience*, 32(4), 1293-1300.

Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science (New York, NY)*, 272(5269), 1791.

Nuechterlein, K. H., Robbins, T. W., & Einat, H. (2005). Distinguishing separable domains of cognition in human and animal studies: what separations are optimal for targeting interventions? A summary of recommendations from breakout group 2 at the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophrenia Bulletin*, 31(4), 870-874.

Ottenbacher K. Cerebral vascular accident: some characteristics of occupational therapy evaluation form. *American Journal of Occupational Therapy*. 1980, 34:268-271.

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., ... & Ballard, C. G. (2010). Putting brain training to the test. *Nature*, 465(7299), 775-778.

Pandyan, A. D., Granat, M. H., & Stott, D. J. (1997). Effects of electrical stimulation on flexion contractures in the hemiplegic wrist. *Clinical rehabilitation*, 11(2), 123-130.

Peckham PH, Knutson JS. Functional electrical stimulation for neuromuscular applications. *Annual Review Biomedical Engineering* 2005; 7:327–360.

Petersen, S. E., Fox, P. T., Snyder, A. Z., & Raichle, M. E. (1990). Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science*.

Peurala, S. H., Pitkänen, K., Sivenius, J., & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clinical rehabilitation*, 16(7), 709-716.

Pineiro, R., Pendlebury, S., Johansen-Berg, H., & Matthews, P. M. (2001). Functional MRI Detects Posterior Shifts in Primary Sensorimotor Cortex Activation After Stroke Evidence of Local Adaptive Reorganization?. *Stroke*, 32(5), 1134-1139.

Polanowska K, Seniow, E. Left-hand Somatosensory Stimulation Combined with Visual Scanning Training in Rehabilitation for Post-stroke Hemineglect: A Randomised, double blind study. *Neuropsychological Rehabilitation*. 2009; 19:364-382.

Popovic MR, Curt A Keller T and Dietz V (2001). Functional Electrical Stimulation for Grasping and Walking: Indications and Limitations. *Spinal Cord*. 2001a; 39:403-412.

Popovic, D. B., Popovic, M. B., Sinkjær, T., Stefanovic, A., & Schwirtlich, L. (2004). Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. *Canadian journal of physiology and pharmacology*, 82(8-9), 749-756.

Popovic, D. B., Popovic, M. B., Sinkjær, T., Stefanovic, A., & Schwirtlich, L. (2004). Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. *Canadian journal of physiology and pharmacology*, 82(8-9), 749-756.

Popovic, M. R., Popovic, D. B., & Keller, T. (2002). Neuroprostheses for grasping. *Neurological research*, 24(5), 443-452.

Posner, M. I., & Petersen, S. E. (1990). The attention of the human brain. *Annual Review of Neuroscience*, 13, 25-42.

Powel J, Pandyan AD, Granat M, Cameron M and Stott DJ. Electrical Stimulation of Wrist Extensors in Post Stroke Hemiplegia. *Stroke*. 1999; 30:1384-1389.

Prokopenko, S. V., Mozheyko, E. Y., Petrova, M. M., Koryagina, T. D., Kaskaeva, D. S., Chernykh, T. V., ... & Bezdenezhniy, A. F. (2013). Correction of post-stroke cognitive impairments using computer programs. *Journal of the neurological sciences*, 325(1), 148-153.

Punt D, Riddoch MJ. Motor Neglect: Implications for Movement and Rehabilitation Following Stroke. *Disability and Rehabilitation*. 2006; 13-14:857-864.

Punt, T. D., Riddoch, M. J., & Humphreys, G. W. (2005). Bimanual coordination and perceptual grouping in a patient with motor neglect. *Cognitive neuropsychology*, 22, 795-815.

Punt, T. D., Riddoch, M. J., & Humphreys, G. W. (2005). Don't think twice, it's all right—contralesional dependency for bimanual prehension movements. *Neuropsychologia*, 43(11), 1547-1558.

Punt, T. D., Riddoch, M. J., & Humphreys, G. W. (2013). Motor extinction: a deficit of attention or intention?. *Frontiers in human neuroscience*, 7.

Radomski, M. V., & Latham, C. A. T. (Eds.). (2008). *Occupational therapy for physical dysfunction*. Wolters Kluwer Health.

Ramachandran, V. S., & Altschuler, E. L. (2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain*, 132(7), 1693-1710.

Ramachandran, V. S., & Hirstein, W. (1998). The perception of phantom limbs. The DO Hebb lecture. *Brain*, 121(9), 1603-1630.

Ramachandran, V. S., & Rogers-Ramachandran, D. (1996). Synaesthesia in phantom limbs induced with mirrors. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 263(1369), 377-386.

Ramachandran, V. S., Altschuler, E. L., Stone, L., Al-Aboudi, M., Schwartz, E., & Siva, N. (1999). Can mirrors alleviate visual hemineglect?. *Medical hypotheses*, 52(4), 303-305.

Ramachandran, V. S., Rogers-Ramachandran, D., & Cobb, S. (1995). Touching the phantom limb. *Nature*, 377(6549), 489-490.

Ramachandran, V. S., Stewart, M., & Rogers-Ramachandran, D. C. (1992). Perceptual correlates of massive cortical reorganization. *Neuroreport*, 3(7), 583-586.

Riddoch, M. J., Bodley Scott, S., & Humphreys, G. W. (2010). No direction home: Extinction is affected by implicit motion. *Cortex*, 46(5), 678-684.

Rijntjes, M., Hamzei, F., Glauche, V., Saur, D., & Weiller, C. (2011). Activation changes in sensorimotor cortex during improvement due to CIMT in chronic stroke. *Restorative Neurology and Neuroscience*, 29(5), 299-310.

Ring, H., & Rosenthal, N. (2005). Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *Journal of Rehabilitation Medicine*, 37, 32-36.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu. Rev. Neurosci.*, 27, 169-192.

Rizzolatti, G., Fadiga, L., Fogassi, L., & Gallese, V. (1999). Resonance behaviors and mirror neurons. *Archives italiennes de biologie*, 137(2), 85-100.

Robertson, I. H. (2001). Do we need the “lateral” in unilateral neglect? Spatially nonselective attention deficits in unilateral neglect and their implications for rehabilitation. *Neuroimage*, 14(1), S85-S90.

Robertson, I. H., & North, N. T. (1994). One hand is better than two: motor extinction of left hand advantage in unilateral neglect. *Neuropsychologia*, 32(1), 1-11.

Rosén, B., & Lundborg, G. (2005). Training with a mirror in rehabilitation of the hand. *Scandinavian journal of plastic and reconstructive surgery and hand surgery*, 39(2), 104-108.

Rossetti Y, Rode G. Prism Adaptation to a Rightward Optical Deviation Rehabilitates Left Hemispatial Neglect. *Nature*. 1998; 395:166-169.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome Jr, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of consulting psychology*, 20(5), 343.

Rushton DN. Functional Electrical Stimulation and Rehabilitation – An Hypothesis. *Medical Engineering and Physics*. 2003; 25:75-78.

Salmelin, R., & Hari, R. (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience*, 60(2), 537-550.

Sartori, L., Cavallo, A., Buccioni, G., & Castiello, U. (2011). Corticospinal excitability is specifically modulated by the social dimension of observed actions. *Experimental brain research*, 211(3-4), 557-568.

Sasaki K, Matsunaga T. Effect of Electrical Stimulation Therapy on Upper Extremity Functional Recovery and Cerebral Cortical Changes in Patients with Chronic Hemiplegia. *Biomedical Research*. 2012; 33: 89-96.

Sathian, K., Greenspan, A. I., & Wolf, S. L. (2000). Doing it with mirrors: a case study of a novel approach to neurorehabilitation. *Neurorehabilitation and Neural Repair*, 14, 73-76.

Schnitzler, A., Salenius, S., Salmelin, R., Jousmäki, V., & Hari, R. (1997). Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *Neuroimage*, 6(3), 201-208.

Selles, R. W., Schreuders, T. A., & Stam, H. J. (2008). Mirror therapy in patients with causalgia (complex regional pain syndrome type II) following peripheral nerve injury: two cases. *Journal of rehabilitation medicine*, 40(4), 312-314.

Shalev, L., Tsal, Y., & Mevorach, C. (2007). Computerized progressive attentional training (CPAT) program: effective direct intervention for children with ADHD. *Child neuropsychology*, 13(4), 382-388.

Sheffler, L. R., & Chae, J. (2007). Neuromuscular electrical stimulation in neurorehabilitation. *Muscle & nerve*, 35(5), 562-590.

Smith GV, Alon G, Roys SR, Gullapalli RP (2003) Functional MRI determination of a dose-response relationship to lower extremity neuromuscular electrical stimulation in healthy subjects. *Exp Brain Res* 150: 33-39

Sohlberg, M. M., & Mateer, C. A. (1987). Effectiveness of an attention-training program. *Journal of Clinical and Experimental Neuropsychology*, 9(2), 117-130.

Spence, C. (2011). Crossmodal correspondences: A tutorial review. *Attention, Perception, & Psychophysics*, 73(4), 971-995.

Spieler, J.F., Lanoe, J.L., Amarenco, P. (2004). Costs of stroke care according to handicap levels and stroke subtypes. *Cerebrovascular Disease*, 17, 134-142.

Stern, H., Jeaco, S., & Millar, T. (1999). Computers in neurorehabilitation: what role do they play? Part 1. *The British Journal of Occupational Therapy*, 62(12), 549-553.

Stern, H., Jeaco, S., & Millar, T. (2000). Computers in neurorehabilitation: what role do they play? Part 2. *The British Journal of Occupational Therapy*, 63(1), 25-28.

Stevens, J. A., & Stoykov, M. E. P. (2003). Using motor imagery in the rehabilitation of hemiparesis. *Archives of physical medicine and rehabilitation*, 84, 1090-1092.

Stevens, J. A., & Stoykov, M. E. P. (2004). Simulation of bilateral movement training through mirror reflection: a case report demonstrating an occupational therapy technique for hemiparesis. *Topics in stroke rehabilitation*, 11(1), 59-66.

Stringer, A. Y. (2003). Cognitive rehabilitation practice patterns: A survey of American Hospital Association. *The Clinical Neuropsychologist*, 17(1), 34-44.

Sütbeyaz, S., Yavuzer, G., Sezer, N., & Koseoglu, B. F. (2007). Mirror therapy enhances lower-extremity motor recovery and motor functioning after stroke: a randomized controlled trial. *Archives of physical medicine and rehabilitation*, 88(5), 555-559.

Sullivan, J. E., & Hedman, L. D. (2004). A home program of sensory and neuromuscular electrical stimulation with upper-limb task practice in a patient 5 years after a stroke. *Physical therapy*, 84(11), 1045-1054.

Sulter, G., Steen, C., & De Keyser, J. (1999). Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke*, 30(8), 1538-1541.

Sumitani, M., Miyauchi, S., McCabe, C. S., Shibata, M., Maeda, L., Saitoh, Y., ... & Mashimo, T. (2008). Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. *Rheumatology*, 47(7), 1038-1043.

Summers, J.J., Kagerer, F.A., Garry, M.I., Hiraga, C.Y., Loftus, A., Cauragh, J.H. (2007). Bilateral and unilateral movement training on upper limb function in chronic stroke patients: a TMS study. *Journal of the Neurological Sciences*, 252, 76-82.

Talairach J., Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Taub E, Uswatte G, Bowman MH, Mark VW, Delgado A, Bryson C, Morris D and Bishop-McKay S. Constraint – Induced Therapy Combines with Conventional Neurorehabilitation

Techniques in Chronic Stroke Patients with Plegic Hands: A Case Series. Archives of Physical Medicine and Rehabilitation. 2012 (accepted manuscript).

Taub E, Uswatte G. (2012) Constraint – Induced Therapy Combines with Conventional Neurorehabilitation Techniques in Chronic Stroke Patients with Plegic Hands: A Case Series. Archives of Physical Medicine and Rehabilitation. (accepted manuscript).

Taylor, P., Humphreys, L., & Swain, I. (2013). The long-term cost-effectiveness of the use of Functional Electrical Stimulation for the correction of dropped foot due to upper motor neuron lesion. Journal of Rehabilitation Medicine, 45(2), 154-160.

Thieme, H., Bayn, M., Wurg, M., Zange, C., Pohl, M., & Behrens, J. (2013). Mirror therapy for patients with severe arm paresis after stroke—a randomized controlled trial. Clinical Rehabilitation, 27(4), 314-324.

Thieme, H., Mehrholz, J., Pohl, M., Behrens, J., & Dohle, C. (2013). Mirror therapy for improving motor function after stroke. Stroke, 44(1), e1-e2.

Thieme, H., Mehrholz, J., Pohl, M., Behrens, J., & Dohle, C. (2012). Mirror therapy for improving motor function after stroke. *Cochrane Database Syst Rev*, 3.

Thornton, K. E., & Carmody, D. P. (2008). Efficacy of traumatic brain injury rehabilitation: Interventions of QEEG-guided biofeedback, computers, strategies, and medications. *Applied psychophysiology and biofeedback*, 33(2), 101-124.

Thrasher TA, Zivanovic V, McIlroy W and Popovic MR. Rehabilitation of Reaching and Grasping Function in Severe Hemiplegic Patients Using Functional Electrical Stimulation Therapy. *Neurorehabilitation and Neural Repair*. 2008; 6:706-714.

Tichelaar, Y. V., Geertzen, J. H., Keizer, D., & Van Wilgen, C. P. (2007). Mirror box therapy added to cognitive behavioural therapy in three chronic complex regional pain syndrome type I patients: a pilot study. *International journal of rehabilitation research*, 30(2), 181-188.

Tominaga, W., Matsubayashi, J., Deguchi, Y., Minami, C., Kinai, T., Nakamura, M., ... & Mitani, A. (2009). A mirror reflection of a hand modulates stimulus-induced 20-Hz activity. *Neuroimage*, 46(2), 500-504.

Traversa, R., Cicinelli, P., Oliveri, M., Giuseppina Palmieri, M., Maddalena Filippi, M., Pasqualetti, P., & Rossini, P. M. (2000). Neurophysiological follow-up of motor cortical output in stroke patients. *Clinical neurophysiology*, 111(9), 1695-1703.

Treisman, A. M., & Gelade, G. (1980). A feature-integration theory of attention. *Cognitive psychology*, 12(1), 97-136.

Tsal, Y., Shalev, L., & Mevorach, C. (2005). The Diversity of Attention Deficits in ADHD The Prevalence of Four Cognitive Factors in ADHD Versus Controls. *Journal of Learning Disabilities*, 38(2), 142-157.

Vaillant, J., Vuillerme, N., Janvy, A., Louis, F., Juvin, R., & Nougier, V. (2004). Mirror versus stationary cross feedback in controlling the center of foot pressure displacement in quiet standing in elderly subjects. *Archives of physical medicine and rehabilitation*, 85(12), 1962-1965.

Van Peppen, R. P., Kwakkel, G., Wood-Dauphinee, S., Hendriks, H. J., Van der Wees, P. J., & Dekker, J. (2004). The impact of physical therapy on functional outcomes after stroke: what's the evidence?. *Clinical rehabilitation*, 18(8), 833-862.

Vusse, A. C., Berg, S. G., Vet, H. C., & Weber, W. E. (2003). Interobserver reliability of diagnosis in patients with complex regional pain syndrome. *European Journal of Pain*, 7(3), 259-265.

Wade DT. Measuring arm impairment and disability after stroke. *International Disability Study*. 1989; 11:89-92.

Wang, J., Fritsch, C., Bernarding, J., Holtze, S., Mauritz, K. H., Brunetti, M., & Dohle, C. (2013). A comparison of neural mechanisms in mirror therapy and movement observation therapy. *Journal of Rehabilitation Medicine*, 45(4), 410-413.

Wieser, M., Haefeli, J., Büttler, L., Jäncke, L., Riener, R., & Koeneke, S. (2010). Temporal and spatial patterns of cortical activation during assisted lower limb movement. *Experimental brain research*, 203(1), 181-191.

Wilcher, D. G., Chernev, I., & Yan, K. (2011). Combined mirror visual and auditory feedback therapy for upper limb phantom pain: a case report. *Journal of medical case reports*, 5(1), 41.

World Health Organization. The global burden of disease: 2004 update.

http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human brain mapping*, 4(1), 58-73.

Yavuzer, G., Selles, R., Sezer, N., Sütbeyaz, S., Bussmann, J. B., Köseoğlu, F., Atay, M. B. and Stam, H. J. (2008). Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, 89, 393-398.

Yozbatiran, N., Der-Yeghiaian, L., & Cramer, S. C. (2008). A standardized approach to performing the action research arm test. *Neurorehabilitation and Neural Repair*, 22, 78-90.

Yun, G. J., Chun, M. H., Park, J. Y., & Kim, B. R. (2011). The synergic effects of Mirror therapy and neuromuscular electrical stimulation for hand function in stroke patients. *Annals of Rehabilitation Medicine*, 35(3), 316-321.

Zhang, Y., Chapman, A. M., Plested, M., Jackson, D., & Purroy, F. (2012). The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke research and treatment*, 2012.

Zigmond, AS; Snaith, RP (1983). "The hospital anxiety and depression scale". *Acta Psychiatrica Scandinavica* 67 (6): 361–370.

Zimmerli L, Krewer C. (2012) Validation of a Mechanism to Balance Exercise Difficulty in Robot-assisted Upper-extremity Rehabilitation after Stroke. *Journal of NeuroEngineering and Rehabilitation*, 9:6.

APPENDICES

Appendix 1:

The five domains of BCoS consist of the following sub-tests: Attention (auditory attention task, Birmingham Rule Finding, Apple Cancellation, Visual Extinction and Tactile Extinction), Language (Picture Naming, Sentence Construction, Sentence Reading, Reading Non Words, Writing Words and Non Words, Instruction Comprehension), Memory (Orientation, Story Recall and Recognition and Task Recognition), Number Skills (Number-Price- Reading and Writing, Calculation) and Praxis (Complex figure copy, Multi-step object use, Gesture production, Gesture recognition and Imitation). Examples of the test are following:







