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Brain Plasticity Induced by Constraint-Induced Movement Therapy: Relationship of fMRI and Movement Characteristics

Urška Puh

University of Ljubljana, Faculty of Health Sciences
Slovenia

1. Introduction

Following stroke, the disturbed motor control results in subsequent movement disorders. Recovery means gradual returning of the specific function, after a deficit caused by a central nervous system damage (Held, 2000). The recovery of upper extremity movement following a stroke is generally poor. Three months after stroke its function remains totally or partially impaired in as much as 80 % of stroke survivors (Parker et al., 1986). Basmajian et al. (1982) reported that only 5% of stroke patients regained a total function of the upper extremity, and in 20% it remained totally non-functional. Majority of the reports indicated that in patients with initially markedly impaired upper extremity function, the recovery is minimal (Basmajian et al., 1982; Wade et al., 1983; Nakayama et al., 1994). In this group, a useful function of the upper extremity was regained in only 15% (Parker et al., 1986) or 18% of patients (Nakayama et al., 1994). It seems, however, that patients with initially partially impaired upper extremity function have a good potential for recovery. In this group, total recovery was reported in as much as 79% of patients (Nakayama et al., 1994).

Although there is evidence from the animal models that at least some of the recovery can be attributed to brain reorganization, the mechanisms of motor recovery after stroke in humans are not clear yet. During the first three to four weeks after stroke a combination of the brain spontaneous recovery processes (oedema and necrotic tissue absorption, collateral blood flow activation), and reorganisation of the neural mechanisms, the so called plasticity (unmasking of unused neuronal pathways, dendritic branching, synaptogenesis) influence the recovery. Later, only plasticity occurs (Lee & van Donkelaar, 1995). To understand the recovery after stroke in humans, a great number of functional imaging studies, using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been conducted. In general, a greater activation of the motor-related brain regions is reported during stroke-affected upper extremity motor tasks as compared to healthy subjects. Additionally, an increased recruitment of non-motor areas is shown consistently. In the 1st to 6th week after stroke, the activation was moved to the *contralesional* hemisphere. In the 3rd to 12th month after stroke the activation moved back to the *ipsilesional* hemisphere, which was concomitant with motor recovery, or stayed in the contralesional hemisphere (for review see: Calautti & Baron, 2003; Baron et al., 2004; Schaechter, 2004). The functional role

of the ipsilateral activation was, however, under debate both in healthy subjects (Salmelin et al., 1995; Kawashima et al., 1998) and patients after stroke (Chollet et al., 1991; Turton et al., 1996; Netz et al., 1997; Marshall et al., 2000) without a clear answer.

Better understanding of the neurophysiological processes underlying brain reorganization and concomitant studying of the effects of the therapeutic techniques which were established to stimulate the brain plasticity may increase their effectiveness and thus improve the outcome of rehabilitation in patients after stroke.

2. Treatment-induced recovery of brain function and movement

It is not known yet if differences in the motor cortex areas between individuals are consequences of inherited genetic differences or of different experiences. It seems that the competition between the neurons for synaptic connections depends on their use. Sensory and motor areas of the brain cortex are constantly changing, depending on the amount of their activation through periphery inputs, environment, motor tasks, experiences, etc. (Jenkins et al., 1990; Shumway-Cook & Woollacott, 2007). In monkeys, a new learned task induced certain long-effecting changes in motor cortex areas (Jenkins et al., 1990; Nudo et al., 1996). However, attention should be paid to the fact that plastic changes can also be negative. Immobilisation of the two fingers, for example, obliterated the boundaries between the areas for an individual finger (Clark et al., 1988). Some reorganisation (adaptation) of the brain cortex always occurs after a stroke. It is assumed, however, that reorganisation can be affected with the experiences or sensory inputs and motor reactions, which are demanded after the lesion, especially in the process of rehabilitation (Carr & Shepherd, 2000). On the other hand, several weeks of inactivity would have a consequence in reorganisation of the brain cortex reflecting non-use (Shumway-Cook & Woollacott, 2007). The possibilities for functional recovery exist, but the methods and mechanisms of how to affect these processes need to be discovered (Lee & van Donkelaar, 1995).

Some authors speculated that there is a certain period of time, in which plastic changes of the brain after stroke can be influenced by therapeutic interventions (Lee & van Donkelaar, 1995). Mainly as a consequence of the brain spontaneous recovery (Hallett, 2001), the greatest possibility for the upper extremity movement recovery is during the first month (Kwakkel et al., 2003) or the first three months after stroke (Nakayama et al., 1994; Parker et al., 1986; Wade et al., 1983). However, after this period a recovery is not complete. The evidence of significant movement recovery in patients involved in constraint-induced movement therapy (CIMT), more than one year (to 20 years) after a stroke exist (Kunkel et al., 1999; Sterr et al., 2002; Taub et al., 2006; Wolf et al., 1989). This evidence was the main proof that neuroplastic changes induced by physiotherapy are possible in the chronic stage after stroke (Blanton et al., 2008). In spite of the assumptions that movement training can have a positive effect regardless of the time period in which a patient received it, because the brain is plastic throughout the whole life (Shumway-Cook & Woollacott, 2007) and the evidence on no time limit for recovery, the first three to six months after stroke seem to be the most important (European Stroke Initiative [EUSI], 2003). It should be emphasised, however, that studies, which reported better recovery included stroke patients involved in an active and task-related training (Buterfisch et al., 1995; Dean & Mackey, 1992; Mudie & Matyas, 1996), for which at least partial ability of the upper extremity function is required.

The examples of therapeutic techniques which have been established to promote recovery of the upper extremity movement through facilitating the brain plasticity in different ways are CIMT, bimanual training, and mirror therapy. They are supplementing or emphasising the concept of task-related training. A tendency of greater upper extremity movement recovery and greater sensory-motor cortex activation of the ipsilesional hemisphere were reported in a group of stroke patients included in the intensive task-related training (Nelles et al., 2001) or bimanual training (Luft et al., 2004) in comparison to the groups receiving conventional rehabilitation. Similar positive effects were reported in other studies investigating task-related training (Carey et al., 2002; Jang et al., 2003) and CIMT (see section 2.1.1). In general, results of all these studies show positive relationship between the ipsilesional hemisphere cortex activation and greater motor recovery, although the return of the activity back to the ipsilesional hemisphere did not occur in all subjects.

2.1 Constraint-induced movement therapy

Deficiency of the majority of therapeutic approaches which facilitate the normal movement is an insufficient amount of the affected upper extremity use in comparison to the unaffected extremity use during the whole day. CIMT is an additional therapeutic technique that is performed for a short period of time, most frequently for two weeks. The aim of CIMT is to prevent or reduce a learned non-use of the affected upper extremity (Van der Lee, 2001) which is frequently developed in patients after stroke. CIMT implies the forced use and the massed practice of the affected upper extremity. It is based on the following two principles: (1) from six to eight hours of restraining the use of the unaffected upper extremity (with a splint, sling or mitten) and thus forcing the use of the affected upper extremity during intensive training and activities of daily living; and (2) intensive massed practice - more than three hours of task-related training with the affected upper extremity. Therefore different therapeutic concepts can be used, including shaping, motor re-learning, and proprioceptive neuromuscular facilitation. Modified versions of CIMT (mCIMT) with shorter restraining (i.e. 5-6 hours) and training periods (3 hours or less) per day and longer treatment periods (i.e. 4 or 10 weeks) were also developed. Through proper and sufficient feedback information, CIMT contributes to a motor learning and thus through facilitation of the brain plasticity influences the affected upper extremity movement recovery.

CIMT is currently experimentally and clinically the most established therapeutic technique for facilitating the movement recovery following stroke (Blanton et al., 2008). Meta-analyses of the currently available randomized clinical trials (RCTs) show that CIMT has a significant effect on increasing upper extremity (arm) function (Langhorne et al., 2009; van Peppen et al., 2004), and has a moderate effect on increasing performance of the activities of daily living immediately following treatment (Sirtori et al., 2009). However, its effects on increasing hand function (Langhorne et al., 2009) were found to be inconsistent, and there was not enough evidence on the long-term effects (Sirtori et al., 2009). The existing evidence suggests that CIMT is a promising intervention for upper extremity function in patients after stroke (Langhorne et al., 2009). The optimal dose of constraint and practice needs further investigation. The identification of integrated approaches combining CIMT and other techniques which facilitate the brain plasticity is a direction for future research.

2.1.1 Studying the effects of CIMT using fMRI

Since CIMT is relatively well defined and more easily administered than longer duration treatment protocols, it seems to be a more practicable way of studying plasticity. The number of brain imaging studies investigating its effect on brain plasticity, including fMRI studies, has emerged since 2001 when the first fMRI study was conducted (Levy et al., 2001). In the first review paper, Mark et al. (2006) concluded that CIMT has been repeatedly associated with significant plastic brain changes in a variety of studies using fMRI and other brain imaging techniques. However, the authors emphasised several uncertainties /unanswered questions. Later, several studies of the effects of CIMT with fMRI were published.

Observations of the 16 currently published studies investigating the effects of CIMT on brain activity using fMRI are summarized in Tables 1 and 2. In three of these studies transcranial magnetic stimulation (TMS) was also performed (Liepert et al., 2004; Hamzei et al., 2006, 2008). The effects of the original form of CIMT (duration two weeks) were investigated in 11 studies (Azpiroz et al., 2005; Butler & Page, 2006; Dong et al., 2006, 2007; Hamzei et al., 2006; Kim et al., 2004; Langan & van Donkelaar, 2008; Levy et al., 2001; Liepert et al., 2004; Schaechter et al., 2002; Sheng & Lin, 2009). In other studies, different types of mCIMT were investigated, varied from three (Lin et al., 2010; Wu et al., 2010) to ten (Szaflarski et al., 2006) weeks of treatment duration. An important deficiency of the majority of the previous studies is the absence of a control group. A control was included only in three studies of the effects of CIMT in patients after stroke using TMS (Grotta et al., 2004; Liepert et al., 2001; Wittenberg et al., 2003) and PET (Wittenberg et al., 2003), and in three studies using fMRI (Table 2). Butler & Page (2006) investigated the effects of CIMT, mental practice, and combination of both in four patients altogether. Later, two RCTs were conducted, comparing the effects of mCIMT with a bilateral training (Wu et al., 2010) and traditional rehabilitation (Lin et al., 2010), respectively.

In the 16 studies with fMRI (Tables 1 and 2), only 72 subjects after stroke who participated in CIMT or its modifications (mean: 4.6 subject per study) and 13 subjects after stroke who participated in the control groups were included. Altogether, male subjects were included in 74.2 % (16 females and 46 males). However, in four studies the subjects' gender was not reported (Dong et al., 2006; Kim et al., 2004; Langan & van Donkelaar, 2008; Liepert et al., 2004). The age of all included subjects after stroke varied from 23 (Azpiroz et al., 2005) to 80 years (Hamzei et al., 2006), with a greatest range of 51 years in the study of Langan & van Donkelaar (2008). However, the age was not reported in two studies (Butler & Page, 2006; Liepert et al., 2004).

In majority of the studies, only patients with right-hand dominance before a stroke appearance were included (Azpiroz et al., 2005; Dong et al., 2007; Hamzei et al., 2006, 2008; Langan & van Donkelaar, 2008; Lin et al., 2010; Schaechter et al., 2002), with the exception of the first two studies (Levy et al., 2001; Johansen-Berg et al., 2002) wherein each one patient with left-hand dominance was included. However, in many studies this subjects' characteristic was not reported (Butler & Page, 2006; Dong et al., 2006; Kim et al., 2004; Liepert et al., 2004; Sheng & Lin, 2009; Szaflarski et al., 2006; Wu et al., 2010).

It is assumed that in majority of the studies, patients after first stroke were included. Although this was specified by few authors only (Dong et al., 2007; Hamzei et al., 2006, 2008;

Johansen-Berg et al., 2002; Schaechter et al., 2002), but Langan & van Donkelaar (2008) included one patient with a second stroke. Patients with ischemic (Dong et al., 2007; Hamzei et al., 2006, 2008; Johansen-Berg et al., 2002; Schaechter et al., 2002) and hemorrhagic types of stroke (Azpiroz et al., 2005; Butler & Page, 2006; Dong et al., 2007; Levy et al., 2001; Wu et al., 2010) were included. However, many authors did not specify the type and/or event of stroke (Butler & Page, 2006; Dong et al., 2006; Kim et al., 2004; Langan & van Donkelaar, 2008; Liepert et al., 2004; Lin et al., 2010; Sheng & Lin, 2009; Szaflarski et al., 2006; Wu et al., 2010).

Study	CIMT type/ duration (weeks)	N	Gender	Age (years)	Time after stroke	Affected body side
Levy et al., 2001	CIMT / 2	2	1 F, 1 M	48, 49	4,5 & 9 months	2 L
Johansen-Berg et al., 2002	mCIMT / 2	7	2 F, 5 M	44-61	6 months - 7 years	4 R, 3 L
Schaechter et al., 2002	CIMT / 2	4	1 F, 3 M	36-77	7-20 months	3 R, 1 L
Kim et al., 2004	CIMT / 2	4	Not reported	43-64	9-38 months	2 R, 2 L
Liepert et al., 2004	CIMT / 2	3	Not reported	Not reported	6 months <	Not reported
Azpiroz et al., 2005	CIMT / 4	3	1 F, 2 M	23-66	48-72 months	3 L
Dong et al., 2006	CIMT / 2	8	Not reported	66±9	3 months <	Not reported
Hamzei et al., 2006	CIMT / 2	6	1 F, 5 M	63-80	1.5-10 years	6 L
Szaflarski et al., 2006	mCIMT / 10	4	2 F, 2 M	54-68	22-178 months	3 R, 1 L
Dong et al., 2007	CIMT / 2	4	1 F, 3 M	25-57	3 months <	3 R, 1 L
Hamzei et al., 2008	mCIMT / 4	8	3 F, 5 M	38-69	2-6 years	Not reported
Langan & van Donkelaar, 2008	CIMT / 2	8	Not reported	25-76	6 months <	4 R, 4 L
Sheng & Lin, 2009	CIMT / 2	1	1 M	71	4 months	1 L

Table 1. Treatment and subjects' characteristics in the studies investigating the effects of constraint-induced movement therapy (CIMT) and its modifications (mCIMT) using the functional magnetic resonance imaging in patients after stroke without a control group. Legends are shown as: N, number of subjects; F, females; M, males; L, left-side hemiparesis; R, right-side hemiparesis.

Time after stroke at inclusion to the study varied from more than three months (Butler & Page, 2006; Dong et al., 2006, 2007; Sheng & Lin, 2009), more than six months (Johansen-Berg et al., 2002; Langan & van Donkelaar; 2008 Liepert et al., 2004), to more than a year (Azpiroz et al., 2005; Hamzei et al., 2006, 2008; Szaflarski et al., 2006). In many cases patients from various stages of recovery after stroke were included to the same study (Butler & Page, 2006; Johansen-Berg et al., 2002; Kim et al., 2004; Levy et al., 2001; Schaechter et al., 2002; Wu et al., 2010).

Study	Experimental group (N) / CIMT type	Control group (N) / treatment	Duration (weeks)	Gender	Age (years)	Time after stroke	Affected body side
Butler & Page, 2006	3 = 1 CIMT + 2 CIMT & mental practice	1 / mental practice	2	1 F, 3 M	Not reported	3-16 months	Not reported
Lin et al., 2010	5 / mCIMT	8 / traditional rehabilitation	3	2 F, 11 M	average: 49	average: 18.3 months	6 R, 7 L
Wu et al., 2010	2 / mCIMT	4 / bilateral training	3	1 F, 5 M	45-68	9-40 months	4 R, 2 L

Table 2. Treatment and subjects' characteristics in the studies investigating the effects of constraint-induced movement therapy (CIMT) and its modifications (mCIMT) using the functional magnetic resonance imaging in patients after stroke, including control group/subject. Legends are shown as: N, number of subjects after stroke; F, females; M, males; L, left-side hemiparesis; R, right-side hemiparesis.

In four studies, only subjects with left-side hemiparesis were included (Azpiroz et al., 2005; Hamzei et al., 2006; Levy et al., 2001; Sheng & Lin, 2009). In others, subjects with right- and left-side hemiparesis were included (Dong et al., 2007; Johansen-Berg et al., 2002; Kim et al., 2004; Langan & van Donkelaar, 2008; Lin et al., 2010; Schaechter et al., 2002; Szaflarski et al., 2006; Wu et al., 2010), giving the common ratio of subjects with the left-side hemiparesis 53.2 % (right-side: 29; left-side: 33). In four studies this probably important subjects' characteristic was not reported (Butler & Page, 2006; Dong et al., 2006; Hamzei et al., 2008; Liepert et al., 2004). Langan & van Donkelaar (2008), however investigated the differences in recovery between the patients with right and left-side hemiparesis, and reported no significant difference in the brain cortex activations and results of the clinical motor function tests/measures between the two groups in their responses to CIMT.

The most commonly performed movement tasks during fMRI were different kinds of active finger flexion-extension or finger-tapping tasks (Azpiroz et al., 2005; Buler & Page, 2006; Dong et al., 2007; Johansen-Berg et al., 2002; Levy et al., 2001; Lin et al., 2010; Schaechter et al., 2002; Sheng & Lin, 2009; Szaflarski et al., 2006; Wu et al., 2010). Other active tasks included finger-thumb opposition without (Kim et al., 2004) or with compression (Dong et al., 2006), and making a fist/power grip without (Kim et al., 2004) or with compression (Langan & van Donklear, 2008). Some authors in the CIMT studies (Hamze et al., 2006, 2008; Liepert et al., 2004) performed passive wrist joint flexion-extension movement, and other studies (Buler & Page, 2006) also imagined finger flexion-extension task. It has been shown,

however, that in patients after stroke the brain cortex activation may differ between simple and complex motor tasks (Puh et al., 2007).

In four studies, fMRI was performed also on healthy subjects. The aim of those studies was to test the reproducibility of fMRI activation (Dong et al., 2006) or to provide data regarding typical activation patterns in response to the movement task performed during fMRI (Dong et al., 2007; Schaechter et al., 2002; Szaflarski et al., 2006). Schaechter et al. (2002) reported similar activation pattern in either hand of healthy subjects and of the unaffected hand of stroke patients. The activation was predominantly in the contralateral/contralesional hemisphere (primary motor cortex (M1), pre-motor cortex (PMC), supplementary motor area (SMA), and somatosensory cortex) and ipsilateral cerebellum; more modest and variable activation was reported for the ipsilateral/ipsilesional brain hemisphere. Before initiating CIMT, the affected hand movement resulted in activation in the same brain regions, although activation in the ipsilesional hemisphere was typically increased (Schaechter et al., 2002). In comparison to healthy subjects, Dong et al. (2007) reported higher activation in the ipsilesional M1 during performance with the affected hand before and after CIMT.

For the affected hand movement during fMRI the results of all studies investigating the effects of CIMT or mCIMT have shown varied patterns of cortical reorganisation after treatment (Table 3). Increased activations in the ipsilesional (Berg et al., 2002; Dong et al., 2007; Hamzei et al., 2006; Johansen-Berg et al., 2002; Kim et al., 2004; Levy et al., 2001; Szaflarski et al., 2006), the contralesional (Kim et al., 2004; Lin et al., 2010; Schaechter et al., 2002; Szaflarski et al., 2006) or in both hemispheres (Azpiroz et al., 2005; Butler & Page, 2006; Levy et al., 2001; Sheng & Lin, 2009; Wu et al., 2010) were reported after treatment. On the contrary, in some studies decreased activation in either hemisphere (Azpiroz et al., 2005; Dong et al., 2006; Kim et al., 2004; Liepert et al., 2004; Schaechter et al., 2002; Szaflarski et al., 2006) was reported after treatment. Some authors (Dong et al., 2006, 2007; Levy et al., 2001; Lin et al., 2010; Schaechter et al., 2002; Wu et al., 2010) calculated the laterality index between the hemispheres, but its changes are also inconsistent (Table 3). In many studies the hemispheric changes and/or changes in cortical regions were not consistent across subjects (Azpiroz et al., 2005; Butler & Page, 2006; Dong et al., 2007; Hamzei et al., 2006; Kim et al., 2004; Langan & van Donkelaar, 2008; Levy et al., 2001; Schaechter et al., 2002; Szaflarski et al., 2006).

In parallel with the decreased activation in the ipsilesional sensori-motor cortex (SM1) after CIMT, Liepert et al. (2004) reported decreased inhibition of the affected hand (measured using TMS). In the following studies (Hamzei et al., 2006, 2008) the effect of the cortico-spinal tract integrity on increase or decrease of SM1 activation after CIMT was established. Stroke lesions in M1 or its cortico-spinal tract have been shown to have consequences in increased ipsilesional SM1 activation, and were accompanied by decreased intracortical excitability; and lesions outside M1 or the cortico-spinal tract had consequences in decreased ipsilesional SM1 activation which was parallel with an increase in intracortical excitability (Hamzei et al., 2006, 2008).

During CIMT procedure, one hand (the affected) is forced to be used and movement of the other hand (the unaffected) is constrained, therefore brain plasticity would be expected during performance of each hand. However, the brain cortex activation during movement of the unaffected hand was analysed only in some studies, in which different, sometimes opposite

findings were reported (Dong et al., 2006; Johansen-Berg et al., 2002; Langan & van Donkelaar 2008; Szaflarski et al., 2006). After CIMT, for example, Langan & van Donkelaar (2008) reported significant changes in the total cortex activation for performance with the affected hand, and no changes for performance with the unaffected hand. For the unaffected hand Dong et al. (2006) also reported no difference in M1 activation across time. For one subject after CIMT, Sheng & Lin (2009) reported differences in the brain cortex activation during movement of the affected (see Table 3), but also during movement of the unaffected hand (decreased activation in the ipsilesional SM1). In the RCT by Lin et al. (2010) following mCIMT, activation in the contralesional hemisphere during movement of the affected (see Table 3) and unaffected hand (SM1) increased significantly. For the control group receiving traditional rehabilitation, a decrease in SM1 cortex activation of the ipsilesional hemisphere during movement of the affected hand, and no changes of the laterality indexes were reported (Lin et al., 2010). In the RCT by Wu et al. (2010), the total activation of each hemisphere during the affected and unaffected hand movement increased after treatment in both, mCIMT and bilateral training groups. During the affected hand movement in the mCIMT group, the laterality index decreased, but in the bilateral group it increased after treatment. For the unaffected hand movement, changes in laterality index were opposite (Wu et al., 2010).

In some studies, the activation in cerebellum was investigated. During the performance of the affected and the unaffected hand, an increased activation in the cerebellar hemispheres bilaterally was reported after CIMT (Johansen-Berg et al., 2002). During bilateral elbow movement, both CIMT patients showed decreased cerebellar activation, whereas three out of four bilateral training patients showed increased bilateral cerebellum activation after treatment (Wu et al., 2010)

Besides the measurements before and after CIMT performed in all 16 studies (Table 3), in some studies measurements were conducted in other periods. Langan & van Donkelaar (2008) performed double baseline measurements (2-3 weeks and 4 days before the start of CIMT). Dong et al. (2006) investigated the brain cortex activation in the middle of the two-week CIMT. For the performance with the affected hand the authors reported four patterns of laterality index evolution for M1 across time ($n = 8$). The long-term effects on the brain cortex activation after CIMT were investigated only in the three studies (Dong et al., 2007; Schaechter et al. 2002; Sheng & Lin, 2009). Two weeks after CIMT, a decrease of extensive cortex activation of each hemisphere and focus to the ipsilesional cortex during the affected hand movement was reported for one patient (Sheng & Lin, 2009). For the affected hand performance, Schaechter et al. (2002) reported a persistent trend toward a reduced laterality index at six months after CIMT, with differences on an individual basis. Also six months after CIMT, Dong et al. (2007) reported a decrease of activation in ipsilesional M1 (one patient) and contralesional M1 (both patients), which was followed by increased activation in M1 of each hemisphere at 12 months after CIMT.

In summation, an increase or decrease of activity in the motor related brain areas and the inclusion of other new areas in the ipsilesional and contralesional hemisphere were reported after CIMT (Table 3). The results about inclusion of new brain areas are rather inconsistent. The studies are inconsistent also with respect to whether the reorganisation changes occur more in the ipsilesional or contralesional hemisphere, as was already established earlier (Mark et al. 2006).

Study	Ipsilesional hemisphere	Contralesional hemisphere	Laterality
Levy et al., 2001	P1: increase near the lesion, association motor cortex; P2: increase near the lesion	P1: increase association motor cortex, M1	Inconsistent
Johansen-Berg et al., 2002	Increase PMC, secondary somatosensory cortex	/	/
Schaechter et al., 2002	Decrease M1 P1: decrease M1, SMA;	P3: increase SMA; P4: increase M1, PMC	Trend of decreased LI
Kim et al., 2004	P1,2: increase M1, PMC, SMA; P4: increase SMA, decrease M1	P3: increase M1, SMA;	/
Liepert et al., 2004	3/3: decrease SM1	/	/
Azpiroz et al., 2005	P1: increase M1, PMC, SMA, PF, dorsolateral; P2,3: decrease activation		/
Butler & Page, 2006	CIMT: increase motor and premotor areas; CIMT + mental practice: 1/2P more focal M1	CIMT: increase motor and premotor areas	/
Dong et al., 2006	/	Decrease M1	M1 -LI inconsistent
Hamzei et al., 2006	Intact M1 & cortico-spinal tract lesions: decreased SM1; M1 & cortico-spinal tract lesions: increase SM1; 5/6P decrease PC; 1P increase, 1P decrease SMA; 2P increase, 1P decrease PMC	1P decrease PC; 1P increase PMC	/
Szaflarski et al., 2006	P1: decrease precentral gyrus, increase cortical and subcortical areas; P2,4: no changes	P1: decrease pre- and postcentral gyrus; P3: decrease inferior frontal gyrus, increase middle frontal gyrus; P2,4: no changes	/
Dong et al., 2007	3P: increase M1; 1P: decrease M1	2P: increase M1; 2P: decrease M1	Increase M1-LI
Hamzei et al., 2008	Group 1: decrease SM1; Group 2: increase SM1	/	/
Langan & van Donkelaar, 2008	Significant change across subjects (total); Cortical regions not consistent across subjects.		/
Sheng & Lin, 2009	Increase apical, frontal lobe	Increase apical, frontal lobe	/

Study	Ipsilesional hemisphere	Contralesional hemisphere	Laterality
Lin et al., 2010	Not significant	Increase PMC and total	Decrease SMA-LI, total-LI
Wu et al., 2010	Increase total hemisphere activation (sum of SM1, PM, and SMA)		Decrease LI

Table 3. Summary of the functional magnetic resonance imaging results: changes in active voxel counts or image commentaries by the study authors from before to after constraint-induced movement therapy (CIMT) or its modifications in patients after stroke. Legends are shown as: P, patient; M1, primary motor cortex; PMC, pre-motor cortex; SMA, supplementary motor area; LI, laterality index; SM1, sensori-motor cortex; PF, prefrontal cortex.

2.1.2 Relationship of fMRI changes and movement recovery

It is assumed that increased affected arm use during CIMT will induce cortical reorganisation and have effects on motor recovery of the upper extremity. Therefore a relationship between movement recovery measured with various clinical motor function tests/measures and changes in brain activation measured by fMRI is expected. It was ascertained already in the review paper by Mark et al. (2006) that in some instances, the initial degree of brain reorganization occurred in parallel with the improvement in spontaneous, real-world use by the affected hand, which in spite of inconsistency of the studies regarding the level of changes in the ipsilesional vs. contralesional hemisphere, suggests that plastic brain changes in some manner support therapeutic effects.

In the studies investigating the brain cortex reorganisation after CIMT or its modifications, the upper limb movement function improved significantly in some (Azpiroz et al., 2005; Kim et al., 2006; Langan & van Donkelaar, 2008; Schaechter et al., 2002; Wu et al., 2010) or all of the investigated parameters (Butler & Page, 2006; Dong et al., 2006, 2007; Hamzei et al., 2006, 2007; Levy et al., 2001; Liepert et al., 2004; Lin et al., 2010; Sheng & Lin, 2009; Szaflarski et al., 2006) (see Table 4), and was accompanied/related with the brain cortex plasticity change after treatment. However, improvement of the affected upper limb function was not reported for all of the patients in the studies (Butler & Page, 2006; Kim et al., 2006; Szaflarski et al., 2006; Wu et al., 2010). Dong et al. (2007) reported that long-term functional gains at six and 12 months after CIMT paralleled with decrease of activation in ipsilesional M1 in both of the two patients.

Correlational analyses to assess the relationship between results of clinical tests/measures of motor function and cortical activation or their changes were performed in few studies only, but the results were rather inconsistent. In the three studies they did not result in any statistically significant outcomes (Dong et al., 2007; Langan & van Donkelaar, 2008; Lin et al., 2010). For example, in the RCT by Lin et al. (2010), significantly greater improvement in the FMA and MAL was reported for the mCIMT group in comparison to the control group. However, an examination of the relationships between functional gains on the clinical measures and the changes in brain activation revealed no significant correlation (Lin et al., 2010). On the other hand, statistically significant correlations ($r = 0.91-0.96$) were reported for improvements in hand grip strength and increases in the ipsilesional hemisphere (see Table 3) and the cerebellum activity during performance of the affected hand (Johansen-

Berg et al. 2002). The authors chose grip strength ratio as the primary behavioural measure and did not calculate correlations with the other two measures (Table 4). Dong et al. (2006) reported no correlation between pre- to post- change in WMFT and change in activation in M1 or dorsal PMC of each hemisphere, except for pre- to mid- change in contralesional M1 voxel count, which correlated with the change in mean WMFT time (pre- to post-) ($r = 0.82$). The midpoint M1 laterality index anticipated post-treatment change in time to perform WMFT (Dong et al., 2006).

Study	Clinical tests/measures of motor function
Levy et al., 2001	MAL#, WMFT#
Johansen-Berg et al., 2002	Motricity index, Jebsen arm test, grip strength (difference not tested)
Schaechter et al., 2002	MAL*, WMFT*, FMA*, grip strength**, frequency of finger flexion, EMG
Kim et al., 2004	FMA*, 9-hole peg test, Jebsen arm test
Liepert et al., 2004	MAL*
Azpiroz et al., 2005	FMA*, Motricity index*, Modified Ashworth scale*, FIM*, Barthel index
Butler & Page, 2006	MAL# (2/3P), WMFT# (2/3P)
Dong et al., 2006	WMFT*
Hamzei et al., 2006	MAL*, WMFT*
Szaflarski et al., 2006	MAL# (3/4P), ARAT# (3/4P), FMA# (3/4P)
Dong et al., 2007	FMA#, WMFT#
Hamzei et al., 2008	MAL*, WMFT*
Langan & van Donkelaar, 2008	MAL*, WMFT, grip strength*, 9-hole pegboard task*
Sheng & Lin, 2009	Upper extremity function test#, Simple test for evaluating hand function#
Lin et al., 2010	FMA*, MAL*
Wu et al., 2010	FMA#, ARAT#, MAL (3/6P)

Table 4. Improvement of the affected hand movement characteristics or its use is shown after constraint-induced movement therapy or its modifications in patients after stroke. Legends are shown as: MAL, Motor activity log; # improvement, statistics not calculated; WMFT, Wolf motor function test; * statistically significant improvement; FMA, Fugl-Meyer assessment; EMG, electromyography; FIM, Functional independence measure; P, patient; ARAT, Action research arm test).

3. Conclusion

The preliminary findings of studying the effects of CIMT using fMRI indicate that brain plasticity may be modulated by specific therapeutic approaches, such as CIMT, although generalisation of the fMRI findings is limited by characteristics of the studies (sample size, control group, etc.). Limitations and future perspectives are as follows.

3.1 Limitations and current developments

Current fMRI findings of post stroke cortical reorganisation studies illustrate the lack of consensus regarding the type of cortical plasticity that is concomitant with movement recovery after CIMT. Some of the differences may be a consequence of small sample sizes, different lesion locations and studying in different periods post stroke, mostly six months or even several years after stroke. An important deficiency of the majority of the current studies is the absence of a control group, which would enable identification of the treatment effects of CIMT from the other influences on brain plasticity. In spite of the greatest possibility for a movement recovery during the first three months after stroke, no currently published study investigated the effects of CIMT on the brain plasticity measured by fMRI in this period. However, two studies with a control group performed in the first month after stroke are in a process (Kwakkel et al., 2008) or waiting for publication (Puh et al., in publication).

It seems that the fMRI data following a successful CIMT (with improved hand function) support two patterns of the brain reorganisation, as it was already suggested by some authors (Azpiroz et al., 2005; Hamzei et al., 2008). This would be: 1) increased or more spatially extensive activation area, indicating a recruitment of new brain areas; and 2) decreased or spatially reduced activation area, indicating more focused activation. Some evidence indicates that these patterns within the affected SM1 may depend on the integrity of the cortico-spinal tract from the M1 cortex (Hamzei et al., 2006, 2008).

The relationship between brain activation and functional gains needs further investigation. It is possible that correlations would be easily detected with the use of more objective or more direct measures of a specific movement recovery, as was in the case of hand grip strength (Johansen-Berg et al. 2002), and not in measures represented by scales or common scores.

3.2 Future perspectives

The heterogeneity of the fMRI findings underscores the need for further studies examining the mechanisms of cortical plasticity with the challenge to control the confounding factors. The effects of CIMT on brain reorganisation during movement of the affected and the unaffected hand should be analysed. A combination of fMRI and other techniques in brain imaging research, such as TMS and diffusion tensor imaging should be used to investigate the influence of the cortico-spinal tract integrity changes on the activation patterns seen with fMRI and might help to understand the functional significance of the contralesional brain hemisphere activity. The main challenge for the future is to identify the specific correlates between different clinical measures of the movement recovery achieved post-treatment and the fMRI data.

There is a need for common methodology of analysing and reporting the fMRI data. Clear presentation of the patients' characteristics such as gender, age, hand dominance before a stroke, type and event of stroke, and lesion location will enable investigations of their influence. More resemble sample characteristics, with emphasise on a time after stroke at inclusion to the same study may contribute to the homogeneity of the brain activation results and to establishment of the optimal time after stroke for CIMT application. The effects of different active and/or passive motor paradigms used during fMRI should not be ignored and need further investigation. Controlling the confounding factors may enable better comparisons and interpretations of the results between studies, aiming to understand and plan the effective treatment programs for patients after stroke based on brain plasticity principles. However, the most important seem to be an increase of sample size and inclusion of the control groups (with traditional rehabilitation or no treatment in this short study period), and execution of statistical analysis on the fMRI data.

Studies using fMRI may precede clinical studies of the optimal dose of constraint and practice in CIMT (comparison of different types of CIMT and mCIMT) which needs further investigation, including investigation of the long-term effects. In future, a comparison of the effects of different therapeutic techniques on the brain cortex reorganisation and upper extremity recovery, and identification of optimal integrated approaches combining CIMT and other techniques which facilitate the brain plasticity is necessary.

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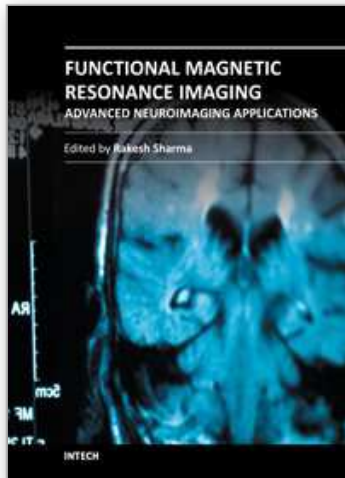
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Phone: +86-21-62489820
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