The neural basis of constraint-induced movement therapy

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Purpose of review

This review describes our current understanding of the changes in brain function and structure that occur in response to an intensive form of motor rehabilitation, constraint-induced movement therapy (CIMT), that has been shown to be efficacious in promoting motor function of the paretic upper limb of stroke patients.

Recent findings

Studies using transcranial magnetic stimulation have demonstrated consistently an increase in the size of the representation of paretic hand muscles in the ipsilesional motor cortex after CIMT. This motor map expansion occurs in response to CIMT delivered at all time periods after stroke, from within days to after several years. Functional neuroimaging studies have shown varying patterns of change in activation within the sensorimotor network after CIMT. This variability may depend on the extent of stroke-induced damage to the corticospinal tract, the major descending motor pathway in the brain. This variability may also stem from interacting plastic changes in brain structure occurring in response to CIMT.

Summary

CIMT is the first well defined poststroke motor rehabilitation to have identified changes in brain function and structure that accompany gains in motor function of the paretic upper limb. However, a causal link between observed changes in brain function/structure and motor gains due to CIMT has not yet been established. There is still much work to be done to understand the relationship between changes in brain function/structure and gains in motor function. Such studies should employ rigorous experimental controls to enable strong conclusions to be drawn regarding the neural effects of CIMT and how those effects confer behavioral efficacy of the therapy.

Keywords

MRI, neurophysiology, plasticity stroke, rehabilitation, transcranial magnetic stimulation

Introduction

A stroke that damages the brain's motor network may cause hemiparesis. At least partial recovery of this lost motor function typically occurs spontaneously over the subsequent days to months after stroke [1]. Motor recovery may be increased beyond that occurring spontaneously by certain poststroke therapies [2]. However, the majority of acute hemiparetic stroke patients never regain full motor function. Accordingly, there is much interest in understanding the neural mechanisms of motor recovery occurring spontaneously and that induced by motor rehabilitation. A poststroke motor rehabilitation that has received much attention is constraint-induced movement therapy (CIMT) because it has been shown repeatedly to have clinical efficacy [3–7]. The efficacy of CIMT offers scientists a means of designing studies that probe the neural mechanisms of motor recovery after hemiparetic stroke.

Constraint-induced movement therapy

Constraint-induced movement therapy is a multifaceted neurorehabilitation technique that aims to improve motor function and increase use of the hemiparetic upper limb in real-world activities [3]. The therapy derives from concepts of learned nonuse of a limb resulting from peripheral or central nervous system injury [8], and overcoming this learned behavior by both shaping its movement through iterative attempts to accomplish tasks and forcing its use through restraint of the contralateral limb [9,10]. These concepts have been translated into a relatively well defined poststroke therapy having three key elements. First, stroke patients participating in CIMT, manifest learned nonuse of the paretic upper limb at baseline, evidenced by relative little functional use of the limb while demonstrating at least moderate volitional motor control of the distal limb. Second, CIMT involves intensive task-oriented training of the paretic upper limb for several hours (usually six) for each weekday of

consecutive weeks (usually two). And, third, the therapy involves restraint of the contralateral upper limb by means of a splint, mitt and/or sling during most of the therapy period. Several relatively small studies have shown efficacy of CIMT in chronic stroke patients [3,4,6,11]. Clinical efficacy of CIMT was supported by the multisite EXCITE randomized clinical trial that involved more than 200 patients with first-ever stroke 3–9 months prior [7]. The study demonstrated greater and more long-lasting gains in motor function of the paretic upper limb after a 2-week period of CIMT than patients who received usual or customary poststroke care.

The repeated demonstration of clinical efficacy of CIMT has sparked a number of studies seeking to understand the neural changes mediating motor recovery after hemiparetic stroke. The relatively short time period required to observe measurable gains in motor function in response to CIMT and its relatively standardized method of implementation have provided scientists with a good tool to be applied in such research efforts. Further, the efficacy of CIMT in chronic stroke patients who are beyond the period of spontaneous recovery facilitates interpretation of neural effects seen after the therapy. The underlying premise of such studies has been that identifying the neural mechanism of motor gains would guide the development of new brain-targeted therapies that might amplify the effects induced by CIMT or facilitate motor gains in patients who, for various reasons, might not be amenable to participation in CIMT.

Methods and caveats of examining neural effects of constraint-induced movement therapy

There are several noninvasive methods for measuring brain function and structure in humans. Among these methods, transcranial magnetic stimulation (TMS) with measurement of motor-evoked potentials (MEPs) can provide information about functional status of the motor cortex [12]. Blood flow changes that accompany neural activity can be measured using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to provide information about recruitment of cortical and subcortical regions of the motor network during performance of a motor task. Properties of brain gray and white matter structure can be evaluated using MRI techniques such as high-resolution T1-weighted imaging and diffusion tensor imaging (DTI). With the exception of DTI, all these methods have been applied to investigate the neural mechanisms underlying the behavioral efficacy of CIMT.

An observed difference in brain function or structure in patients who received CIMT does not necessarily mean that the measured change caused the motor gain. To date, the results of studies in stroke patients cannot distinguish between scenarios (a) and (b) depicted in Fig. 1. Stroke

Figure 1 Observed changes in the brain and behavior after CIMT do not allow distinguishing between causal relationships depicted in scenarios (a) and (b)
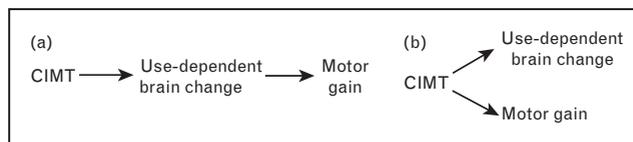
patients who participate in CIMT will, by design, increase the amount they use their paretic upper limb in motor activities. This increased limb use may cause a measurable change in brain structure or function, comparable to use-dependent changes observed in the intact adult brain [13–15]. This use-dependent change in brain structure/function may underlie the gain in motor function seen after CIMT [scenario (a)]. However, it is also possible that increased use of the paretic limb causes a change in brain structure/function that is epiphenomenal, not causally linked, to the motor gain after CIMT [scenario (b)]. The CIMT-induced gains in motor function might be caused by an undetected change in brain structure/function, or a change in motivation, or possibly a change in properties of musculoskeletal components of the paretic limb. To our knowledge, no study to date has been designed to test rigorously a causal relationship between changes in brain structure/function and motor gains after CIMT by either blocking development of the brain change suspected as conferring efficacy of CIMT (to prevent motor gains) or blocking expression of the brain change once developed (to reinstate motor deficits). Such testing might be possible in future studies that use TMS or transcranial direct current stimulation in an interference mode. Given the current lack of strong evidence supporting a causal link between the brain and behavioral changes observed after CIMT, we are left with understanding that these effects simply accompany one another.

With this caveat in mind, we describe below the current state of knowledge of the neural changes occurring in response to CIMT as measured by TMS and brain imaging methods for examining function and structure of the human brain. We emphasize knowledge acquired over the past few years.

Transcranial magnetic stimulation and constraint-induced movement therapy

In 1998, Liepert and colleagues [16] were the first to report a change in the brain in response to CIMT in stroke patients. Using TMS, they found an increase in the number of scalp locations that produced an MEP in the paretic hand. The ipsilesional motor map was shown to be smaller than normal at baseline and enlarge after CIMT, whereas the contralesional motor map showed changes in the

opposite direction. In this way, CIMT appeared to rebalance the motor representations of the hand in the two brain hemispheres. Subsequent studies have confirmed an expansion of the motor map in the ipsilesional hemisphere, making this finding one of the most reproducible in the field of neurorehabilitation [17–20,21•,22] (Table 1). Further, a subset of these studies has shown that the degree of map expansion correlates with improvement in some measure of motor ability after CIMT [16,21•]. Whereas such a statistical correlation does not prove causality, it provides stronger evidence of a biological link between motor map expansion and motor gains than a simple association between the two outcomes.

Most of the studies that have used TMS to examine changes in motor cortex function after CIMT have lacked adequate experimental control conditions, which prevents strong conclusions about the relationship between changes in motor map size and motor gains after CIMT. Most TMS studies have had either no control group, or a waiting period (usual care) control, or a much less active therapy (Table 1). A favorable exception is the study by Liepert and colleagues [23] who tested motor map and behavioral effects in patients early after stroke after a period of conventional therapy and again after a period when CIMT was added. They found that only after the addition of CIMT did patients show significant increases in map size and motor function of the paretic hand. In another study that used adequate control conditions, acute/subacute patients were randomized to CIMT or an intensive form of traditional therapy that was matched to approximate the frequency and duration of CIMT [22]. On the basis of measurement of motor function of the paretic upper limb by assessors blinded to group assignment, motor gains in the two groups did not differ significantly based on the primary outcome measure (3-month Fugl-Meyer Stroke Scale Score). However, some secondary outcome measures of motor function showed significantly, or trended toward, greater gains in the CIMT group compared to the control group. In parallel, the patients who received CIMT showed a trend toward greater map expansion at follow-up testing compared to those who received the control therapy. Together, these few controlled studies bolster support of a close link between motor gains induced by CIMT and motor map expansion. The hypothesis that map expansion is a mechanism supporting motor recovery induced by CIMT in stroke patients is consistent with results of studies in normal adults that have shown gains in motor skill accompanied by map expansion in the contralateral motor cortex as measured by TMS [30,31].

How does one interpret motor map expansion from a neurobiological perspective? Map expansion as measured by TMS does not necessarily mean that the absolute borders of a muscle representation have changed. Rather, map expansion may indicate increased responsiveness of neural elements at the edges of the muscle representation. An elevation in excitability at map edges could theoretically be accounted for by a reduced motor threshold at the map center. However, studies have generally found no change in motor threshold after CIMT (e.g. [21•]). Further, most studies adjusted the intensity at which the motor cortex was stimulated relative to the resting motor threshold determined at each session, thereby experimentally controlling for possible changes in motor threshold. An apparent change in map size could result from a change in the stimulus–response curve of motor cortex neurons in a geometrically unchanged map. However, the recent study by Sawaki and colleagues [21•] also ruled out a change in the stimulus–response curve as accounting for map expansion. Further, a change in the stimulus–response curve seems an unlikely mechanism because a very dramatic change in slope would be required to yield the observed degree of map size expansion after CIMT. This leaves us with the most likely explanation – that neuronal elements of the motor cortex [not necessarily the upper motor neurons (UMNs) themselves] at a greater distance from the map center become more able to trigger UMN activity after CIMT. This may occur through disinhibition of UMN, reduced lateral inhibition and/or strengthening of excitatory lateral connectivity.

Neurophysiological studies in nonhuman primates with partial lesion to the primary motor cortex have demonstrated spatial shifts in motor maps after intensive motor therapy that restored motor skill of the impaired forelimb [32]. Similarly, in stroke patients who participate in CIMT, spatial shifts of the motor map have been found in several of the aforementioned studies describing map expansion. Initial findings suggested that a lateral shift in the motor map supported recovery [16]. However, subsequent studies have reported motor map shifts in various directions [16,23,33], raising the possibility that individual patterns of remapping accompany gains in motor function after CIMT. It is also possible that the impression of a map shift results from the high degree of variability in the amplitude of MEPs recorded from the paretic hand, introducing nonsystematic errors in determining a map's center of gravity. MEP variability represents a general problem in the use of TMS to measure motor cortex parameters in stroke patients. Since MEPs caused by TMS depend on corticospinal tract (CST) activity, when the CST is damaged due to stroke, measurement of TMS effects on the ipsilesional motor cortex may become unreliable or undetectable.

Brain imaging and constraint-induced movement therapy

In 2001, Levy and colleagues [34] were first to report on changes in brain activation in two patients with chronic

Table 1 Selected studies that examined brain effects of CIMT in stroke patients

Reference	Modality	Cohort	Results	Controls/caveats
Liepert et al. [16]	TMS	6 chronic (0.5–17 years)	Thumb map enlarges, lateral shift correlated with motor gain	No control group
Liepert et al. [17]	TMS	13 chronic (0.5–17 years)	Thumb map enlarges, eventual equality with contralesional motor map	No control group
Liepert et al. [23]	TMS	9 subacute (4–8 weeks)	Thumb map enlarges after period of added CIMT, not after conventional therapy only, mixed medial/lateral shift	Conventional therapy first, then conventional therapy and CIMT
Johansen-Berg et al. [24]	fMRI	7 chronic (6–84 months)	Increased activation in ipsilesional dorsal premotor cortex, ipsilesional secondary somatosensory cortex and bilateral cerebellum correlates with motor gains after CIMT	No control group. Modified CIMT (home-based)
Schaechter et al. [25]	fMRI	4 chronic (7–20 months)	Shift in laterality of activation toward contralesional motor cortices (trend)	No control group
Wittenberg et al. [18]	TMS, PET	16 chronic (1–7 years)	Finger extensor or thumb map enlarged in half of patients after CIMT, none in controls; reduced ipsilesional motor cortex activation after CIMT	Passive/bilateral therapy control group. Only maps of two of eight control patients could be evaluated
Dong et al. [26]	fMRI	8 subacute–chronic (>3 months)	Time-dependent decrease in contralesional motor cortex activation; early change in contralesional motor cortex activation correlated with motor gain after CIMT	fMRI before and after CIMT and mid-way. Healthy control group to test fMRI reproducibility.
Hamzei et al. [27]	TMS, fMRI	8 chronic (1.5–10 years)	Dichotomy: reduced ipsilesional sensorimotor cortex activation and increased intracortical excitability after CIMT if intact CST at baseline; increased activation and decreased intracortical excitability if damaged CST at baseline	No control group. Passive finger movement during fMRI
Hamzei et al. [28•]	TMS, fMRI, structural MRI	6 chronic (2–6 years)	Same dichotomy as above: increased/decreased sensorimotor cortex activation and excitability depended on extent of CST damage	No control group. Passive finger movement during fMRI. Modified CIMT (less intense, longer)
Boake et al. [22]	TMS	23 acute–subacute (<2 weeks)	Thumb map appears/expands in both groups; no significant difference in map expansion between groups	Intensive traditional therapy control. Early map progression unknown due to high thresholds
Gauthier et al. [29]	Structural MRI	36 subacute–chronic (3.6 ± 3.6 years)	Increased gray matter density in bilateral sensorimotor cortex and hippocampus after CIMT; no change in density and lesser gains in motor function after control therapy	Control therapy involved all components of CIMT except 'transfer package'
Sawaki et al. [21•]	TMS	30 subacute–chronic (3–9 months)	Finger extensor map enlarges (strong trend) after CIMT, contracts in controls; one force measure correlates with map change	Usual care control group

CIMT, constraint-induced movement therapy; fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation.

stroke who received CIMT. Using fMRI, they showed that gains in motor function after CIMT were accompanied by increased activation in the contralesional hemisphere and peri-infarct zone in one of the patients, and in the ipsilesional hemisphere in the other patient. Among the several subsequent studies that examined a link between CIMT-induced gains in motor function and changes in brain activation in stroke patients, perhaps the most striking aspect is the lack of consistency among study findings. For example, using PET, Wittenberg and colleagues [18] showed decreased activation in the ipsilesional sensorimotor cortex during a motor task performed by the paretic hand. In contrast, using fMRI, Johansen-Berg and colleagues [24] showed that gains in motor function correlated with increased activation in the ipsilesional premotor, ipsilesional secondary somatosensory cortices and bilateral cerebellum. Further adding to the inconsistency, Schaechter and colleagues [25] found a shift in the laterality of fMRI-measured activation toward the contralesional motor cortices relative to the ipsilesional motor cortices. Whereas differences in image acquisition and data analysis among these studies may have contributed to these discrepancies, the profound divergence of findings suggests that one or more other factors strongly influence the response of the sensorimotor network to CIMT.

Time-dependent changes in brain response

Recent studies have begun to shed light on three factors that may contribute to the divergent changes in brain activation after CIMT in stroke patients. First, a study by Dong and colleagues [26] showed that changes in brain activation during the course of the 2-week therapy varied over time and among individual stroke patients. On a group basis, greater gains in motor function by the end of the 2-week therapy correlated with greater decreases in activation in the contralesional primary motor cortex (M1) from before therapy to the mid-way point of therapy, but not with the magnitude of decreased contralesional M1 activation from before to after therapy. These results imply that multiple brain processes accompany CIMT-induced gains in motor function. The initial process may involve a reduction in contralesional M1 activation that relates linearly to motor gains to be achieved by the end of the therapy. Subsequent process(es) occurring from the mid-point to the end of therapy may involve redistribution of sensorimotor network activity that results in reduced contralesional M1 activation, yet the level of this reduction is not related linearly to motor gains. Notably, the finding that the degree of change in contralesional M1 activation during the early period of CIMT had predictive value for endpoint motor recovery may have future clinical utility in the development of tools for monitoring and adjusting poststroke motor therapies to maximize motor recovery in individual patients.

Effect of corticospinal tract damage

A second factor contributing to individual differences in brain reorganization in response to CIMT may be infarct location. Hamzei et al. [27] showed that the presence or absence of stroke-induced damage to the CST corresponded to the direction of change in fMRI and TMS measures of function of the ipsilesional sensorimotor cortex after CIMT. Damage to the CST, the major pathway in the brain controlling volitional movement, was determined by the presence of abnormal TMS-induced MEPs and lesion visualization on structural MRI. Accompanying the motor gains after CIMT, patients with CST damage exhibited increased fMRI activation of the ipsilesional sensorimotor cortex. Using a paired-pulse method of TMS, these patients also exhibited reduced intracortical excitability of the ipsilesional motor cortex. In contradistinction, patients with no stroke-induced damage to the CST showed the opposite changes in brain function after CIMT – decreased activation of the ipsilesional sensorimotor cortex accompanied by elevated intracortical excitability. These authors suggested that this dichotomy reflects utilization of different brain reorganization processes to achieve motor gains induced by CIMT. In stroke patients without CST damage, the observed brain changes may reflect improved efficacy of synapses within the ipsilesional sensorimotor cortex. In patients with CST damage, the observed brain changes may reflect reorganization of the ipsilesional sensorimotor cortex in conjunction with changes in inter-regional communication within the broader sensorimotor network. Along these lines, after CIMT, stroke patients with presumed damage to the CST have shown changes in local and remote activation within the sensorimotor network, measured by PET in response to subthreshold TMS delivered to the ipsilesional M1 [35].

A recent follow-up study by Hamzei and colleagues [28•] implemented a lesion map analysis based on structural MRI to obtain more refined measurement of CST damage. They showed that patients who exhibited increased sensorimotor cortex activation and decreased intracortical excitability after CIMT had greater damage to the CST than patients with decreased sensorimotor cortex activation and increased intracortical excitability after therapy [28•]. It would be of interest to learn in the future, based on study of a sufficiently large group of patients, the threshold level of damage to the CST that switches responses to CIMT from decreased activation/increased excitability to increased activation/decreased excitability in the ipsilesional sensorimotor cortex. Such information could become important in the development of an algorithm for predicting brain reorganization in response to CIMT, which could be used to monitor the efficacy of this therapy.

A recent study by Gauthier and colleagues [29] found that the magnitude of motor gain in chronic stroke patients in

response to CIMT was independent of lesion location. Together with that described above, these findings suggest that multiple patterns of reorganization that utilize spared regions of the sensorimotor network can support comparable levels of improvement in motor function induced by CIMT in chronic stroke patients.

In contrast, a recent study by Kuhnke and colleagues [36•] suggests that the extent of CST damage does influence the magnitude and domains of improvement in motor function due to CIMT. These investigators studied pediatric patients with congenital hemiparesis who exhibited functional CST projections exclusively from either the ipsilesional motor cortex or the contralesional motor cortex, determined by detection of MEPs in the paretic hand caused by TMS. Both patient groups showed improved quality of paretic limb movement after CIMT. However, only those patients with functional CST projections from the ipsilesional motor cortex showed improvements in movement speed. Whereas it is unknown whether the brain processes mediating CIMT-induced gains in motor function are the same in patients with acquired (adult onset stroke) versus congenital damage, this study raises the interesting possibility that different aspects of the behavioral gains seen after CIMT are mediated by different neural substrates.

Structural plasticity
The third factor that may contribute to the divergent patterns of brain activation observed after CIMT is structural plasticity. There is growing knowledge that plastic changes of gray and white matter occur in the adult brain after stroke [37,38]. Gauthier and colleagues [39•] were the first to report a change in gray matter structure in response to CIMT. After CIMT, and not a comparison therapy, chronic stroke patients showed an increase in the density of gray matter in bilateral sensorimotor cortices and hippocampi, measured by voxel-based morphometry applied to high-resolution T1-weighted magnetic resonance images. Further, the magnitude of increased density of these gray matter regions correlated significantly with greater gains in motor function of the paretic upper limb. The cellular changes that underlie the observed increases in gray matter density are not known. It is possible that CIMT-induced changes in gray matter structure interact with those in brain function, making measurement of activation responses after CIMT a more complex marker of brain plasticity underlying the behavioral gain.

Recent findings are beginning to point to the possibility that remodeling of white matter may contribute motor gains after CIMT. Maier and colleagues [40•] recently demonstrated in an animal model of CST damage that postinjury casting of the unimpaired forelimb (as in CIMT applied to patients) resulted in full behavioral recovery, whereas those animals whose impaired limb was casted remained impaired. Notably, behavioral recovery of the animals with unimpaired forelimb casting was accompanied by an increase in the density of CST axon collaterals terminating in the denervated spinal cord, as measured histochemically after axonal transport of a molecular label injected into the contralesional sensorimotor cortex. In chronic stroke patients, recent work using DTI has suggested that bilateral CST remodeling may contribute to motor recovery occurring spontaneously after stroke [41]. By extension, it is possible that future DTI studies may reveal that CST remodeling contributes to motor recovery promoted by CIMT.

Conclusion
Transcranial magnetic stimulation and brain imaging studies have demonstrated that the brain undergoes plastic changes in function and structure that accompany the gains in motor function in stroke patients who participate in CIMT. These plastic changes appear to vary among patients depending on the extent of damage to the CST. However, some functional changes, such as expansion of the ipsilesional motor map and an initial decrease in contralesional M1 activation, may be relatively strongly correlated with motor gains induced by CIMT independent of CST damage. Future studies aimed at understanding the relationship between changes in brain function/structure and gains in motor function should employ rigorous experimental controls to enable strong conclusions to be drawn regarding the neural effects of CIMT. Further, future studies should aim to test directly a causal link between observed changes in brain function/structure and motor gains due to CIMT.

References and recommended reading
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This study tested whether the clinical efficacy of CIMT differed in pediatric patients with congenital hemiparesis depending on whether functional CST projections to the paretic hand were exclusively from the ipsilesional or contralesional motor cortex, as determined the presence of MEPs cause by TMS. They found that CIMT improved movement quality in both patient groups, but movement speed in only the patients with functional CST projections from the ipsilesional motor cortex. These data suggest that integrity of the crossed CST may be critical for CIMT to reduce motor impairment. Other brain structures may be involved in improving other aspects of motor function due to CIMT.

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38   Dancause N, Barbay S, Frost SB, et al. Extensive cortical rewiring after brain injury. J Neurosci 2005; 25:10167–10179.

39   Gauthier LV, Taub E, Perkins C, et al. Remodeling the brain: plastic structural
•   brain changes produced by different motor therapies after stroke. Stroke 2008; 39:1520–1525.
This structural MRI study showed an increase in gray matter density in bilateral sensorimotor cortices and hippocampus in patients after CIMT, and not those who received a comparison therapy. The comparison therapy included most of the elements of CIMT but excluded the 'transfer package' that is intended to reinforce increased use of the paretic upper limb in real world activities outside the therapy setting.

40   Maier IC, Baumann K, Thallmair M, et al. Constraint-induced movement
•   therapy in the adult rat after unilateral corticospinal tract injury. J Neurosci 2008; 28:9386–9403.
This study was conducted in rats with experiment lesion of unilateral CST in the brainstem and then treated with casting of the unimpaired forelimb (analogous to that applied in CIMT) or the impaired forelimb. Animals with the unimpaired, and not the impaired, forelimb casting regained full motor function and showed remodeling of the intact CST projecting from the contralesional motor cortex and innervating the denervated spinal cord.

41   Schaechter JD, Fricker ZP, Perdue KL, et al. Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Hum Brain Mapp 2009 [E-pub ahead of print].