



Review Article

Post-stroke motor recovery and cortical organization following Constraint-Induced Movement Therapies: a literature review

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Abstract. [Purpose] This review synthesizes findings from studies on two forms of Constraint-Induced Movement Therapies: the original Constraint-Induced Movement Therapy and the modified Constraint-Induced Movement Therapy, in adult stroke patients including the evidence, current limitations and future directions. [Methods] We critically reviewed studies evaluating the effectiveness of Constraint-Induced Movement Therapies in chronic stroke focusing on the functional (i.e. motor recovery) and the neural (i.e. cortical organization) levels. [Results] Constraint-Induced Movement Therapies seemed to improve the upper limb functional usage in chronic stroke with no reliable neurophysiological underlying mechanisms. The Motor Activity Log was the common outcome measuring motor recovery. The work that has been done on modified Constraint-Induced Movement Therapy was far less than the work done on the original Constraint-Induced Movement Therapy. [Conclusion] Evident lack of understanding of the association between changes in motor recovery and the underlying neural mechanisms in-terms of measures of assessing and defining functional recovery (i.e Motor Activity Log) that lacks sufficient sensitivity to characterize changes in movement strategies and thereby lack of distinction between recovery and behavioral compensation. Future studies should employ using kinematic metrics to quantify and explain the training-related changes in behavior following Constraint-Induced Movement Therapies in chronic stroke.

Key words: Stroke, Brain, Constraint-Induced Movement Therapy

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INTRODUCTION

Stroke is considered the fifth leading cause of death and affects at least 6.4 million persons in the United States¹⁾. Projections show that by 2030, an additional 3.4 million people above 18 years old will have had a stroke which is approximately a 20.5% increase in prevalence from 2012 statistics¹⁾. Above all, Stroke is a leading cause of serious long-term disability¹⁾.

Arm paresis is one of the most common impairments after stroke²⁾. After six months, about two-thirds of patients continue to suffer from arm sensorimotor impairment that impacts the individual's activities of daily living³⁾. Motor deficits consist of weakness of specific muscles⁴⁾, abnormal muscle tone⁵⁾, abnormal postural adjustments⁶⁾, abnormal movement synergies⁷⁾, lack of mobility between structures at the shoulder girdle⁶⁾, and incorrect timing of components within a movement pattern⁸⁾. As a result of such impairment, patients may progressively avoid using the affected arm in favor of the unaffected arm for successful ADL, resulting in a learned non-use phenomenon⁹⁾.

The complications after a stroke may persist for many years and the need for rehabilitation may be a lifetime endeavor. As a result of that, theories in stroke rehabilitation vary in the interventions applied to address motor deficits. Theories in stroke rehabilitation involve the use of conventional treatment such as Range of Motion (ROM) and strengthening exercises

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in a technique depending on the compensatory strategies in recovery¹⁰). Other theories using neurodevelopmental (NDT) approach¹¹) and the Proprioceptive Neuromuscular Facilitation (PNF) technique¹²). Motor learning principles^{13, 14}), i.e., intense and structured training using Constraint-Induced Movement Therapies (CIMTs) including the original Constraint-Induced Movement Therapy (CIMT) and the Modified Constraint-Induced Movement Therapy (mCIMT) have been shown to improve arm functionality even in the chronic stage of stroke. The focus of these two therapies lies with forcing the patient against the non-use phenomenon to use the affected limb by restraining the unaffected one. The affected limb is then used intensively under a massed practice for several hours per week by employing rehabilitation approaches that are based on theories of motor learning¹⁵). As a result, the patients engage in repetitive exercises with the affected limb with the hope that the brain grows new neural pathways. Practitioners say that stroke victims disabled for many years have recovered the use of their limbs using CIMT. In fact, CIMT therapy is “at the forefront of a revolution” in the field of neuro-rehabilitation in terms of recovery for stroke survivors¹⁶). Although there are differences between the two therapies, they both share the concept of incorporating physical constraint of the unaffected limb in order to facilitate use of the paretic limb¹⁷). CIMT involves massed practice of the affected arm (4–6 hours per session) and restraint of the unaffected arm during most waking hours (90%). On the other hand, mCIMT involves a less intensive form of practice (0.5–2 hours/session) and restraining the nonaffected arm for 5–6 hours/day. However, the clinical feasibility of CIMT has been questioned because of the nature of the duration of the intervention applied so that patients may not participate and the therapist would report that their facilities could not administer such an intensive time-consuming protocol¹⁸). Therefore, mCIMT has been proposed as a less intensive form and is considered one of the promising interventions for improving upper limb performance in stroke patients.

A major limitation is rehabilitation generally and in CIMTs specifically is the lack of understanding of recovery in-terms of measures of motor recovery used in assessing and defining functional recovery and the underlying neurological recovery. Such Understanding for this relationships would add more in-depth insights on the functional relevance of plastic brain changes in stroke following CIMTs to optimize the field of neuro-rehabilitation.

This review is an in-depth evaluation of research on CIMTs in the management of upper limb dysfunction following a stroke. We conducted a quality review for the literature on the effectiveness of both forms of therapies (i.e. level of evidence) to bridge the gap between functional (i.e. motor recovery) and the neural (i.e. cortical organization) recovery in patients in the chronic stage following stroke.

METHODS

We conducted a literature search to meet the objective of our systematic review. MEDLINE database was used to search the literature between January 2000 and October 2018. The search was limited to articles written in English and the database was accessed online through the local university’s library system in November 2018.

Specific key words and their combinations using the “AND” operator were used for the purpose of the literature search. These key words include: “Constraint-induced movement therapy” “stroke” “chronic” “brain organization” “cortical organization” “fMRI”. The screening process were done by one reviewer. The inclusion criteria were: (1) adult patients (≥ 18 years) clinically diagnosed with a stroke; (2) level of evidence (levels I=large randomized controlled trial, low error risk; level II=small randomized trial, moderate to high error risk; (3) the experimental intervention conformed to the definitions of CIMTs including CIMT and mCIMT; (4) outcomes measured post intervention and/or at follow-up; and (5) articles published in the English.

In part one of this review, a qualitative review process was used to account for the variety of the study designs, outcome measures and analysis used. A modified version of Sackett’s 1981¹⁹) critical appraisal criteria (random assignment, blinding, intervention monitoring, dropouts, reliability and validity of measurements) was used to modify the quality of the studies. When information within an article was not sufficient to ascertain if a criterion had been fulfilled, a “No” rating was given. The level of evidence supported by each study design and the grade of recommendation for identified outcomes were then determined as described by Sackett²⁰).

Part two of this review aimed to synthesize finding from studies on the effects of CIMTs on cortical reorganization to analyze the neural substrates of motor learning after stroke following CIMTs and how they may relate to recovery.

RESULTS

Table 1 and 2 summarizes the finding from our review on CIMT and mCIMT, respectively. We found four articles^{21–25}) describing results following the use of CIMT (Table 1) and four articles^{25–28}) describing results following mCIMT in patients with chronic stroke (Table 2) that met our criteria. The total number of participants (patients and normal participants) in each study varied from seven to two hundreds twenty two and from seventeen to thirty-five in CIMT and mCIMT, respectively. All participants included were in the chronic stage after stroke. For CIMT, the treatment protocol varied from ten days—three weeks with daily sessions by restraining the affected arm for six hours per day 90% of waking time (Table 1). For mCIMT, the treatment protocol varied from three to ten weeks. The nature of less intense form of CIMT varied by reducing the session time or frequency or both (Table 2).

CIMT and mCIMT are forms of therapy that help stroke victims regain the use of affected limbs (American Stroke Asso-

Table 1. Evidence of the motor recovery of Constraint-Induced Movement Therapy (CIMT) on upper limb function

Study	Design	Level of evidence	Time after stroke	Treatment protocol	Outcome measures	Results (sig, not sig)*	Follow up
Myint et al., 2008 ²³⁾	RCT Single blinded	II	2–16 weeks (Total 43: 23 treatment group, 20 control group)	CIMT: 10 days, 4 hrs/day 90% of waking time	MAL, Action Research Arm (ARA) Test and modified Barthel Index	Sig	12 weeks (Sig)
Wolf et al., 2006 ²⁴⁾	RCT	I	3–9 months (222 stroke)	CIMT: 2 weeks, 7 days/ week, 6 hrs/session 90% of waking time	Wolf Motor Function Test (WMFT), (MAL)	Sig	12 months (Sig)
Bonifer et al., 2005 ²¹⁾	Within- participants design; pre- and posttesting	III	>12 months (7 participants)	CIMT, 3 weeks, daily, 6 hrs/day 90% of waking time	Fugl-Meyer Assessment (FMA), Graded Wolf Mo- tor Function Test (GWMFT), and (MAL)	Sig	1 month (Sig)
Brogårdh et al., 2006 ²²⁾	RCT	II	Average 28.9 months (16 stroke patients)	CIMT: 12 days, 6 hrs/day 90% of waking time	Modified Motor Assessment Scale (MAS), MAL	Sig	3 months (Sig)

ciation, 2004)¹⁶⁾. For CIMT, the level of evidence varied from level III to level I (Table 1). For mCIMT, the level of evidence was level II for all studies (Table 2). Although CIMTs were the independent variable in all studies, the overall treatment days and hours per session varied among studies and had an average of 20–45 minutes. The CIMTs protocols in all studies were predetermined and applied equally to all participants included in each study. All studies were prospective and the included participants were clinically diagnosed with an stroke in the subacute to chronic stages.

Results of the quality review for CIMT and mCIMT are presented in Table 3. Overall the results were satisfactory. Overall, the intervention in all studies was well monitored and supported the aim of the studies. All studies included chronic stroke survivors to avoid contamination with other recovery potentials following stroke²⁹⁾. Blinded assessment were reported in most studies to reduce or eliminate bias even though in most studies it was a single-blinded design³⁰⁾.

Studying the cortical reorganization associated with CIMTs has been done using many methods including Functional magnetic resonance imaging (fMRI), Transcranial Magnetic Stimulation (TMS) and Positron Emission Tomography (PET). Studies on the effects of CIMTs on cortical reorganization were discussed to analyze the neural substrates of motor learning after stroke following CIMTs (Table 4). We found six studies describing results following CIMT and one study following mCIMT. The total number of participants (patients and normal participants) in each study varied from one to sixteen in CIMT and mCIMT. All participants included were in the chronic stage after stroke.

DISCUSSION

Although allocation of stroke recovery services have been traditionally based on the belief that recovery occurs within the first three months and is complete by twelve months³¹⁾, further improvement has been shown to occur with intervention beyond that period^{32, 33)}. With time available for upper limb training rapidly diminishing, the search for effective and efficient strategies to maximize upper limb recovery has become more pressing. Many studies showed that CIMT is effective in improving upper limb functional recovery so that it enhances the recovery within the first year and even after one year, immediately after the treatment and on the follow up assessment in most of the studies (Table 1).

Post-stroke upper limb functional recovery has been evaluated by using several outcome measures³⁴⁾. Examples on such measures and specifically those in CIMTs studies include the Motor Activity Log (MAL)³⁵⁾, Fugl-Meyer Assessment (FMA)³⁶⁾, Motor Assessment Scale (MAS)³⁷⁾ and the Wolf Motor Function Test (WMFT)³⁸⁾. However, the criteria for assessing and defining functional recovery have been ambiguous. Most studies have used clinical indicators of impairment and/or kinematic outcomes (i.e., movement speed) to measure intervention effectiveness without consideration of how these gains were attained (i.e., movement quality). Indeed, many outcomes used in stroke rehabilitation have limited objective ability to characterize movement strategies³⁹⁾. For example, the WMFT assesses gross- and fine-motor components during a set of functional tasks. All tasks are timed and rated based on the functional ability. However, several concerns are present in regard to using WMFT in stroke rehabilitation field. One limitation related to the validity of using this outcome in severely impaired patients who cannot complete many of the tasks considering the time limit of 120 seconds for each task. Therefore, this test has limited ability to quantify overall changes in performance in moderate to severely impaired patients⁴⁰⁾. Another common tool used in stroke rehabilitation is Fugl-Meyer Upper Extremity Assessment (FMUE). FMUE, composed of scales for sensa-

Table 2. Evidence of the motor recovery of Modified Constraint-Induced Movement Therapy (mCIMT) on upper limb function

Study	Design	Level of evidence	Time after stroke	Treatment protocol	Outcome measures	Results (sig, not sig)*	Follow up
Wu et al., 2007 ²⁵⁾	RCT	II	0.5 to 31 months (13 participants, 13 traditional treatment)	mCIMT The unaffected limb. 3 weeks, 5 times/wk, 2 hrs/session. With restraining the arm for 6 hours each week day	FMA, FIM instrument, MAL, and Stroke Impact Scale (SIS,	Sig	N/A
Page et al., 2008 ²⁷⁾	Multiple-baseline, randomized, pretest-posttest control group	II	20–60 months (35 participants: 13 treatment group, 12 traditional treatment, 10 no treatment)	mCIMT protocol: half-hour/session, 3 times/week, 10 weeks, with restraining the nonaffected arm for 5 hours every weekday during the same 10-week intervention	The Action Research Arm Test (ARAT), MAL	Sig	N/A
Lin et al., 2007 ²⁶⁾	RCT	II	13–26 months (32 participants: 16 treatment group, 16 control)	mCIMT with intensive treatment, 3 weeks (daily), 2 hrs/session and restriction for 6 hrs/day	MAL, FIM	Sig	N/A
Page et al., 2004 ²⁸⁾	Multiple-baseline, pre-post, single-blinded RCT	II	>1 year (Total 17 participants: 7 treatment group, 4 regular treatment, 6 no treatment)	mCIMT with intensive treatment, 10 weeks, 5 days/wk, 5 hrs/day	FMA, ARA test, MAL	Sig	N/A

Table 3. Quality review

	Avoided contamination and co-intervention	Random assignment to conditions	Blinded assessment	Monitored intervention	Accounted for all participants	Reported reliability of measures used	Reported validity of measures used	Total number of criteria met
Constraint-Induced Movement Therapy								
Myint et al., 2008 ²³⁾	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Wolf et al., 2006 ²⁴⁾	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Bonifer et al., 2005 ²¹⁾	Yes	No	No	Yes	Yes	Yes	Yes	5
Brogårdh et al., 2006 ²²⁾	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Modified Constraint-Induced Movement Therapy								
Wu et al., 2007 ²⁵⁾	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Page et al., 2008 ²⁷⁾	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Lin et al., 2007 ²⁶⁾	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Page et al., 2004 ²⁸⁾	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

tion, proprioception, joint pain, range of motion (shoulder, elbow, wrist and fingers), reflex activity, and joint co-ordination and having an excellent intra-rater and inter-rater reliability^{41, 42)}, is one of the most comprehensive quantitative measures of motor impairment after stroke⁴³⁾. However, the FMUE components neither assess purposeful reaching tasks nor quantify the functional impairments due to spasticity or weakness⁴³⁾. In addition, ceiling effect, particularly for the patients with mild

Table 4. The cortical organization following Constraint-Induced Movement Therapies (CIMTs)

Intervention	Study	Number of participants	Outcome measures	Results
CIMT	Levy et al., 2001 ⁶⁵⁾	2 participants	fMRI	Participant No. 1 showed activity bordering the lesion, bilateral activation in the association motor cortices, and ipsilateral activation in the primary motor cortex (inconsistent lateralization), Participant No. 2 showed activation near the lesion site.
	Schaechter 2002 ⁶⁷⁾	4 participants	fMRI	Increased unlesioned hemisphere activation post treatment and at 6-month follow-up.
	Kim et al., 2004 ⁸⁶⁾	5 participants	fMRI	Three patients increased lesioned (contralateral) hemispheric activity, 1 patient increased unlesioned activity and 1 patient reduced lesioned hemisphere activity.
	Liepert et al., 2000 ⁸⁷⁾	13 participants	TMS	Expansion of the more affected arm representation post treatment.
	Park et al., 2004 ⁵⁷⁾	Case study	TMS + fMRI	TMS: Increased excitability of the contralateral (left) motor cortex fMRI: contralateral (left) motor cortex activation with smaller ipsilateral activation.
	Wittenberg et al., 2003 ⁵⁶⁾	16 participants	TMS + PET	TMS: Greater map volume of the more affected arm than the control group PET: reduced area activation of the more affected hand movement than controls.
Modified Constraint-Induced Movement Therapy	Szaflarski et al., 2006 ⁸⁸⁾	4 participants	fMRI	Only 3 participants showed cortical changes which was positively related to the degree of increase in the affected arm use and ability. 1 participant exhibited minimal affected arm use changed with no cortical fMRI changes.

impairment, and the presence of some components (such as reflexes) that do not make a significant contribution to the assessment of impairment⁴⁴⁾ have been identified as further limitations of FMUE. Furthermore, FMUE scores can be obtained by using combined measures of the trunk and shoulder flexion movements during a reach-to-grasp task⁴⁵⁾. Therefore, it may be reasonable to exclude some components, i.e., reflexes, and to decompose FMUE score in sub-scores accordingly to proximal and distal segments. In summary, the WMFT and FMUE assessments provide valuable information regarding motor performance and motor impairment after stroke, yet they do not provide precise quantitative data on movement strategies and thereby lack the sufficient sensitivity to characterize changes in movement strategies especially longitudinally over time.

For most of the studies that examined the effectiveness of CIMT, there was a significant improvement in all the outcome measures. Among these outcome measures, the Motor Activity Log (MAL) was the most commonly used one and showed a significant result in all studies (Table 1). Further, MAL is a reliable and valid real-world, upper-extremity rehabilitation outcome and functional status in patient with chronic stroke specifically following CIMTs⁴⁶⁾. In this analysis; MAL will be used for the purpose of showing whether there are similar effects of the mCIMT on participants post stroke.

The Motor Activity Log (MAL) is a scripted, structured interview that was developed by Taub et al.³³⁾ to measure the effects of CIMTs on use of the affected arm outside the laboratory in individuals with stroke. This measure is represented by measuring two categories: the amount of use and the quality of movement of the affected arm. The MAL scores varies from 0 to 5 so that 5 given to normal functioning of the upper limb. Uswatte et al.⁴⁷⁾ examined the reliability and the validity of MAL as a common measure in the assessment of the upper limb functioning after the use of CIMTs. In their study, they examined the reliability and the validity of the measure by measuring the outcomes before and after the application of the CIMT. They concluded that MAL can be used exclusively to reliably and validly measure real-world, upper-extremity rehabilitation outcome and functional status in chronic stroke patients with mild-to-moderate hemiparesis. However, just like the previously discussed FMA and WMFT, MAL is a self-rated, patient reported Outcome measure with high subjectivity. Therefore, it is reasonable to conclude that MAL lack the sufficient sensitivity to characterize changes in movement strategies and thereby lack of distinction between recovery and behavioral compensation.

As shown in Table 1, most studies' designs are Randomized Controlled Trials. One of the studies, Wolf et al.²⁴⁾ was a RCT with a large sample size (Two hundred twenty-two individuals) who were clinically diagnosed with ischemic stroke. This study showed a strong level of evidence of the effectiveness of CIMT in improving the functional activities of the hemiparetic limb that persisted one year after the treatment. The MAL quality of movement scale increased significantly from 1.26 to 2.23 and the improvement in the MAL amount of use after the treatment was 1.21 to 1.65.

Table 2 showed some of the studies that examined the effects of mCIMT on participants after a stroke. As for the CIMT, the MAL was the common clinical outcome measure for examining the effect of mCIMT on the upper limb function. All

of the studies showed that mCIMT is an effective, promising and feasible intervention that could be a better option for rehabilitation other than the original CIMT. Unfortunately, the studies have limitations that made the comparison unfair or unequal. Although the studies were randomized controlled trials, they shared few common limitations including small sample size with a lot of independent variables. For most of the studies the number of participants was relatively small, so that no study had a strong level of evidence that could be equal in strength for Wolf et al.²⁴⁾ study of CIMT. The second limitation of the studies is that they had no follow up assessment so that no evidence of persistence effects was available to support the long term effects of mCIMT.

As a summary, mCIMT is a promising treatment for stroke patients for improving the motor function of the hemiparetic arm. MAL is one of the commonly used clinical measures to assess upper limb motor functioning after applying CIMTs on stroke participants. When difficulties are affecting the use of CIMT because of too much effort and time being used by the patients and the therapists; mCIMT appears to be a promising and alternate intervention that saves time and could be applied with less efforts to achieve the expected and the satisfying goals from rehabilitation. More work should be done to examine the effectiveness of mCIMT using randomized controlled trials with large sample sizes. Also future research should focus on assessing the performance of the participants at retention by having a follow-up assessment to ensure the longitudinal effects of mCIMT on patients after a stroke. Finally and most importantly, the argument that has been raised with regard to the measures of recovery such as FMA, WMFT and MAL. Kinematic motion analysis is an effective quantitative tool to capture movement strategies during movements with the impaired arm⁴⁸⁻⁵⁰⁾. Indeed, movement kinematics can be used to distinguish between recovery and compensation. Many studies have documented an indirect relationship between the use of behavioral compensation and the impaired reaching ability characterized by decreased active range of elbow/shoulder movements^{39, 48-52)}. For example, Roby-Brami and her team used the increase in active range of elbow extension as a main outcome measure to quantify intervention-related arm motor recovery after an intervention⁵¹⁾. In fact, the assessment of the elbow extension during a reaching task predicts the performance on both WFMT and FMUE⁵³⁾. Thus, we propose that future studies should employ using kinematic metrics to quantify the training-related changes in behavior following CIMTs.

Recently, richer understanding of the functional recovery has been accompanied by a better understanding of its neurobiological basis. Cortical organization is often described in terms of maps that has a broad somatotopic representation of the different upper and lower body segments in an arrangement called “motor homunculus”⁵⁴⁾. The homunculus is arranged in an upside-down map of the contralateral body segments. For example, the upper extremities and the facial body segments are closer to the lateral sulcus than lower extremities such as the leg and toes that are located more medially⁵⁵⁾. Neuroplasticity refers to the changes that occur in the organization of the brain (re-mapping) as a result of experience. Also, neuroplasticity is a fundamental issue that supports the scientific basis for treatment of acquired brain injury (such as stroke) with goal-directed experiential therapeutic programs (such as CIMT) in the context of rehabilitation approaches to the functional consequences of the injury. Brain activity, represented by brain maps and neuroplasticity, has been studied through noninvasive neuroimaging methods such as functional Magnetic Resonance Imaging (fMRI) or by exciting neuron in the brain to measure the brain plasticity using Transcranial Magnetic Stimulation (TMS) and Positron Emission Tomography (PET). By using these methods, the functionality of the circuitry and connectivity of the brain can be studied.

By using TMS^{56, 57)}, weak electric currents are induced in the tissue by rapidly changing magnetic fields at a fixed point on the scalp to induce electrical currents on the underlying cortex. In this way, researchers were able to map the expanse of the cortex that is associated with the activation of specific contralateral limb muscles. In addition, the degrees in cortical electrical activity following the application of therapy could be evaluated as excitatory or inhibitory using TMS. TMS is used currently clinically to measure activity and function of specific brain circuits in humans. The most robust and widely-accepted use is in measuring the connection between the primary motor cortex and a muscle.

On the other hand, fMRI is one of the most recently developed forms of neuroimaging that measures the haemodynamic response (blood flow in the brain) related to neural activity in the brain. fMRI is simply represented by the Blood-oxygen-level dependent, when a certain areas of the brain get activated, its need for a source of energy increase so that the blood flow to this area increase for oxygen delivery, and that what fMRI detects. In this way, detecting the areas of the brain underlying the changes of the brain after applying an intervention could be easily detected.

After a stroke, the size of the cortical representation of the affected hand is known to decrease^{58, 59)} possibly due to limb nonuse⁶⁰⁾. However, in normal individuals- during task-specific protocols in which the affected arm is repetitively and functionally used—the size of the cortical areas representing the limb increases⁶¹⁻⁶⁴⁾. On the other hand, a recent interest to understand how the brain recovers and the cortical reorganization accompanied with the motor recovery including the spontaneous recovery or the recovery after applying our rehabilitation techniques has been developed. For the CIMT and mCIMT, another recent interest also has been developed to study the relationship between CIMTs and brain reorganization after a stroke especially when it showed a significant effect on the upper limb functional recovery.

Unfortunately, studies that examined the effect of applying CIMTs on cortical reorganization were relatively scarce. CIMT seemed to be effective in changing the cortical organization when the post treatment images were compared to pre-treatment images (baseline). However; the findings regarding these “re-mapping” changes across the studies were not consistent. In spite of the consistent CIMTs treatment that was applied and the consistent behavioral changes in the quality and the amount of movement using the MAL, the results failed to find consistent cortical reorganizations among each other and even among the participants in each study separately.

The cortical reorganization changes that occurred after the treatment are interesting and deserve more consideration. When most of the studies showed improvement in the MAL (Table 4), variability in the accompanied cortical changes has been found. Some studies⁶⁵⁾ showed that the lesioned hemisphere is more altered by CIMT than the unlesioned hemisphere. This alteration was represented by more activation being seen near the lesioned area or by expansion of the cortical motor representation of the more affected arm. Other studies⁶⁶⁾ didn't report a clear difference in the activated hemisphere; while others⁶⁷⁾ reported increased unlesioned hemisphere activation post treatment. Wittenberg et al.^{56, 68)} reported that TMS showed greater map volume of the more affected arm than the control group while PET showed reduced area activation of the more affected hand movement than controls. They reported that, by using the TMS, the change in map ratio, affected-to-unaffected, may be due, in part, to the map shrinkage on the unaffected side as a result of prolonged restraint. On the other hand, they reported that the different changes that were shown by PET may be due to the longitudinal decrease in activation, suggesting a reduced task-related synaptic input after CI therapy. This reduction, as though seemingly paradoxical, may be due to a more favorable recruitment of motor neurons in a way that the patients were able to perform the expected movement in a relatively better manner after the treatment than they did before the treatment at the baseline.

CIMTs strictly apply the principle of motor learning. Motor learning depends on the plasticity of neurons (regional activation) and circuits (functional connectivity)⁶⁹⁾ within the motor system. The motor system consists of cortical (primary and non-primary motor areas) and extracortical areas (basal ganglia and cerebellum). Therefore, the interaction between sensory and motor systems is a prerequisite for proper motor learning⁷⁰⁾. A recent review of the stroke rehabilitation literature revealed 12 randomized controlled trials comparing specialized patient rehabilitation with conventional care in 2,813 stroke survivors⁷¹⁾. Improved functional outcomes and reduced length of hospital stays were reported among patients receiving specialized rehabilitation¹³⁾. Intensive and structured training is one key element of such rehabilitation programs and the improvement in the desired outcomes is likely to depend on two elements: the intensity of the training and the specificity of the task practiced⁷²⁾. Motor learning principles, i.e., intense and structured training, have been now included in two of the most used therapeutic approaches in this population including CIMTs¹³⁾ and motor relearning program developed by Carr and Shepherd¹³⁾. CIMTs have been shown to improve arm functionality even in the chronic stage of stroke^{14, 73–75)} by inducing neuronal plasticity^{67, 76)} (Table 3). However, further investigations are needed not only to confirm these findings in a larger sample but also to assess whether these neural changes are related to recovery or compensation. This is indeed a real problem for fMRI studies investigating brain changes related to an intervention. Motor compensation could lead to changes in brain activation even though they have nothing to do with the recovery. Thus, this review suggests: i) to study the relationships between task-related motor activation and not only clinical (MAL, FMA and WMFT) but also kinematic metrics of arm motor impairment in the chronic stage of ischemic subcortical stroke ii) to longitudinally investigate the changes in cortical motor function at two levels, regional (micro-circuitry, regional activation) and network (macro-circuitry, functional connectivity).

In summary, although there is enormous research on the neural mechanisms underlying motor recovery in humans, these mechanisms are still largely unknown. Limited number of stroke studies examined the relationship between motor improvements and brain activation pattern following different therapeutic approaches^{77–81)}. Despite methodological and sample differences, three findings were consistently found: i) before training, cortical activation is predominantly bilateral; ii) after training, the cortical activation is shifted from the contra—to the ipsilesional hemisphere, at least in those patients with return of motor function; and iii) training-induced plasticity is possible in chronic phases of stroke. As stated before, bilateral activation of primary and non-primary motor areas and recruitment of additional sites have been reported in the early stages after a stroke and persist to the chronic stages especially in those with more severe impairments⁸²⁾. A trend toward more normalized activation patterns has been seen specifically in patients with moderate to mild impairments⁸¹⁾. However, these findings suggest that central nervous system retain the ability to reorganize toward a more physiological (more efficient) activation pattern even in the chronic stage of stroke. Furthermore, the main mechanism underlying recovery of motor abilities involves enhanced and predominant activity in preexisting networks within the affected-side.

Further investigations are needed not only to confirm these findings in a larger sample as well as to assess whether these neural changes are related to post-stroke recovery. This is indeed a real problem for fMRI studies investigating brain changes related to an intervention. Thus, future studies should examine the relationships between task-related motor activation and clinical and kinematic metrics of arm motor impairment in the chronic stage of stroke following CIMTs. Such understanding for the relationship between kinematic motion analysis and the associated brain changes would be a significant addition to the current literature and fulfills several gaps that have not been addressed for years. Finally, trials in neurologic rehabilitation have reported long-lasting functional improvements after 2–12 weeks of skilled motor practice in patients who were weeks to years past onset of hemiparesis^{83–85)}. Therefore, it is reasonable to conclude that more promising results in terms of understanding cortical organization following mCIMT as it involves less intense but longer course of training and thereby provides enough time to adapt to new changes resulting from such form of training.

Conflict of interest

The author certifies that he has no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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