

Constraint-induced Movement Therapy, Neuroplasticity, and Upper Extremity Motor Recovery after Stroke

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ABSTRACT

Stroke is a leading cause of disability. There are common motor impairments after stroke such as hemiparesis in the upper extremity contralateral to the affected hemisphere. Many stroke patients may suffer long term upper limb motor deficits. This decrease in hand dexterity could negatively affect the performance of daily activities that need skilled upper limb use such as grasping force control and coordination as well as appropriate fine motor skills. Participation, satisfaction and activity of stroke patients decline, and difficulty in using the paretic hand in daily tasks and functional limitation have been associated with decrease in participation and quality of life. Thus, improving the affected hand function of chronic stroke patients is vitally important.

It has been reported that there is functional reorganisation after stroke and that such cortical plasticity might be correlated with upper limb motor recovery. Understanding the neurophysiological changes after stroke and how these changes are associated with hand motor recovery as well as how to promote such plastic changes would assist in developing effective therapeutic interventions that are based on neurophysiological evidence in order to resolve upper limb motor impairments in stroke patients. During the last two decades, the significant progress in neuroscience has led to novel concepts for rehabilitation interventions post stroke. The constraint-induced movement therapy (CIMT) has been shown to improve function and amount of use of the paretic hand of chronic stroke patients and is thought to induce cortical plasticity.

This review aims to explore and discuss the role of cortical reorganisation (neural plasticity) in motor recovery of the paretic upper extremity of chronic stroke patients as well as the efficacy of constraint-induced movement therapy in improving upper extremity motor function of chronic stroke patients and its potential underlying mechanism. This review also aims to explore the potential cellular mechanisms that underlie neural plasticity.

Keywords

Constraint- Induced Movement Therapy, Neuroplasticity, Stroke.

Cortical Plasticity in Healthy Subjects

The cortical representations might increase or decrease depending on use and such functional plasticity has been observed during learning motor tasks in humans. Several human studies indicate that long term practice of a specific sensorimotor skill can produce functional reorganization in relevant cortical representations. It has been observed that cortical representations of the digits of the skilled hand in the somatosensory cortex increases in string

musicians [1] and blind Braille readers [2] in comparison to that of the unskilled hand and in controls. In addition, functional cortical reorganization can occur even in a short time period as motor maps have been shown to change after short time of motor training [3]. These studies suggest that sensorimotor cortex has the potential for rapid and significant functional changes in response to motor skill learning, indicating there might be a positive correlation between increase in cortical motor map of the hand and improved hand function. This process of functional reorganization in healthy subjects may be the key to understand and enhance the reorganization of remaining cortical tissue in the affected

hemisphere of stroke patients.

The Motor Cortex

Individual movement representations are distributed and overlapped in the motor cortex [4]. The motor cortex is located in the precentral gyrus, and it is the part of the cerebral cortex (a major part of the central motor system) that needs electrical stimulation to evoke skeletal muscles movement. The motor cortex is responsible for planning, execution and control of voluntary movements. The motor cortex can be divided into distinct areas based on anatomical, physiological or functional criteria, which includes the primary motor cortex, the supplementary motor area (SMA), the premotor cortex and the cingulate motor area (located along the ventral and dorsal banks of the cingulate sulcus [5]). SMA (located on the medial side of Brodmann's area six [6] initiates and controls voluntary movement. The premotor cortex (located on the lateral side of Brodmann's area six [7] is connected to primary motor cortex and is important for movement generation as well as execution and observation of object related hand movements [8]. The main non-primary motor areas that are activated during hand and arm movements are the premotor cortex and SMA [9].

Early Changes in Brain Function and Brain Plasticity after Stroke

There are a number of brain mapping studies that have investigated the association between the degree of motor recovery and changes in brain activation pattern during stroke recovery. It has been demonstrated that there are abnormalities in brain function early after stroke that are correlated with motor recovery and those abnormalities may improve over time [10-12]. The major cortical abnormalities are a decrease in the excitability of ipsilesional motor cortex, over activation of several regions of bilateral sensorimotor network, and the laterality of activation of primary sensorimotor cortex being shifted toward contralesional motor cortex. Each of these abnormalities is considered in the following paragraphs.

The ipsilesional motor cortex excitability may be reduced in the early post stroke period, and this reduction tends to decline over time in association with improvements in the paretic hand motor recovery [12,13]. One study found that the excitability of the ipsilesional motor cortex was decreased early post stroke (about two weeks) in comparison to that of the contralesional motor cortex (evidenced by a decreased amplitude, increased threshold and delayed latency of motor evoked potential (MEP) that were recorded from muscles in the paretic hand using focal transcranial magnetic stimulation (TMS)) [12]. Another study demonstrated that the excitability of the ipsilesional motor cortex as well as the hand motor map size decreased early after stroke when compared with the contralesional motor cortex and compared with healthy control subjects [13]. In the Later post stroke period (about one year), the excitability of the ipsilesional motor cortex and the size of the paretic hand motor map increase (toward the measurements in healthy control subjects) and are associated with improvements in the paretic hand motor function [12,13]. In addition, the extent of the increase in motor map size over time is associated with

the degree of improvements in upper limb motor function [13]. These results indicate that normalization of the ipsilesional motor cortex excitability and then the increase in cortical motor map size may improve the motor function of the affected upper limb in hemiparetic stroke patients.

In addition, in the early post stroke period, there is an increase in the activity of several areas of bilateral sensorimotor network (not exclusively the damaged motor cortex), while normalization of its activity is associated with the recovery of paretic motor hand function [10]. One study found that the activity of several regions of bilateral sensorimotor network early after stroke (approximately seven weeks), including the premotor areas, SMA, the cerebellum and the prefrontal cortex, was greater during movement of the affected hand of stroke patients than during hand movement of healthy control subjects [10]. The abnormal activation in the bilateral sensorimotor network during the affected hand movement was reduced (normalized) over time in association with improved motor recovery of the paretic hand. In addition, it has been reported that poorer motor recovery of the paretic hand of stroke patients is associated with greater activation in several sensorimotor areas, including the premotor cortex, SMA, cingulate motor areas, posterior parietal cortex and cerebellum, during movement of the paretic hand compared with hand movement of healthy control subjects [14]. In contrast, the degree of paretic hand motor recovery is associated with decrease in brain activation toward a more normal pattern [15]. These findings indicate that promoting normalization of early excessive activation of sensorimotor network would lead to better hand motor recovery post stroke.

One of the early abnormalities post stroke is that the laterality of activation of the primary sensorimotor cortex is likely to be shifted toward the contralesional motor cortex [11]. Such reorganization and its association with the degree of motor recovery after stroke have been investigated by a number of functional neuroimaging studies. One study found that the laterality of activation in the primary sensorimotor cortex ,early after stroke (approximately one week), was shifted toward the contralesional (ipsilateral) motor cortex during affected hand movement compared to the activation of contralateral sensorimotor cortex during movement of the unaffected hand [11]. However, the activation of the sensorimotor cortex was shifted toward normality (increase in activation of the ipsilesional sensorimotor cortex and decrease in activation of the contralesional sensorimotor cortex) later post stroke (3-6 months), and this later shift was correlated with motor recovery of the paretic hand function. This finding is consistent with another study result, which concluded that motor recovery of the paretic hand is associated with a shift in laterality of primary sensorimotor cortex activation during affected hand movement from the bilateral to the ipsilesional hemisphere [16]. These studies demonstrate that enhancing the normalization of the laterality of activation of the primary sensorimotor cortex could result in better improvements in paretic hand motor control and function post stroke. Similarly, a review suggested that the involvement of the ipsilesional hemisphere during affected hand movement early after stroke is a good indicator for recovery, while the involvement

of contralesional pathways is correlated with poorer functional recovery [17].

However, another study suggested that the contralesional sensorimotor cortex can contribute to motor recovery post stroke [18]. Also, it has been concluded that normalization of the laterality of activation is more related to the ipsilesional sensorimotor cortex integrity and its corticospinal tract than to motor recovery [18,19]. However, a review concluded that although non-motor and contralesional motor areas may contribute to motor recovery post stroke, the greater the involvement of ipsilesional motor network, the better the recovery [20]. It seems that there is a competition between ipsilesional and contralesional pathways, and the poorly functioning contralesional pathways are prominent when functional ipsilesional pathways cannot recover. Therefore, motor recovery post stroke may be re attributed to cortical reorganization. Functional reorganization in the affected hemisphere might be most efficient in producing the best motor recovery. Nevertheless, motor recovery from hemiparesis post stroke is associated with a complex pattern of brain reorganization and a better understanding of such plasticity and its underlying mechanisms could help in developing and providing an effective rehabilitative management for stroke.

Mechanisms Responsible for Brain Plasticity

There are several potential cellular mechanisms that are responsible for neural plasticity. The main potential mechanisms are unmasking, strengthening or weakening of existing synapses and developing anatomical changes. One of the major possible mechanisms of cortical reorganization is unmasking in which adjacent cortical areas expand once pre-existing excitatory connections are unmasked by reduced intra-cortical inhibition [21]. The balance of inhibition and excitation of neurons can be altered quickly. Neurons or neuronal pathways have a larger area of anatomical connectivity than their usual region of functional influence. Some regions might be kept in check by tonic inhibition, and once the inhibition is removed, the area of influence can be increased or unmasked.

Another potential mechanism for cortical plasticity is strengthening or weakening pre-existing synapses. The modification of synaptic strength is a relatively fast process and includes two processes; long term potentiation (LTP) [22] or long term depression (LTD) [24]. These authors conclude that there is a possibility of activity dependent modification of synaptic connections within the horizontal connections of the superficial cortical layers. The horizontal connections prosperities provide activity dependent mechanisms for plasticity of adult cortical representations. The activity dependent strengthening of synaptic efficacy, which is induced by LTP, may enhance the cortical excitability.

The third possible mechanism is the occurrence of anatomical changes such as formation of new synapses and sprouting of new axon terminals. Toni, Buchs, Nikonenko, Bron, & Muller [24] investigated the morphological changes that are associated with synaptic LTP. After inducing LTP, the authors observed that new

mature dendritic spines (which have well-defined necks and spine heads) were formed and at least two dendritic spines contact the same axon terminal. They also found that synapses were duplicated and new synapses were formed between the same dendrite and axon terminal. They concluded that LTP can promote formation of spine synapses, thus duplicating activated synapses. These three processes can occur in different time periods, thus one mechanism might be followed by another serially.

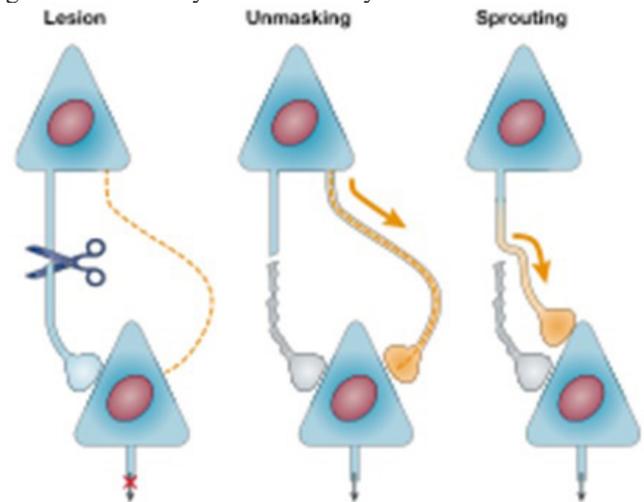


Figure 1: Unmasking and sprouting processes [22].

The efficacy of constraint-induced movement therapy and cortical plasticity after stroke

CIMT is a task oriented approach that aims to improve motor function of the paretic upper limb of stroke patients. This intensive therapy is derived from basic research with monkeys that are given somatosensory deafferentation [25] and is based on a neurobehavioural theory of the learned nonuse model of the paretic limb, where the residual movement capabilities of the paretic hand of stroke patients are not utilized to their potential because the paretic hand “learns” not to be used. It has been thought that there are two potential mechanisms that underlie the therapeutic effects of CIMT. These mechanisms are overcoming learned nonuse as well as use dependent neuroplasticity [26]. CIMT encourages use of the affected hand in daily life rather than just focusing on achieving the daily living activities by using the non-paretic upper extremity. CIMT comprises of restriction of the unaffected upper limb use and intensive training of the affected extremity to achieve functional goals. The unaffected hand is restrained in a sling during waking hours for two weeks, and patients are given six hours of practice in using the affected upper limb by shaping (adaptive task practice) during consecutive 10 weekdays. These two components are thought to be important to overcome the learned nonuse that develops early post stroke as a consequence of failed attempts to use the paretic hand.

CIMT is an effective therapeutic intervention on improving upper extremity motor function of chronic stroke patients [25,27-32]. This evidence demonstrates that CIMT can enhance the motor functional ability of the paretic hand of stroke patients during chronic phase (e.g. more than one year post stroke) and that the

improvements persist for a long time. This evidence also shows that CIMT is effective in the self-report use of the affected limb in daily living activities and motor control parameters. A randomized controlled trial (RCT) investigated the efficacy of CIMT in improvements in upper limb function of stroke patients who suffer mild to moderate deficits three to nine months post stroke [31]. The participants (222 participants) were divided into two groups. One group received a two week programme of CIMT and the other group received usual care. The CIMT group received an intensive training (by shaping) of the paretic hand for six hours a day on ten consecutive weekdays, while the unaffected hand restrained for about 90% of waking hours during 14 day treatment period. The Wolf Motor Function Test (WMFT) (a measure of laboratory time and strength-based ability as well as movement quality) and the Motor Activity Log (MAL) (comprises of thirty tasks reflecting daily living activities and contains two scales for the quality of movement and the amount of use) were implemented. The functional ability, amount of use and quality of movement of the paretic hand of the CIMT group had greater improvements than the control group. At one year follow up, the improvements in the affected hand motor function of the CIMT group persisted. This study did not only use a measurement of daily living activities (MAL), but also used WMFT as a good marker for manual dexterity of the paretic hand [33]. In stroke, the WMFT test has been concluded to have high validity [34] and reliability [35].

In addition, another RCT similarly concluded that CIMT provides greater improvements in reaching control, less motor hand impairments and higher functional ability for chronic stroke survivors than traditional treatment [36]. Furthermore, it has been suggested that CIMT is superior to the dose-matched conventional intervention in chronic stroke patients as this therapy provides better improvements in the affected hand function and health related quality of life [28]. One study using kinematic analysis as a sensitive assessment of the hand motor recovery to evaluate CIMT effectiveness in chronic stroke patients concluded that the improvements in the paretic hand use in daily living activities is not only attributable to greater hand dexterity, but is also because of increased movement speed and greater coordination between elbow and shoulder joints [37].

CIMT may have long term benefits for chronic stroke patients. Neurophysiological research has shown that the improved hand function may persist up to four year post CIMT [38]. A four year follow up study concluded that the improvements in function and self-reported use of the paretic hand of chronic stroke patients after CIMT maintain up to four year follow up, as measured by the Sollerman hand function test and MAL [38]. Wolf, et al. [32], similarly, concluded that the significant improvements in the paretic hand function of stroke patients who have mild to moderate deficits three to nine months post stroke can be maintained two years after CIMT, as measured with WMFT and MAL. However, the improved affected hand function might be decreased two years after CIMT [25]. Nevertheless, a second repetition of modified (less intensity) CIMT can provide additional improvements in functional use of the paretic hand of chronic stroke patients who

received CIMT two to three years before the second modified CIMT version [39]. The intensive training of the paretic hand could be responsible for the use dependent increase in the cortical reorganization that is observed by using TMS [12]. The CIMT-induced cortical plasticity is believed to be the basis for the long term increase in the amount of use and the quality of movement of the paretic hand.

Research shows that the normalization of activity in ipsilesional motor cortex of stroke patients (improve its excitability and increase cortical map for the affected hand) might be one of the mechanisms that underlie the effectiveness of CIMT. Liepert, et al. [40] investigated the cortical reorganization that are induced by CIMT of chronic stroke patients. TMS was used to map the motor cortex in both hemispheres before and after a two-week treatment period. Motor output areas of the abductor pollicis brevis (APB) muscle, centre of gravity location (the distribution centre of MEP amplitudes within the motor output area) and motor evoked potential (MEP) amplitudes of motor cortex output were measured. Post intervention, the authors found that motor output map size and MEP amplitudes that were measured from the affected hemisphere were significantly increased, suggesting that there was enhancement in the neural excitability of the motor cortex in the affected hemisphere for the target muscles. Also, the mean centre of gravity of the motor map in the affected hemisphere was shifted in a mediolateral axis, indicating the recruitment of adjacent cortical motor areas. These cortical changes correlated with increased motor recovery of the affected hand that was measured by the MAL. MEP amplitudes that were measured from the unaffected hemisphere remained unchanged, while the cortical representational area of the healthy APB muscle was slightly reduced.

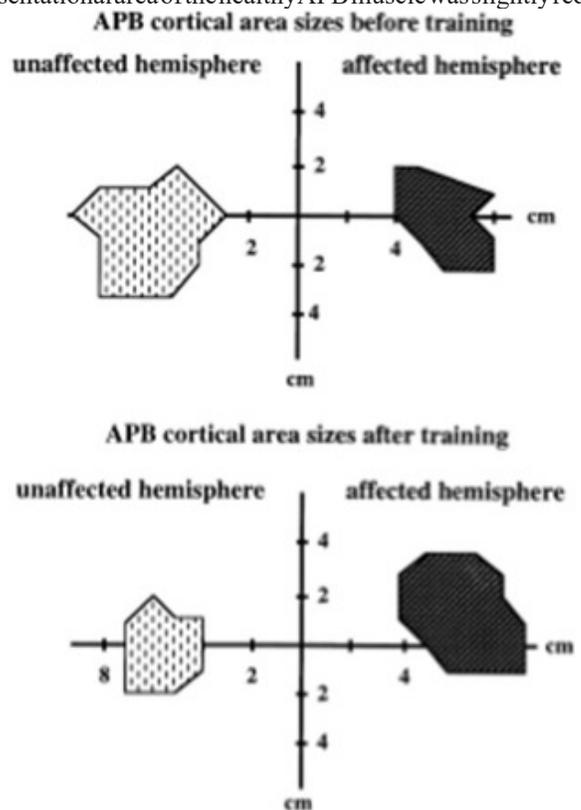


Figure 2: changes in the APB muscle cortical map size in both hemispheres of a single subject before and after CIMT.

The decrease in the cortical motor output size of the unaffected hand muscle might be because of the less frequent use of the non-paretic hand during and after intervention as immobilization could reduce the cortical representation map size [45]. Another potential factor for such decrease is that the treatment-induced increase in activation of the affected motor cortex may inhibit the excitability of the contralateral hemisphere. This interhemispheric inhibition has been reported in normal subjects [42] and in stroke patients [43]. Nevertheless, Liepert, et al. [40] suggested that the reduction in the motor cortex representations of the paretic upper extremity of chronic stroke survivors may be enlarged and increased in the excitability by CIMT. However, the main limitation of this study is that the sample size is too small (only six patients) which is considered a threat to the external validity and then may affect the generalisability of the study. Despite this, the study results are consistent with results of several studies that investigated plastic changes in the motor cortex of chronic stroke patients that are induced by CIMT. One study concluded that the cortical motor output area size of APB muscle of the paretic hand is enlarged and the centre of the output map in the damaged hemisphere is shifted in parallel with significant improvements in the affected hand motor recovery that was measured by MAL [44]. It also suggested that the motor recovery and the enlargement of cortical motor map size of the paretic hand persist up to six months and the balance of the excitability of the two hemispheres return toward the normal. A recent review explored the neural basis of CIMT and concluded that CIMT leads to an increase in the size of the map of the paretic hand muscles in the ipsilesional motor cortex [45]. These findings are consistent with the notion that normalizing the excitability of the ipsilesional motor cortex and increase cortical map size of the paretic hand could improve the hand motor function [13].

Normalizing cerebral over-activation could be another mechanism that underlies the efficacy of CIMT. One study found that, before CIMT, cerebral activation of the affected hemisphere during a motor task of the paretic hand was greater in stroke patients than healthy subjects (increased activation occurred in ipsilesional sensorimotor cortex, cingulate motor area, SMA and medial cerebellum) [46]. This over-activation might be because of the increase in synaptic input into the primary motor cortex that is needed to achieve movement in a specific motor task. Post intervention, cerebral activation during a motor task reduced significantly only among stroke patients who received CIMT, suggesting that there may be a reduction in task related synaptic input post CIMT. This decrease in cerebral activation has been also reported in healthy subjects who learn complex motor tasks [47]. Also, the cortical map of the paretic hand muscle (APB muscle) of the CIMT group had significant enlargement, while the other group had no change. These physiological changes in CIMT group were associated with better improvements in motor recovery of the paretic upper limb than the other group. These results are consistent with the notion that normalization of cerebral over-activation that occurred after stroke is accompanied by improvements in the affected hand function [15].

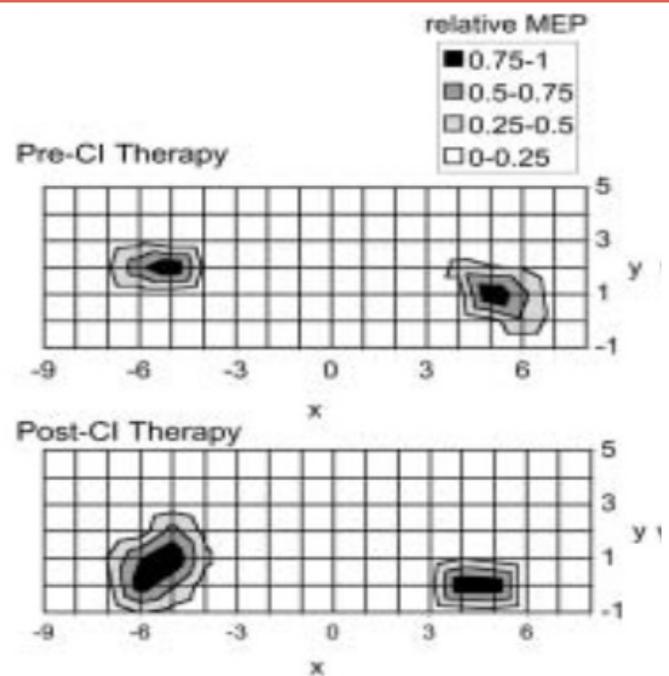


Figure 3: Example cortical maps from the CIMT group subjects [2003].

In addition, the increase in recruitment of the contralesional motor cortices is a mechanism that may underlie the effectiveness of CIMT. A preliminary study, using functional magnetic resonance imaging, demonstrated that motor improvements in the paretic upper limb function of chronic stroke patients after CIMT was associated with a shift in the laterality of activation of motor cortices (primary motor cortex, premotor cortex and SMA) during the affected hand movement toward the contralesional hemisphere [48]. At six month follow up, the laterality shift and improved motor function still persisted. However, only four patients participated in this study, and thus it establishes only preliminary evidence regarding the association between the shift in the balance of motor cortical recruitment toward the contralesional hemisphere and motor recovery after CIMT, which means further investigations are needed to confirm these findings. In addition, these results are inconsistent with the notion that the greater the involvement of ipsilesional motor network, the better the recovery [20]. However, this variability of cortical reorganization after CIMT might also depend on the corticospinal tract integrity [45].

Optimal timing of any therapeutic intervention is vitally important. Most studies have investigated the efficacy of CIMT in the chronic stage of stroke and this intensive therapy has been demonstrated to be effective as has been shown above. Some studies have examined the effectiveness of CIMT in stroke patients in the subacute stage of their illness. Time since stroke is found to have no effect on motor improvements in the paretic hand induced by CIMT for patients receiving CIMT 6 months to 17 years after stroke [29]. This study suggested that CIMT may benefit very chronic stroke patients who suffered stroke as many as 17 years earlier. This is against the traditional point of view in rehabilitation field that stroke survivors reach their plateau in motor recovery six months to one year post stroke in which there will be little or no further

motor improvements in the rest of their lives [42]. Miltner, et al. [29] also indicated that CIMT could be effective for stroke patients in the subacute stage. Two recent studies supported this finding by suggesting that CIMT is effective on improving the paretic hand function, as measured by WMFT, of stroke patients in the subacute phase of recovery (three to nine months post stroke) and the improvements in the affected hand function maintained up to 24 month follow up [50,51].

In addition, CIMT could produce increase in motor map in the motor cortex of subacute stroke patients, as mapped by TMS [50]. The practical importance of these findings is that subacute stroke patients might be more accessible for therapists than chronic stroke patients as they are more likely to be in the treatment system. An RCT examined the efficacy of CIMT on improving the paretic hand function of acute stroke patients [52]. The study concluded that CIMT provides significantly less motor improvements in the paretic hand when compared with traditional therapy. This can be explained through rodent brain infarct models in which immediate immobilization of the unaffected limb after stroke may cause lesion enlargement by an excitotoxic mechanism [53,54], and can be associated with a decrease in motor recovery [55]. Forced overuse of the affected upper limb through restraining the unaffected limb early after injury (e.g. first week) may result in expansion of brain lesion and poorer motor function [56]. These studies indicate that increased dose of exercise does not necessarily give better improvements in acute stroke if not harmful. This use-dependent exacerbation of brain lesion might occur early after stroke making the timing of CIMT crucial.

The effectiveness of CIMT in chronic stroke patients with mild to moderate motor impairments who have some wrist and finger movement has been shown in this paper. However, investigation of the efficacy of CIMT in chronic stroke patients with severe deficits is overlooked in the literature. Few studies indicated that CIMT might benefit chronic stroke survivors who suffer severe upper extremity motor impairments [57-59]. Two of these studies are only case studies and the third one has very small sample size. RCTs with larger sample size have to be undertaken to examine the short-term and long term benefits of CIMT in stroke patients with severe motor deficits. In addition, most studies that have looked at the efficacy of CIMT have patient samples with different lesion locations and severity. Therefore, it is hard to make a correlation between lesion location and severity and CIMT efficacy in stroke patients.

However, one study found that although infarct location is positively correlated with poor motor ability, there is no association between infarct location and motor improvements in the affected hand after CIMT in chronic stroke patients [60]. In addition, it has been shown that lesion severity is not correlated with efficacy of CIMT and does not affect its therapeutic outcomes [61], although lesion severity can predict the motor impairments after stroke [62]. These studies findings suggest that brain plasticity induced by CIMT might explain such dissociation, supporting the hypothesis that cortical reorganization after CIMT in chronic stroke patients

may reduce the effect of infarct. However, the main limitations of CIMT are that patients must have at least 10 degrees of wrist and finger extension to be eligible for CIMT. In addition, CIMT cannot be applied in acute phase of stroke because it has no significant therapeutic impact and if not harmful. Therefore, many stroke patients would be excluded.

According to a principle of plasticity (use it and improve it), using the affected upper limb of chronic stroke patients in daily living activities is important for maintaining and increasing cortical maps size and thus improving motor function [63]. This principle was used to suggest CIMT [26]. Nevertheless, CIMT can also benefit other conditions in which upper extremity motor deficits manifest such as hemiparetic cerebral palsy and multiple sclerosis. It has been shown that CIMT can significantly improve upper limb function in children with hemiparetic cerebral palsy [64,65] as well as in people with multiple sclerosis [66].

Conclusion

Functional reorganization of the motor cortex is a fundamental mechanism that is involved in recovery of the paretic upper limb motor control and function post stroke. The injury-induced cortical reorganization phenomenon has been well documented in stroke [10,11,16]. Early cortical abnormalities such as a reduction in the excitability of ipsilesional motor cortex may improve over time in correlation with significant improvements in motor recovery of the affected upper extremity of stroke patients [13]. Therefore, there is an association between cortical reorganization and the degree of the affected upper limb motor recovery of stroke patients. Nevertheless, CIMT is effective on improving paretic hand motor function when applied in chronic and subacute stages of stroke [28,51], and this therapy has long term therapeutic impacts [38]. The main potential mechanisms that underlie the effectiveness of CIMT is enhancing the normalization of ipsilesional motor cortex excitability and increasing cortical map size as well as reducing cerebral over-activation [44,46]. This type of use dependent plasticity has also been found in healthy people who acquire new motor skills [67]. There are a number of potential cellular mechanisms underlying neuroplasticity such as unmasking, synaptic strength modification and occurrence of anatomical changes [21,22,24].

Nevertheless, it is important to note that CIMT may have no significant therapeutic effects on affected hand function of acute stroke patients and can be harmful [52]. The effects of factors such as hemiparesis severity and lesion location and severity on the degree of recovery of the paretic hand of stroke patients after CIMT need to be investigated in greater detail. However, in chronic stroke, although motor impairments are generally considered to be stable and permanent, CIMT is an effective rehabilitation procedure in restoring significant paretic upper extremity motor function in chronic stroke patients with upper limb motor deficits [25,32]. Good understanding of how brain reacts to injury and how stroke patients reacquire the lost behaviours and functions by training as well as integrating the behavioural science with neuroscience have provided an effective therapeutic model for neurorehabilitation.

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