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# REORGANIZATION OF BRAIN FUNCTION DURING FORCE PRODUCTION AFTER STROKE: A SYSTEMATIC REVIEW OF THE LITERATURE

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## *ABSTRACT*

*Damage to motor areas of the brain, caused by stroke, can produce devastating motor deficits, including aberrant control of force. Reorganization of brain function has been identified as one of the fundamental mechanisms involved in recovery of motor control after stroke, and recent advances in neuroimaging have enabled study of this brain reorganization. This review focuses on neuroimaging studies that have examined reorganization of brain function during force production and force modulation after stroke. Type and extent of reorganization after stroke was characterized via three factors: severity of injury, time after stroke and the impact of therapeutic interventions on brain activation during force production. Twenty-six studies meeting the inclusion criteria could be identified in MEDLINE (1980 to 2007). Relevant characteristics of studies (lesion location, chronicity of stroke, motor task) and mapping techniques varied widely. During force production, increased activation in secondary motor areas occurred in persons with more severe strokes. Also, reduced recruitment of secondary motor areas during force production was found as a function of increased time since stroke. During force modulation, increased activation in motor areas occurred with greater force generation. In addition, persons with more severe stroke showed relatively greater activation with rising force as compared to persons with less severe stroke. Lastly, alteration of brain activation during and after rehabilitative interventions in persons with stroke occurred in some studies. This systematic review establishes that reorganization of brain function during force production and force modulation can occur after stroke. These findings imply that therapeutic strategies that may be able to target brain reorganization to improve force control and functional recovery after stroke.*

***KEYWORDS:*** *Stroke, Brain Function, Force Production*

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## INTRODUCTION

As humans, generation and control of force is a central part of our lives. Control of force output is required to walk, manipulate objects, and play musical instruments and sports. Even the simple act of manipulating a Styrofoam cup requires control of force, as too little may result in the cup slipping from grip and too much can result in crushing the cup and contents inside. When producing a movement, the force output of a skeletal muscle can be changed over a large range. [1] This ability to accurately produce the various ranges in force can be accomplished through modifying the firing

properties and recruitment order of motor units. [2] Rate coding, or adjustment of motor unit firing rate frequency, is one method used to vary force production, and force level can also be altered in steps by recruiting motor units in order of increasing strength. [1] Normally, recruitment and firing rate modulation are the two most common strategies used in combination to produce variations in muscle force, and the relative contribution of each is determined by the type of muscle being used, as well as the level of force required. [3] In order to generate force voluntarily the motor areas of our brains must be able to communicate effectively with the motor neurons in the spinal cord that are responsible for force generation of our muscles. In the case of humans, the primary output of motor information descends from the primary motor cortex (M1) and terminates in the spinal cord, where it may connect directly with motor neurons. [4]

As grip force control depends on the integrity of the sensorimotor system, when injury to sensorimotor areas of the brain occurs there may be impairment in controlling force. [5] Stroke is one example of such a neurological disorder and is the leading cause of serious, long-term, adult disability. [6] Persons with stroke can experience a range of motor control deficits including exaggeration of grip force, [7–9] which is considered a compensatory strategy to maintain grip when sensorimotor processes may be affected [10]. In addition persons with stroke may exhibit timing deficits, such as impairments in the time to reduce force [11] as well as abnormal time to achieve stable grip force, [7] which may be partially attributed to the extra time required to reach the abnormally high grip forces. [12] Alternatively, this prolonged time to reach or reduce force may indicate inefficient communication between descending voluntary motor commands and spinal motoneurons, as correlations have been observed between the amount of damage to descending white matter tracts and these timing deficits. [7] Lastly, even once grip is achieved around an object persons with stroke may have difficulty in maintaining a constant force during a grip task. [8, 9]

Results from past studies suggest that these force production deficits (measured via grip dynamometer) exist as anatomically and functionally distinct from impairments in dexterity (measured via 9HPT), with both having a distinct pattern of recovery. [13] Moreover, weakness in force production is a more significant contributor than loss of dexterity to physical disability after stroke. [14] Thus, as deficits in force production seem to comprise a distinct impairment after stroke, it is important to concentrate on the contributing factors specific to abnormal force production after stroke. In the past, an abundance of literature has focused on irregularities in muscle fiber and motor unit properties contributing to abnormal force production and modulation after stroke. More recently, technology has enabled the study of supraspinal contributions underlying motor activity. [15–17] As stroke involves direct injury to the brain, it provides an appropriate model to investigate the supraspinal contributions of force control.

Past literature has suggested that after stroke, there are certain processes that occur in the brain in order to generate movement. Examination of spinal termination patterns of efferents from secondary cortical motor areas (supplementary motor area, cingulate motor area and premotor cortex) has shown that some corticospinal projections also originate in these areas, similar to those from M1. [4, 18] These findings suggest that secondary motor areas have the potential to control movement, and thus may represent a substrate for motor recovery after stroke that impacts M1. [4] Neuroimaging techniques provide the ability to examine the brain reorganization associated with recovery after CNS damage and recent studies using these techniques have published patterns of brain area recruitment involved in force generation and modulation after stroke (eg. Ward et al., [19]) However, it is difficult to ascertain the effects of stroke on force generation with individual papers due to the use of a variety of experimental protocols (e.g., different muscles, varied tasks) and the heterogeneity of the population of people with stroke (e.g., types and severity of stroke, lesion location, time since injury); mixing of these factors has resulted in varying and even conflicting results. Reviewing all the relevant literature within one

paper allows past findings to be summarized and contextualized to determine commonalities and conflicts in the literature. Thus, the present article systematically reviews the literature to determine how patterns of brain activation vary during force production and modulation after stroke.

More specifically, the literature was synthesized to determine if brain activation patterns change during force production from the early to late stages post stroke. In addition, this review aimed to determine if the severity of stroke influences brain activation during force production. Lastly, the literature was examined to verify whether rehabilitation interventions after stroke alter brain activation patterns during force production.

## History

Episodes of stroke and familial stroke have been reported from the 2nd millennium BC onward in ancient Mesopotamia and Persia.[241] Hippocrates (460 to 370 BC) was first to describe the phenomenon of sudden paralysis that is often associated with ischemia. Apoplexy, from the Greek word meaning "struck down with violence", first appeared in Hippocratic writings to describe this phenomenon.[242][243] The word *stroke* was used as a synonym for apoplectic seizure as early as 1599,[244] and is a fairly literal translation of the Greek term. The term *apoplectic stroke* is an archaic, nonspecific term, for a cerebrovascular accident accompanied by haemorrhage or haemorrhagic stroke.[245] Martin Luther was described as having an *apoplectic stroke* that deprived him of his speech shortly before his death in 1546.[246]

In 1658, in his *Apoplexia*, Johann Jacob Wepfer (1620–1695) identified the cause of hemorrhagic stroke when he suggested that people who had died of apoplexy had bleeding in their brains.[46][242] Wepfer also identified the main arteries supplying the brain, the vertebral and carotid arteries, and identified the cause of a type of ischemic stroke known as a cerebral infarction when he suggested that apoplexy might be caused by a blockage to those vessels.[46] Rudolf Virchow first described the mechanism of thromboembolism as a major factor.[247]

The term *cerebrovascular accident* was introduced in 1927, reflecting a "growing awareness and acceptance of vascular theories and (...) recognition of the consequences of a sudden disruption in the vascular supply of the brain".[248] Its use is now discouraged by a number of neurology textbooks, reasoning that the connotation of fortuitousness carried by the word *accident* insufficiently highlights the modifiability of the underlying risk factors.[249][250][251] *Cerebrovascular insult* may be used interchangeably.[252]

The term *brain attack* was introduced for use to underline the acute nature of stroke according to the American Stroke Association,[252] which has used the term since 1990,[253] and is used colloquially to refer to both ischemic as well as hemorrhagic stroke.[254]

## Methods

Medline (1980–2007) database was used to search the literature. This database was accessed online through the local university's library system in September 2007. Only the Medline database was searched as we thought it unlikely that other databases (Psycinfo, Cinhahl EMBASE, CENTRAL) would contribute unique articles pertaining to our topic. The search was limited to articles written in English. Searches were performed using combinations of the key words: stroke, neuroimaging, functional magnetic resonance imaging (fMRI), transcranial magnetic stiumlation (TMS), electroencephalography (EEG), magnetoencephalography (MEG), positron emission topography (PET), near infrared spectroscopy imaging (NRIS), motor. The inclusion criteria consisted of the following: (1) study participants had a diagnosis of a stroke, (2) brain plasticity in motor areas was examined, (3) study participants performed movement that

was active and against resistance. The search was limited to active movement against resistance because these paradigms controlled the force produced during the motor task. In addition, active movement against resistance is highly relevant to activities of daily living (e.g., lifting a cup, opening a door). Neither theses, conference proceedings, nor case studies were included. A total of 1098 articles were identified using the key words. The titles of these references were examined and a total of 197 titles were identified as relevant and their abstracts were subsequently examined. Of the 197 abstracts screened, 64 articles remained for further review of appropriateness and out of these, 26 articles fell within our inclusion criteria. Reasons for exclusion of abstracts and articles were as follows: use of motor imagery, use of motor tasks involving only passive movement or active movement that was not against resistance, and brain plasticity of motor areas was not examined. The level and quality of evidence of reviewed studies were not assessed as it was not appropriate for this review as the majority of studied did not employ an intervention.

## RESULTS

### Study Descriptions

Twenty-six articles were found describing brain plasticity post stroke within our search criteria. Twenty-two of these articles involved force production against resistance either at only one level or at multiple levels, but the differences in brain activation between levels was not described or the focus. [20–41] A subset of these studies specified a target force (ranging from 10% to 100% of maximum voluntary contraction (MVC), and at 1N). The four remaining articles involved a motor task requiring force to be produced at more than one level, [19, 42–44] and aimed to determine brain activation in response to force modulation (varying levels of force production) of a motor task. In all of these force modulation articles, two or more target forces (ranging from 5% to 100% of MVC) were specified and the differences in brain activation between levels were described.

When comparing persons with stroke and healthy controls, 14/26 studies compared the groups at equivalent relative forces (i.e., percent MVC). [19–21, 23, 24, 27, 30, 31, 35–37, 42–44] Note, in these cases, the absolute force values would be lower for the persons with stroke during force generation of the more affected limb compared to healthy controls. One study out of 26 compared the groups at an absolute force value of 1N. [32] The remaining studies did not specify the target forces used. None of the 26 studies compared different rates (i.e., speed) of force generation within the same study and some studies did not specify the rate of force. Where rate and force of movement were not specified, it was assumed that the participants self-selected the movement rate and force. For studies that did specify the rate of movement, it included self-paced, [22, 38, 45] 40% of maximum rate, [30, 31, 42] 75% of maximum rate, [27] 0.5 Hz,[29] 1 Hz,[26] 0.4–3.0 km/h, [39] 0.2 km/hr, [41] and 49.5–55.3 steps/min. [40]

### Subject Characteristics of Reviewed Studies

The number of persons with stroke in each study ranged from 2 to 25. Time after injury ranged from 10 days to 15 years; participants were tested in the early phase after stroke (>10 days, <3 months) in nine studies, [28–31, 38–41, 43, 44] and all but two [43, 44] of these studies re-tested subjects in the late phase after stroke (> 3 months). In the remaining studies, subjects were tested only in the late phase after stroke (> 3 months). Time since stroke was not specified in one study.[34] The location and extent of stroke lesions was variable among studies, including exclusively subcortical lesions (12 articles [19–21, 28, 32, 33, 35, 37–39, 43, 44]), exclusively cortical lesions (1 article [29]), cortical and subcortical lesions (12 articles [22–27, 30, 31, 36, 40–42]) and 1 article did not specify lesion location. [34]

In terms of participant characteristics, it is important to note that most of these studies often included a restricted sample of individuals with stroke having relatively pure paresis and minimal deficits in other areas, eg. neglect, aphasia. Additionally, even though the populations be investigated was often restricted and somewhat uniform, these studies may still have considerable variability within their samples, such that some participants are very far from the mean performance. Thus, conclusions represent average performance and are more difficult to interpret with respect to individual participants.

## Imaging Modalities Used in Reviewed Studies

A number of imaging modalities were used to determine brain mapping in the articles, with the primary modality being fMRI (11 articles) and the others including TMS (5 articles), EEG (5 articles), MEG (2 articles), and functional NIRS (fNIRS) (4 articles). In one instance, more than one imaging modality was used to assess brain reorganization. [32] These imaging modalities measure reorganization of brain function differently. In brief, fMRI measures neural activation indirectly via changes in blood oxygenation. [17] Through detection of positron-emitting radioactively labeled molecules (e.g. [15] O-labeled water to studyblood flow), PET can provide measurements of blood flow and metabolic activity within the brain. [17] In comparison, EEG records electrical impulses from the cortex directly through electrodes placed on the scalp, [16] while fNIRS, or optical imaging, uses near infrared spectroscopy to measure cortical activation via changes in blood oxygenation in the cortex and can be used during human gait. [28] MEG measures magnetic fields generated by cortical neuronal activity, and these magnetic fields are analyzed to find the location of the neuronal sources of activity within the brain. [17] These techniques (fMRI, PET, EEG, NIRS and MEG) allow measurement of changes in brain activation during overt movement. TMS measures the electrical excitability of the cortex, allowing detection of remapping in the primary motor cortex. [15] Importantly, only fMRI and PET allow imaging of deep brain structures such as the basal ganglia. The other technologies employed in the characterization of force control after stroke only permit characterization of the cortex of the brain, and TMS can only be used to map regions where motor responses may be evoked. (For reviews of these neuroimaging techniques and their application to the sensorimotor system and rehabilitation see [15–17, 46])

## Motor Tasks Used in Reviewed Studies

Although all studies included active movement tasks against resistance, there was some variation to the motor tasks utilized in the studies. Tasks that were performed against resistance included hand grip, [19–24, 29–31, 35, 38, 42, 43] pinch grip, [27, 32, 43, 44] wrist extension, [36] key/button press [25, 26, 33, 34, 37] and gait [28, 39–41]. Most studies considered movement performed by both the more affected and less affected limb of persons with stroke, [23, 24, 26, 28, 29, 32, 33, 35–37, 39–41, 44] however some studies required participants to perform movement with only the more affected limb, [19–22, 25, 27, 30, 31, 38, 42] with only the less affected limb [43] or with only the dominant limb [34]. All but four studies included movement of the upper extremity; four studies looked at brain plasticity during gait.[28, 39–41]

## Influence of Stroke Severity on Brain Activation after Stroke

Among twenty-two studies looking at production at one force level, nine showed changes in brain activation in motor areas associated with increasing severity of stroke. [19–25, 31, 38] Specifically, within a group people with chronic subcortical stroke (n=11), those having greater corticospinal tract damage showed increased activation in several motor areas, including bilateral M1, bilateral premotor cortex (PM), supplementary area (SMA), and prefrontal cortex (PFC), [21] during grip with the more affected hand. Similarly, one study examined Wallerian Degeneration (WD) of the pyramidal tract among persons with subacute, internal capsular stroke (n=18). [38] Results showed that people with WD activate the affected and

unaffected PM more frequently than people without WD. [38] Another study found that within a group of persons with chronic stroke (n=20), a correlation occurred between decreased functional outcome (via several measures, including grip strength and timed 10 m walk) and increased activation of motor areas, such as M1, PM, cerebellum, SMA and parietal cortex. [42] Likewise, there appears to be a relationship between decreased function after stroke and changes in patterns of brain activation as demonstrated by coherence between EEG signals during force production. For example, regardless of stroke location, when function was impaired by stroke (n=25) higher levels of task-related coherence occurred between medial cortical areas of right and left hemisphere EEG sources. [24] The increases in coupling between medial cortical areas suggest that these areas may aid in compensating to produce movement during recovery. [24] Coherence measures from scalp EEG signals can also be used to provide information regarding the predominant direction of information flow between two coupled areas. Using coherence measures in this way, coupling between the contralesional and ipsilesional sensorimotor cortices (SMC) was more likely to originate from the contralesionial, unaffected hemisphere in persons with chronic stroke in varying locations (n=25), having less functional hand movement (measured by the 9HPT and hand muscle strength). [23] This finding implies that the unaffected hemisphere aids in generating movement in persons with stroke who do not make a full recovery.

Eight of 26 studies reported whether there was a preferred recruitment of either the affected or unaffected hemisphere during a force production task in persons with stroke when compared to controls (Tables 1–2). Specifically, 3 of the 8 articles demonstrated that the unaffected hemisphere plays a large role during movement of the more affected arm (Table 1) (total participants n=32). [23, 26, 36] Five of the 8 articles showed that motor areas of the affected hemisphere were preferentially recruited rather than areas of the unaffected hemisphere (Table 2) (total participants n=60). [22, 25, 32, 33, 35] Two studies demonstrated a reduction in unaffected hemisphere activation over time associated with improved function in persons with stroke (Table 3). [27, 40] Across studies, lesion location was not a determinant of which hemisphere (contra- or ipsilesional) was recruited; individuals in this work had a mix of cortical and subcortical lesions. Thus, to summarize the effects of stroke severity on brain activation, increased activation in secondary motor areas occurs with increasing severity of stroke, independent of imaging modality or lesion location.

**Table 1: Comparisons for Subjects, Modality, Motor Task and Findings Across Studies Demonstrating Preferred Recruitment of the Unaffected Hemisphere Over the Affected Hemisphere in Persons with Stroke**

| Author | N stroke | Lesion Location | Time Post Injury | Assessment of recovery or severity | Modality; Motor task | Findings |
|---|---|---|---|---|---|---|
| Serrien et al. 2004 | 25 | cortical and subcortical | > 12 months | Subjects were considered recovered (n = 11) if they could perform the 9HPT and had MRC power of 4/5 in each of 4 muscles | EEG; isometric grip task 25% MVC | Stroke subjects with less function had coupling between SMC's that originated from the **unaffected** cortex. |
| Newton et al. 2002 | 3 | cortical and subcortical | > 6 months | Average Rivermead Arm Assessment Score at time of stroke: 1.67/15; Average paretic wrist extension force at time of scan: 74% of nonparetic wrist | fMRI; wrist extension (near isometric) (10%, 20% MVC) | During affected wrist movement, increased **unaffected**/ipsilateral M1 activation in stroke compared to controls. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Kopp et al., 1999 | 4 | cortical and subcortical sparing M1 | 4–15 years | Behavioral measures (AAUT, MAL, WMFT, AMAT) showed improved affected arm use post treatment. The study-wide effect size was 2.38 pre- to post-treatment and 1.92 pre-treatment to follow-up | EEG; key press | 3 months after stroke, affected hand movement-related dipole sources shifted from the affected to the **unaffected** hemisphere . |

Note: MVC = maximum voluntary contraction; SMC = sensorimotor cortex; M1 = primary motor cortex; SRT = simple reaction time. Behavioral measures: 9HPT = nine hole peg test; MRC = medical research council; AAUT = actual amount of use test; MAL = motor activity log; WMFT = Wolf motor function test; AMAT = arm motor ability test.

**Table 2: Comparisons for Subjects, Modality, Motor Task and Findings Across Studies Demonstrating Preferred Recruitment of the Affected Hemisphere Over the Unaffected Hemisphere in Persons with Stroke**

| Author | N stroke | Lesion Location | Time Post Injury | Assessment of recovery or severity | Modality; Motor task | Findings |
|---|---|---|---|---|---|---|
| Braun et al., 2007 | 9 | subcortical | > 9 months | MRC score: range 3–5, mean 4.22 ± 0.28; Subjects were grouped into fair (MRC = 4) or excellent (MRC > 4) recovery | MEG, TMS; precision grip at 1N | Crossed cortico-spinal connectivity in recovered stroke subjects showed that the **affected** hemisphere was recruited. |
| Fridman et al., 2004 | 4 | subcortical | > 2 years | All subjects had 3+ or more on the MRC scale | TMS; simple reaction time task (SRT) via key press | Only TMS applied to **affected** hemisphere (PMd) of stroke led to delays in SRT in the affected hand. |
| Mima et al., 2001 | 6 | subcortical | > 1 year | Mean max power grip force: 13.5 ± 8.6 (affected hand) and 17.3 ± 5.9 (unaffected hand) kgs | EEG, EMG; elbow flexion, wrist extension, power grip at 10–20% MVC | EEG-EMG coherence occurred with the **affected** but not unaffected SMC. |
| Stinear et al., 2006 | 21 | cortical and subcortical | > 6 months | Mean FM score of 16, range 4–25 (out of max 32); mean NIHSS score of 4 (range 0–7). | fMRI, TMS; squeezing of saline bag | During movement of affected hand, activation was weakly lateralized towards **affected** hemisphere. In patients without MEPs, higher FM scores were predicted by stronger lateralization of cortical activity towards **affected** M1. |
| Werhahn et al., 2003 | 20 | cortical and subcortical | > 2 months | MRC of 3.6 ± 4.0 in hand and forearm muscles (range, 1–4+); FM score (upper extremity) = 66.3 ± 23.1% (of max score) for the arm | TMS; finger flexion, key press | Only stimulation of **affected** hemisphere impaired affected hand performance. |

Note: MVC = maximum voluntary contraction; SMC = sensorimotor cortex; M1 = primary motor cortex; PMd = premotor dorsal; SRT = simple reaction time.
Behavioral measures: MRC = medical research council; FM = Fugl Meyer; NIHSS = National institue of health stroke scale.

**Table 3: Subject, Modality, Motor Task Characteristics and Findings for Studies Demonstrating Reduction in Unaffected Hemisphere Activation Over Time Associated with Improved Function in Persons with Stroke**

| Author | N stroke | Lesion Location | Time Post Injury | Assessment of recovery or severity | Modality; Motor task | Findings |
|---|---|---|---|---|---|---|
| Miyai et al., 2003 | 8 | cortical and subcortical | At initial session: 32–112 days | Cadence (steps per minute) and swing-phase LI were used as measures for gait. Mean FM score for lower extremity: 8.5 first session, 21.9 second session. | NIRS; gait | Improvement in gait via changes in swing-phase LI significantly correlated with changes of LI in SMC over time, where asymmetrical activation in the SMC improved. |
| Dong et al., 2006 | 8 | sparing M1 hand region | > 3 months | FM score: 33–62. Mean WMFT (6 items) time decreased from 33.40±37.69 to 16.59±22.462 s for the paretic hand after therapy (P = 0.03) | fMRI; pinch grip at 50% MVC | Affected hand movement showed reduction in unaffected M1 activation over time, and this reduction predicted most improvement. |

Note: MVC = maximum voluntary contraction; M1 = primary motor cortex.
Behavioral measures: FM = Fugl Meyer; WMFT = Wolf motor function test

## Differences in Cortical Reorganization between Acute and Chronic Stroke

Although most research assessed force control during the late, or chronic, phase after stroke, 3 studies tested at multiple time points starting in the acute phase (0–14 days post-stroke; [29–31]). Among these studies, recruitment of motor areas changed during force production as recovery improved. In one longitudinal study, decreases in activation occurred over time, from 10–14 days post stroke to 6 months post stroke, in bilateral M1, PFC, SMA, cingulate motor area, temporal lobe, striate cortex, cerebellum, thalamus and BG during more affected hand grip. [31] In addition, in a separate study the same authors determined that the recruitment of other areas such as the affected PMC and non-affected middle intraparietal sulcus, that occurred 10–14 days after stroke, disappeared by a 3 month follow-up assessment. [30] Thus, in general, reduced recruitment of secondary motor areas during force production is observed as a function of increased time since stroke.

## Brain Activation during Force Modulation after Stroke

Among force modulation studies, increased activation in motor areas occurred with increasing relative force generation in persons with stroke as well as controls. [19, 42,44] In using TMS to compare activation between 16 persons with MCA stroke and 11 healthy controls, Renner et al., [44] found that increased excitability of the affected motor system occurred with higher force in both groups. When comparing fMRI activation of 20 persons with stroke that spared hand representation of M1 and 17 healthy controls, Ward and colleagues [42] found increased activation during increasing relative force in both groups, but with no significant differences between the two groups. The lack of group differences may be in part due to the variability in brain activation within the stroke group that appeared to be related to recovery. In particular, persons with stroke with poorer functional outcome showed greater activation in response to increased relative grip force with the more affected hand in many areas, including contralateral SMC, dorsal PMC, middle temporal gyrus, ipsilateral cerebellum, SMA, and putamen, among others. [42] Going a step further, these same authors in a separate study looked at brain activation with increasing force in relation to cortical spinal tract integrity and demonstrated that the degree to which activity in brain

regions co-varies with the amount of force produced is related to the extent of corticospinal tract damage. [19] More specifically, they found that persons with stroke having less corticospinal tract damage had increased activation with increasing force output in affected M1, SMA and unaffected cerebellum. [19] In comparison, persons with stroke having greater corticospinal tract damage had higher activation with increasing force in affected dorsolateral PM, bilateral ventrolateral PM and unaffected cerebellum. [19] Thus the combination of articles on force modulation demonstrates that during force modulation, increased task-related activation in motor areas occurs with greater force generation. Moreover, persons with more severe stroke show relatively greater activation with rising force compared to persons with less sever stroke.

### Influence of Rehabilitation on Brain Activation after Stroke

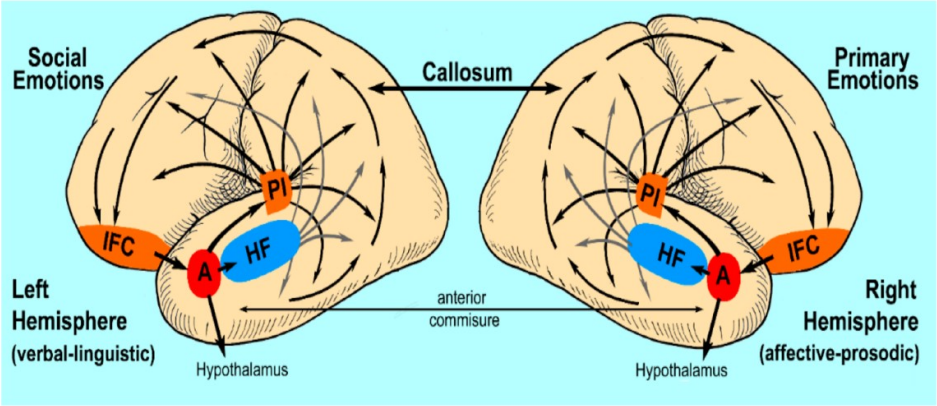
Five studies included in this review examined motor reorganization in persons with stroke during a force production task before, after, or during an intervention. For example, one study evaluated cortical activation patterns using fNIRS during gait on a treadmill with partial body weight support (BWS; 10%). [28] This study found that during BWS training, activation in SMC was lowered and changes in SMC activation correlated with improvement in gait performance (decreased time for the more affected leg swing phase, improved asymmetry of swing phase) in 6 persons with subcortical stroke. [28] Another study compared brain activation using fNIRS during gait using two different interventions under partial body weight support. [41] Results demonstrated that increased activation of cortical motor areas (including PM and preSMA) and improved gait performance occurred in walking with therapists who facilitated hip, pelvis and knee positioning rather than when therapists assisted the foot and thigh in a more mechanical pattern. [41] The same authors also examined brain activation longitudinally using the same fNIRS technique during gait before and after two months of inpatient rehabilitation. [40] Before rehabilitation, gait was associated with increased SMC activation that was greater in the unaffected vs. Affected hemisphere, as well as increased activation in the PM and SMA. [40] After rehabilitation, activation in the affected PM increased and asymmetry in SMC activation decreased. (i.e., became more equal between the hemispheres) which significantly correlated with improvement of gait parameters. [40] Dong et al., [27] considered the impact of a 2 week bout of constraint induced movement therapy (CIMT) and found that in persons with chronic (3 months post) stroke, sparing the hand motor representation, activation of the non affected M1 decreased after training. This decrease in unaffected M1 activation was assessed via an increase in laterality index (LI). In contrast, in 4 persons with chronic stroke who participated in CIMT, Kopp and colleagues [26] found a shift in activation away from the affected hemisphere and towards the non-affected hemisphere during more affected hand movement. Yet regardless of these differences, it is apparent that these articles demonstrate that rehabilitative interventions can alter force production task-related brain activation and motor performance of persons with stroke.

## DISCUSSION

### Brain Activation after Stroke

**Higher Levels of activation with increased severity** A number of studies examined in this review investigated brain reorganization in relation to severity of stroke. All of these studies demonstrated increased activation in secondary motor areas with increasing severity of stroke, independent of imaging modality or lesion location. Figure 1 depicts those areas of the brain that showed higher levels of activation with increased severity or decreased outcome in persons with stroke during force production or modulation. This pattern of activation could be due to several reasons. Based on the similarity of corticospinal projections from numerous cortical motor areas, Dum and Strick [4] suggested that a number of motor areas

has the potential to generate an output to the spinal cord in order to produce and control movement. Thus, if damage occurs in M1, greater recruitment of secondary motor areas may occur to compensate. However, projections from secondary motor areas are less numerous and have an overall lower excitatory effect than those from the primary motor area. [47] Thus, secondary motor recruitment also may be associated with poorer functional outcome. [21, 42] The importance of intact M1 projections for the generation of voluntary movement has also been demonstrated by Wenzelburger et al., [7] where it was noted that in persons with stroke that disrupted projections descending from M1, more severe chronic motor deficits were exhibited.




**A.** Non-affected hemisphere shows increased activation in M1, SMA, PM, cingulate sulcus, intraparietal sulcus, cerebellum. **B.** Affected hemisphere shows increased activation in M1, SMA, PM, cingulate sulcus and intraparietal sulcus.
Note: M1 = primary motor cortex, SMA = supplementary motor area, PM = premotor cortex.

**Figure 1: Medial and Lateral Views of the Non-Affected Hemisphere (A) and Affected Hemisphere (B) of the Brain Depicting Areas Having Increased Activation with Increased Severity OR Decreased Outcome in at Least Two or More Studies.**

An alternative explanation for the association of secondary motor area recruitment with poorer functional outcome is that these individuals may find certain motor tasks more effortful than individuals with stroke who are more recovered, and thus they recruit additional motor regions. [23, 24] However, the majority of studies (5/7) used force generation at a relative percentage of MVC, which eliminates the discrepancies in effort between subject groups. Strens et al., [24] also offer the explanation that increases in activation in secondary areas may occur as a result of increased attention used by some subjects as additional compensation to generate movement. Similarly, based on data from their study, Ward et al., [21] speculate that when performing a visuomotor task, subjects with increased stroke severity pay more attention to the motor task. This increased attention is associated with greater fronto-parietal activity, which ultimately may facilitate in recruitment of motor areas to aid in generating movement. [21] In addition the effortful and attentionally demanding nature of generating movement after stroke may stimulate motor fatigue which can also affect brain activation, specifically in the SMA and frontal areas of the brain. [48] Thus, individuals with stroke with poor functional outcome may show increased activation in secondary motor areas due to higher levels of motor fatigue.

## Role of the Undamaged, Contralesional Hemisphere?

The role of the undamaged, contralesional hemisphere during movement of the more affected hand after stroke was addressed in 8 studies and an obvious discrepancy was noted between these studies. Some (3/8; [23, 26, 36]) report increased levels of recruitment of the contralesional hemisphere, whereas others (5/8; [22, 25, 32, 33, 35]) do not. One possibility for this

seeming contradiction in results may relate to the time after injury; shifts in activation from the unaffected hemisphere during the acute phase to the affected hemisphere in the chronic phase have been demonstrated after stroke. [49] However, the sole factor of time after injury cannot explain all of these findings as 7/8 studies included persons with chronic stroke.

Other studies have shown that recruitment of areas in the undamaged, contralesional cortex during motor tasks is associated with poor motor performance [50] or decreased function. [23] Moreover, some persons with stroke having poor motor outcome show no motor output from the affected, ipsilesional hemisphere, while large amounts of motor activation are noted in the affected hemisphere in those with good outcome. [51] Accordingly, two studies included in this review [27, 40] have demonstrated a reduction in unaffected hemisphere activation over time that correlated with functional improvement in persons with stroke. In this way, the balance of activation between hemispheres seems to play a role in motor function after stroke. As has been mentioned previously, projections from secondary motor areas are less numerous and have a decreased excitatory effect on the spinal cord than those from the primary motor area. Thus, recruitment of secondary motor areas has been associated with poorer functional outcome. [21, 42] The findings from this review suggest that this is also true for projections descending from the undamaged, contralesional hemisphere. In addition, as persons with stroke with greater disruption of primary motor projections exhibit more severe chronic motor deficits, [7] it is not surprising that during movement of the more affected hand, activation is more likely to be lateralized towards the affected hemisphere if the motor cortex is intact. [22] Thus, it is likely that more severe strokes are those that impart larger amounts of damage to M1 and its projections and result in increased recruitment of secondary motor areas, including the unaffected, contralesional cortex. And as secondary areas are not as adept in generating functional movement as M1, motor outcome and likely overall function are decreased in these individuals. Unfortunately, not all of the studies reporting a preferred recruitment of either hemisphere directly indexed severity of injury making it difficult to ascertain whether more severe strokes do indeed stimulate recruitment of the unaffected hemisphere during force production.

### Differences in Cortical Reorganization between Acute and Chronic Stroke Stages

The initial increase in secondary motor area activation early after stroke, demonstrated in 3 studies, likely reflects a compensatory strategy to produce functional movement of the more affected hand. At a cellular level, increases in synaptogenesis [52] and dendritic branching occur in the cortex early after a lesion in rats, while over time branching is reduced. [53] Ward and colleagues suggest [31] that this branching is followed by subsequent pruning back, and may explain the activation reduction seen in the chronic phase as compared to the acute phase of stroke.

It is also possible that changes in brain activation between the acute and chronic phase may be due to the fact that early after stroke, when motor deficits are greatest, persons with stroke pay more attention to task performance [31] and increase error monitoring. Increases in task-related brain activation as a result of increased attention due to error awareness have been observed in a number of motor regions, including SMA and cingulate cortex. [54] In addition, in the acute phase, persons with stroke activate the middle parietal sulcus, [31] an area used for tasks requiring increased visuomotor attention. [55]

### Influence of Rehabilitation on Brain Activation

This review examined studies employing both upper extremity tasks, as well as lower extremity movement (gait) during neuroimaging, where the majority (4/5) of gait studies looked at brain activation during or after an intervention. Although these two categories of movement are quite distinct, similar results of altered activation patterns as a function of intervention were reported using either type of movement. However, it is important to keep in mind that during gait, the ability to examine subcortical regions is hindered as the modality used (fNIRS) does not enable study of subcortical

structures. In addition, as gait is a bilateral task, and most of the upper extremity tasks employed are unilateral, this may affect the lateralization of brain activation observed during either type of movement. Thus, although general conclusions regarding the influence of interventions on activation patterns are similar for both upper and lower extremity movement, specific regions that are identified using these two types of movement will differ due to the different performance of the motor tasks and imaging modalities available to the tasks.

In general, all 5 studies employing rehabilitation interventions using repetitive tasks demonstrated changes in brain activation post intervention. [26–28, 40, 41] Moreover, four of these studies identified changes in brain activation that were associated with improved upper limb [27] or lower limb [28, 40, 41] motor performance after stroke.

Although all 5 studies demonstrated altered brain activation with rehabilitation, some discrepancies were apparent in the patterns of brain activation between studies employing the same intervention. Specifically, Dong et al., [27] showed reduction in activation of the undamaged, contralesional hemisphere after a CIMT intervention, while Kopp et al., [26] found that the contralesional hemisphere was recruited more after a CIMT intervention. As sample sizes are low in both studies (n=4 and n=6), it is difficult to determine whether these differences are due to subject severity, stroke chronicity, lesion location or some other combination of factors. Importantly, different imaging modalities were used in these two studies (EEG vs fMRI) making a direct comparison of results difficult if not impossible.

The ability to determine how patterns of brain activation shift with improved motor performance has great implications for current research designed to inform the development of treatments to manipulate brain reorganization. For example, repetitive TMS applied to the cortex is being examined as a tool to promote cortical plasticity in persons with stroke [56] and could be used with other rehabilitation therapies to further promote functional motor programs. [57] In addition, as was shown by the studies of CIMT [26, 27] consideration of whether and how interventions shift activation in brain regions associated with the control of force is critical to determine the effectiveness of new treatment approaches. However, it appears that a prerequisite for these types of interventions is some degree of residual sparing of the primary motor areas and the associated network of secondary regions in order to produce functional movement and allow for treatment success. Thus, the use of fMRI and other neuroimaging techniques to identify residual anatomical areas and their relative contribution to functional movement may aid in determining which persons with stroke will benefit the most from these treatments.

## CONCLUSIONS AND LIMITATIONS

This review concludes that motor reorganization occurs with respect to force generation and modulation after stroke. Key findings across studies are that during force production increased activation in motor areas, including the undamaged, contralesional hemisphere, occurred in persons with more severe stroke, and recruitment of these motor areas often diminishes as recovery improves. With respect to force modulation, increased activation in motor areas occurred with greater force generation in persons with stroke and individuals with more severe stroke showed greater activation with rising force production levels. This review provides evidence for reduced recruitment of secondary motor areas during force production as a function of time since stroke. Lastly, and very importantly, brain activation can be shifted by certain rehabilitative interventions in persons with stroke.

This review has several limitations that stem from the highly varied subject characteristics and tasks that were employed across individual studies. One caveat of the conclusions formed from this review comes from our decision to

only include studies that investigated the performance of active movement against resistance; thus we excluded studies employing tasks performed passively or active tapping tasks that were not against resistance. These experimental paradigms can provide valuable information on reorganization after stroke and are often used in more severe stroke populations. However, changes during these types of movements do not necessarily reflect the adaptations that take place during activities of daily living that require force generation and modulation (eg. opening a door, holding a cup) and thus were excluded.

In addition, limitations within included studies may stem from the use of fMRI as a tool to examine brain activation in persons with stroke. Past studies have determined that brain damage may affect the BOLD response measured by fMRI, as evoked changes in cerebral blood oxygenation in the stroke affected brain have been shown to differ from those in the normal brain. [58, 59] Also, analysis techniques applied to fMRI data of persons with stroke can have limitations. For example, when comparing across groups, the brains of each individual subject are often warped (i.e.: normalized) to a reference template. This approach, however, may introduce inaccuracies when normalizing a lesioned brain, [60] as normalization depends on the morphology of the brain, which is often abnormal in these cases. This limitation has stimulated the generation and use of analysis techniques, such as a region of interest analysis, that do not rely on warping of brains to a common template. [61, 62]) Despite these advances, it is important to remember that all brain imaging techniques in humans are indirect measures of neural activity and should be interpreted cautiously.

## Clinical Implications

This review provides evidence that rehabilitative interventions can positively alter brain activation and motor performance of persons with stroke. We believe that consideration of whether and how clinical interventions shift activation in brain regions associated with the control of force is critical to determine the effectiveness of new treatment approaches. Based on the literature available, it appears that a prerequisite for clinical treatments that seek to restore the control of force is some degree of residual sparing of the primary motor areas and the associated network of secondary motor regions.

Specifically, the results from this review can be used to facilitate our understanding of the mechanisms that underpin current models of rehabilitation. For example, the evidence for CIMT as a technique aimed to increase motor recovery is promising; however the inclusion criteria for enrollment in this therapy are very strict (at least 20 degrees of active wrist extension and at least 10 degrees of extension at two digits in addition to the first digit of the affected hand. [63] These criteria are based on indications that voluntary movements of finger and wrist extension predict the recovery of independent limb use, [63] and thus ability to benefit from CIMT. This review demonstrates that recovery of motor function is accompanied by brain activation changes, indicating a rewiring of the neural control of movement over time. Thus, it is possible that reorganization of the brain after stroke may be as useful as a predictor of functional recovery of force control compared to the minimal motor criteria that were established for CIMT. Hence, this may imply that as an approach to facilitate the recovery of force control, CIMT may be successfully extrapolated into populations with more severe initial presentation. Future work will have to verify this prediction.

As the use of imaging techniques expands and continues to inform clinical practice, it is critical we recognize the benefits and limitations of varied technological approaches. For example, corticomotor maps as assessed by TMS, and brain activation as assessed by fMRI, have previously been shown to not be predictive of functional potential after stroke. [22] However, other neuroimaging data may predict recovery such as MEPs via TMS to assess CST integrity, or DTI measures of white matter connectivity [22]. For example, using TMS to assess CST integrity, Stinear et al., [22] offer the

hypothesis that individuals with stroke exhibiting MEPs in the more affected limb have great functional potential and are likely to benefit from intensive rehabilitation treatments. In persons with more severe stroke, MEPs cannot be elicited through TMS and thus DTI can be used to assess disruption of white matter tracts and can predict functional potential. [22] Taken together these data strongly suggest that it is possible to use neuroimaging techniques, such as DTI and TMS, to evaluate functional potential in order to select appropriate rehabilitation strategies for persons with stroke.

In summary, through our review of the literature we discovered that several key parameters appear to critically determine how the brain is recruited during force control and modulation after stroke. First, time since stroke is an important factor, with a return to more normal patterns of brain recruitment occurring as individuals move from the acute to chronic stage. Second, the extent of brain damage and the residual integrity of M1 and its outflow tract determines whether force control requires the additional recruitment of secondary and or contralesional motor areas. Thirdly, and likely in strong relationship to the extent of brain damage, the severity of stroke appears to influence whether and how force control in the more affected side returns. Taken together these three factors may be used in the clinical setting to infer how the control of force may be recovered in people with stroke. Finally, it was clear from the available literature that rehabilitation interventions positively shift both patterns of brain activation and functional ability with respect to force control and modulation after stroke.

## CONFLICT OF INTEREST

NO any conflict of interest exists

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