MECHANISMS OF RECOVERY IN PATIENTS WITH SEVERE ARM IMPAIRMENT AFTER STROKE

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MECHANISMS OF RECOVERY IN PATIENTS WITH SEVERE ARM IMPAIRMENT AFTER STROKE

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ABSTRACT

**Background** Arm hemiparesis is a common consequence of stroke. Patients with more severe arm impairment demonstrate nonlesioned hemisphere activation during brain imaging of motor function. Determining lesion characteristic differences between patients with mild and severe arm impairment may help to explain this activation. To better plan intervention strategies, it is necessary to understand if nonlesioned hemisphere activation is contributing to movement.

**Objective** The objectives of this project were to explore which lesion characteristics result in severe arm impairment and to determine the contribution of the nonlesioned hemisphere to reaching function in these patients, specifically the contribution of the nonlesioned dorsal premotor cortex (PMd).

**Methods** Lesion characteristics were mapped and compared between a group of patients with mild and severe arm impairment. Lesion location was compared to various aspects of reaching movement. During a reaching task, online double-pulse transcranial magnetic stimulation (DP-TMS) was applied to lesioned and nonlesioned primary motor cortex (M1) and PMd in patients with mild and severe arm impairment and to nonlesioned M1 and PMd in a larger group of patients with severe impairment to measure changes in movement time and reaching kinematics.

**Results** A significantly larger percentage of patients with severe arm impairment had lesions involving the posterior limb of the internal capsule (PLIC) and patients with lesions in PLIC had
significantly worse reaching performance. There was no significant main effect for patients with mild or severe impairment after perturbation of the lesioned hemisphere, however, patients with severe impairment demonstrated a significant change in movement time after perturbation of the nonlesioned hemisphere and this effect was greatest after DP-TMS to PMd. In patients with severe impairment, only DP-TMS to PMd, and not to either control site, resulted in a change in movement time in the nonlesioned hemisphere.

**Summary** Overall, this study demonstrates that some patients with severe, chronic impairment have sites within the nonlesioned hemisphere that can contribute to post-stroke movement and it may be possible to identify these patients by examining their lesion characteristics. Future research into non-invasive brain stimulation as a method to improve the efficiency of intervention after stroke should consider nonlesioned PMd as a potential site for upregulation in this group of patients.
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CHAPTER 1
INTRODUCTION

Stroke is a highly prevalent and often devastating health issue. In the United States, 795,000 people per year have a stroke and as public health and awareness of stroke signs and symptoms continue to improve, stroke deaths have declined by 18.2% (Mozaffarian et al., 2016). As a result, more American adults are surviving into the chronic stage post-stroke leading it to be the most frequent cause of long-term disability in adults costing upwards of 33 billion dollars annually (Mozaffarian et al., 2016). Some degree of upper-extremity hemiparesis presents itself initially in 88% of patients who have a stroke (Bonita & Beaglehole, 1988). Spontaneous recovery plateaus in the first three to six months post-stroke (Hendricks et al., 2002), after which, 11-30% of patients regain full function of the arm and 30-38% regain partial use. The remaining patients are left with chronic, severe impairment (Bonita & Beaglehole, 1988; Kwakkel et al., 2003; Nakayama et al., 1994). Severe arm impairment is one of the most disabling consequences post-stroke, impacting quality of life, independence, and activities of daily living (Nichols-Larsen et al., 2005).

Post-stroke arm impairment is typically the result of damage to upper-motor neurons or to subcortical areas after middle cerebral artery stroke. Long upper-motor neuronal axons are bundled within the corticospinal tract (CST), originating in primary motor cortex (M1) and surrounding motor regions with ~90% terminating contralaterally at the spinal cord (Dum & Strick, 2002; Kuypers & Brinkman, 1970). A lesion at any point within this pathway (cortical or subcortical) may cause some degree of damage to motor control. Damage ranges from a mild change in strength and dexterity, to a severe impairment in strength with little to no voluntary
extension of the wrist and fingers, to complete paralysis (Cho et al., 2007; Macciocchi et al., 1998; Schiemanck et al., 2008).

There are marked differences in the recovery patterns of patients with mild and severe arm impairment. Patients with post-stroke arm impairment demonstrate a proportional recovery of 63% from 3 weeks to 3 months post stroke, but only if CST is relatively intact (Stinear et al., 2017). Patients with initially mild or moderate deficit are 10 times more likely to recover full function than patients with an initially severe deficit and the plateau in spontaneous recovery can take up to three months longer (Bonita & Beaglehole, 1988; Duncan et al., 1992). Transcranial magnetic stimulation (TMS) physiology studies have shown that contralateral motor evoked potentials (MEPs) can be found in multiple muscles within the impaired arm of patients with mild impairment but that MEPs cannot be produced in patients with more severe impairment (Turton et al., 1996). Brain imaging studies have shown that patients with mild impairment primarily have activation of the perilesional areas while patients early in recovery and with more severe impairment have bilateral brain activation including M1 and the premotor cortices of the nonlesioned hemisphere (Calautti & Baron, 2003; Ward et al, 2003). Activation of the nonlesioned hemisphere has been associated with poorer recovery, though whether the bilateral brain activation is adaptive or maladaptive is unclear (Rehme et al., 2012).

Increasingly, more data are becoming available on recovery of mild arm impairment after stroke with activity-based rehabilitation paradigms (such as Constraint Induced Movement Therapy). However, often only patients with mild arm impairment (who retain voluntary extension of the wrist or fingers) fall within the inclusion criteria for these trials (Corbetta et al., 2010). The effect of these paradigms has yet to be fully elucidated in patients with more severe
impairment after stroke. Additional therapy options are emerging with the use of non-invasive brain stimulation (NIBS) with repetitive transcranial magnetic stimulation (rTMS), a relatively painless form of stimulation that can induce sustained facilitation or inhibition of specific neural sites. Several studies of NIBS in the motor system suggest that the effects of high-frequency rTMS over nonlesioned M1 can increase cortical excitability, as measured by MEP amplitude, for anywhere from 6-30 minutes (Fitzgerald et al., 2006). Considering the limited window of time available to pair intervention with spontaneous recovery, NIBS has the potential to be a powerful tool to increase the gain from rehabilitation. So far, however, studies combining NIBS with post-stroke rehabilitation have had inconsistent results and meta-analysis suggests that there is insufficient evidence to demonstrate that NIBS and rehabilitation are more effective than rehabilitation alone (Graef et al., 2016). The lack of positive results may be due to a homogenous approach to stimulation site selection, which is unlikely to be effective in a heterogeneous population with demonstrated differences in neural reorganization and connectivity (Rehme et al., 2012; Turton et al., 1996). Before researchers can decide which area to target with NIBS, we have to determine the mechanisms of post-stroke motor recovery across the spectrum of post-stroke motor severity.

The motor system is incredibly redundant and neuronal networks for particular, complex movements are often distributed throughout the motor, premotor, and supplementary motor areas (Graziano et al., 2002; Fried et al., 1991). Post-stroke, the motor cortex undergoes a period of neuroplasticity during which axonal sprouting and activity-dependent remapping occur (Murphy & Corbett, 2009). Due to redundancies within the motor system, remapping often takes place by forming new circuits with perilesional tissue that previously held roles in similar functions. This
remapping, however, can only successfully regain function when there are available perilesional neurons and a method of CST relay to the lower-motor neurons (Murphy & Corbett, 2009). In the case that neither of those conditions are met, activity-dependent remapping must occur in areas previously uninvolved in the movement.

There are two competing models for the pattern of functional reorganization that produces the best outcomes post-stroke and these models have opposite implications for stimulation parameters and site selection for NIBS. The Interhemispheric Competition model suggests that the best post-stroke outcomes should result from rebalancing interhemispheric inhibition after stroke by inhibiting the nonlesioned hemisphere or exciting the lesioned hemisphere (Ward & Cohen, 2004). This model suggests that the correlation between nonlesioned hemisphere activation and worse post-stroke motor outcomes is the result of an imbalance in interhemispheric inhibition (Ward & Cohen, 2004). The dense transcallosal fibers connecting the homologous M1s exert a paired inhibitory force that typically remains balanced, with dynamic modulation as needed for movement (Ferbert et al., 1992, Duque et al., 2005). Post-stroke, however the lesioned hemisphere can no longer exert the same amount of inhibition on to the nonlesioned M1, increasing its cortical excitation. This increased cortical excitation of nonlesioned M1, in turn, increases the inhibition from the nonlesioned hemisphere on to perilesional motor areas, thus decreasing excitability in the lesioned hemisphere (Duque et al., 2005; Murase et al., 2004). Several studies have attempted to use NIBS to rebalance this interhemispheric disparity by decreasing excitability of nonlesioned M1 or increasing excitability of lesioned M1, but these studies have had mixed results (Ackerley et al. 2010; Bradnam et al. 2013; Corti et al. 2012; Hsu et al. 2012; Nowak et al. 2009; Takeuchi et al. 2005, Graef et al.,
The second model, the vicariation model, posits that residual networks within the remaining tissue form new circuits to recover lost function, even in the nonlesioned hemisphere (Finger, 2009). For patients who do not retain adequate perilesional tissue or have severe CST damage, this model would suggest that increased activation of areas within the nonlesioned hemisphere is contributing to post-stroke movement and NIBS should be used to excite the nonlesioned hemisphere to encourage vicarious activity.

Both models invariably have limitations. The Interhemispheric Competition model cannot apply to patients that do not retain enough perilesional, redundant tissue and/or remaining descending CST fibers in the lesioned hemisphere to produce functional arm movement. The vicariation model cannot account for the fact that patients with more lateralized, lesioned hemisphere activation have better outcomes. In an attempt to reconcile these faults, Di Pino et al. (2014) proposed the Bimodal Balance Recovery model. The Bimodal Balance Recovery model reconciles Interhemispheric Competition with Vicariation by introducing a graded parameter that they term structural reserve. This model suggests that researchers quantify the strategic neural pathways and relays spared by the lesion that can contribute to recovery in an individual patient before deciding on a stimulation paradigm for NIBS. If patients have a high level of structural reserve, they will have better outcomes when the balance of activity between hemispheres tends toward the previous equilibrium. If patients have a low level of structural reserve and are far from reaching a physiological restoration to their original state, persistence of the interhemispheric imbalance promotes vicarious activity in the nonlesioned hemisphere, allowing for compensatory plasticity (di Pino et al., 2014).
Missing from this model is a definition of what constitutes the gradient of structural reserve. Currently, there is incomplete evidence as to how lesion characteristics relate to impairment levels. Chen et al. (2000) indicated that a specific threshold of lesion size within cortical areas, corona radiata, internal capsule, putamen, or thalamic regions determined levels of severity. Other studies have found that patients are more likely to recover function following cortical as opposed to subcortical strokes, specifically subcortical strokes involving the posterior limb of the internal capsule (PLIC), thalamus, corona radiata, and basal ganglia (Macciocchi et al. 1998; Shelton et al., 2001). Further studies suggest that lesions within PLIC correlate with the poorest recovery (Schiemanck et al., 2008) and that retention of descending tracts from the primary motor cortices and dorsal premotor cortices correlate with treatment gains (Burke-Quinlan et al., 2015; Riley et al., 2011). The lesion characteristics that constitute the gradient of high and low structural reserve need to be better defined.

This model suggests that researchers take a different approach to designing trials and interventions for patients with mild and severe arm impairment after stroke. Studies of patients with high structural reserve should continue to target the interhemispheric imbalance reducing cortical excitability in the lesioned hemisphere. For patients with low structural reserve, however, the implications are less clear. There are several factors that need to be determined before researchers can begin to design NIBS trials for patients with low structural reserve. While the nonlesioned hemisphere is more active in these patients, it has yet to be conclusively proven that the nonlesioned hemisphere contributes to post-stroke movement in patients. If the nonlesioned hemisphere can contribute to post-stroke movement in patients with severe arm impairment, it is still to be ascertained if there is a specific site within the nonlesioned
hemisphere that could play a compensatory role and contribute to post-stroke movement. Finally, it is unclear what specifically constitutes high and low structural reserve, specifically whether the gradient of structural reserve relates to available perilesional tissue or descending CST connections.

There is evidence that the nonlesioned hemisphere could play a role in ipsilateral motor control post-stroke. In macaques, tracer studies have shown that almost one quarter of projections from supplementary motor area terminate in the ipsilateral spinal cord, as do 18% from M1, (Dum & Strick, 1996). Strokes have resulted in both contralateral and ipsilateral deficits, which suggest some degree of ipsilateral control prior to the infarct (Gonzalez et al., 2004). In humans, ipsilateral MEPs were elicited from patients with severe stroke impairment but not from those with good recovery (Netz et al., 1997; Turton et al., 1996). Additionally, children who undergo hemispherectomies demonstrated ipsilateral activation comparable to the contralateral activation of controls during a brain imaging study of a foot dorsiflexion task, demonstrating that in the developing brain, the remaining hemisphere can reorganize and control motor function of the ipsilateral side (de Bode et al., 2005). The nonlesioned hemisphere has the cortical connections necessary to control arm movement from several motor sites, but the nonlesioned hemisphere site that may be most likely to contribute to ipsilateral arm function post-stroke is the dorsal premotor cortex (PMd).

PMd is well designed for compensatory neural reorganization of arm function post-stroke. While often thought of in the context of movement planning, PMd also has a role in movement execution. 30% of descending CST fibers originates in PMd (Martino & Strick, 1987). In animal studies, single-unit recordings from PMd have shown activation during bilateral
proximal arm reaching movements (Cisek et al., 2003). There is also evidence for direct
tipsilateral connections between the premotor cortex and the spinal cord (Bucy, 1933; Kuypers &
Brinkman, 1970). In human studies, after rTMS inhibition of PMd, the homologous PMd
becomes active during an ipsilateral action selection task. When contralateral PMd inhibition is
followed by double-pulse TMS (DP-TMS) perturbation to the ipsilateral PMd, reaction time
slows during the same task (O’Shea et al., 2007). In patients with mild impairment, single-pulse
TMS perturbation of nonlesioned PMd slowed response time during a finger movement task and
the size of the response to TMS perturbation correlated with more bilateral brain activation
during brain imaging of performance of the same task (Johansen-Berg et al., 2002). These
studies demonstrate the possibility of a functionally relevant role for nonlesioned PMd,
specifically in control of ipsilateral arm function post-stroke. The role of nonlesioned PMd has
not been examined in patients with severe arm impairment.

As in the O’Shea study, one way to identify the contributions of specific neural sites is
with the use of an online DP-TMS paradigm. Unlike rTMS, which can excite or inhibit cortical
activity for a sustained period of time, the effect of DP-TMS last only milliseconds (Harris-Love,
2012). Often used in reaction time studies, DP-TMS produces a transient alteration in the pattern
of activation in the site of interest. When DP-TMS is applied to a region of interest immediately
prior to initiation of a movement and the region of interest contributes to completion of that
movement, reaction time should slow (Harris-Love, 2012). DP-TMS could identify the
contribution of specific regions of interest within nonlesioned PMd to movement after severe
stroke.
The objective of this research is twofold. The first objective is to explore lesion characteristics associated with more severe impairment by examining how lesions differ patients with mild and severe arm impairment in our sample. The second objective is to determine a potential stimulation site for NIBS in patients with more severe impairment by examining the contributions of the nonlesioned hemisphere in reaching movements. We hypothesize that patients with CST lesions will have more severe arm impairment than those with cortical lesions. We also hypothesize that sites within the nonlesioned hemisphere, specifically PMd, will contribute to reaching movements in patients with severe, but not mild, post-stroke arm impairment.

In the first study, we examine the lesion size and lesion characteristics of patients with mild and severe impairment. In our primary analysis, we compare lesion size and location between groups of patients with mild and severe arm impairment to identify their lesion characteristics. In our secondary analysis, we explore how those lesion characteristics relate to measurements of reaching ability. In the second study, we apply DP-TMS to M1 and PMd of the lesioned and nonlesioned hemispheres in patients with mild and severe arm impairment during a reaching task. We compare percent change in movement time in each hemisphere within the sites and between the groups. In the final study, we apply DP-TMS to M1 and PMd of the nonlesioned hemisphere in a larger group of patients with severe arm impairment during the same reaching task. We compare percent change in movement time and kinematic measures within the sites. DP-TMS is applied to DLPFC in a subset of these patients as a control.

The results from the first study will provide evidence that PLIC, an area vulnerable to middle cerebral artery stroke that contains densely packed CST fibers, plays a role in the gradient
of structural reserve between patients with mild and severe arm impairment. The second and third study will provide evidence for the contribution of nonlesioned hemisphere PMd to severely impaired post-stroke reaching movements. Together, the results of this dissertation will provide a basis for patient selection and intervention design of a NIBS trial targeting nonlesioned hemisphere PMd.
CHAPTER 2
LESION LOCATION AND SEVERITY OF POST-STROKE ARM IMPAIRMENT

2.1 BACKGROUND

795,000 Americans have a stroke each year, and ~60% of those patients are left with permanent movement deficits in the paretic arm (Mozaffarian et al., 2016). Research into the causes and best tools for rehabilitation of stroke have been ongoing for almost two hundred years (Jackson, 1872). During the early stages of stroke research, post-mortem identification of lesion location combined with clinical presentation was used to infer which regions of the brain were responsible for specific functions (Rorden & Karnath, 2004). This approach, however, had flaws. It did not allow for evaluation of living patients and failed to account for network effects from a lesioned brain region, often citing the damaged region as the sole area responsible for the lost function. With brain imaging techniques such as MRI, stroke location can now be visualized in recovering patients. This technology allows for the process of lesion-symptom mapping, or identifying lesion characteristics from a large sample of patients and determining how those lesion characteristics statistically relate to shared behavioral outcomes.

There is incomplete evidence regarding how lesion characteristics relate to chronic severity of paretic arm impairment, specifically in regard to cortical vs. subcortical involvement and lesion size. Chen et al. (2000) found that there is a lesion size threshold in cortex, corona radiata, internal capsule, putamen, or thalamic regions that results in more severe post-stroke motor outcomes. Others suggest that functional motor recovery is generally greater after cortical strokes (Macciocchi et al., 1998) as opposed to subcortical strokes involving the posterior limb of the internal capsule (PLIC), thalamus, corona radiata, and basal ganglia (Shelton et al., 2001). Additional studies associate lesions in PLIC with poor recovery of motor function (Schiemanck
et al., 2008) and retention of corticospinal tract (CST) projections from the primary motor cortices (M1) and dorsal premotor cortices (PMd) correlates with treatment gains (Burke-Quinlan et al., 2015; Riley et al., 2011). Determining the lesion characteristics in patients with varying levels of post-stroke arm impairment may help to increase our understanding of which brain areas are critical for a certain level of recovery to take place, as well as the areas that may be available to contribute to additional recovery.

According to the Bimodal Balance Recovery model, patients with post-stroke arm impairment demonstrate different patterns of neural reorganization depending on the amount of structural reserve, or remaining functional tissue, in the lesioned hemisphere (di Pino et al., 2014). Patients with high structural recruit perilesional areas while patients with lower structural reserve recruit areas previously uninvolved in the movement (e.g. motor regions of the nonlesioned hemisphere). How to identify where an individual patient is on this gradient of structural reserve is unclear. For this model to successfully impact the design of future non-invasive brain stimulation (NIBS) trials, the characteristics of structural reserve need to be defined in more detail. One potential way to identify the key contributors to structural reserve is to identify lesion characteristics that differ between patients with mild and severe motor impairment.

The aims of this retrospective study were two-fold. First, we sought to identify differences in lesion characteristics between patients with and without recovery of distal arm movements. Second, we examined the association between lesion characteristics and performance of a proximal arm movement. Understanding how lesion characteristics relate to recovery of distal movements and performance of proximal arm movements can provide insight
into what constitutes structural reserve for different types of arm movements. This information can provide useful insight into which patterns of neural reorganization may be most beneficial for recovery a specific type of movement given a specific lesion profile, as suggested by the recently proposed Structural reserve, Task Attributes, Connectivity (STAC) model (Harris-Love & Harrington, 2017).

2.2 METHODS

Participants

The study cohort was recruited from MedStar National Rehabilitation Hospital and the surrounding community. The protocol was approved by the MedStar Health Research Institute Institutional Review Board and all patients provided written informed consent prior to their participation in the study. Inclusion criteria included being 18-85 years old and having had a single hemispheric subcortical stroke >6 months prior to study enrollment, with or without cortical involvement. Patients had no previous or co-existing neurological disorders or orthopedic disease or injury of the upper extremities. Patients were excluded if they had lesions involving the brainstem or cerebellum, were unable to perform the reaching tasks or had contraindications to MR imaging.

Imaging

Anatomical, T1-weighted, high-resolution MRI brain scans were recorded without contrast using the following parameters: Phillips CV Intera 1.5T MRI Centre; repetition time = 1400 ms; echo time = 4.76 ms; flip angle = 25°; 172 contiguous 1 mm sagittal slices; field of view = 250 x 250 cm; voxel size = 1 x 1 x 1 mm; slice thickness = 1 mm (n=22) and Siemens 3T Tim Trio; repetition time = 1900 ms; echo time = 2.52 ms; flip angle = 9°; 160 contiguous 1 mm
sagittal slices; field of view = 250 x 250 cm; voxel size = 1 x 1 x 1 mm; slice thickness = 1 mm (n=8).

Clinical Measures

The Upper Extremity Fugl-Meyer Assessment (UEFM; Fugl-Meyer et al., 1975; Gladstone et al., 2002; Page et al., 2012), National Institutes of Health Stroke Scale (NIHSS; NINDS; Meyer et al., 2002) and Mini-Mental Status Exam (MMSE; Folstein et al., 1975) were administered by a licensed physical therapist, a neurologist, and a trained researcher, respectively, according to published protocol with the exception of the MMSE which was modified slightly for patients with mild aphasia.

Proximal Arm Movement Assessment

Patients were seated in an adjustable chair with the shoulders and upper torso restrained by a 4-point seat belt. The chair was positioned in front of a table with a semi-circular cutout. The height of the chair was adjusted so that the patient’s thighs were just below the tabletop and the torso was in contact with the front of the table. Patients were asked to respond to a visual ‘Go’ signal by moving their affected hand forward to contact a 3 x 3 inch response pad placed at 80% of their individual maximum voluntary forward reach distance (E-Prime 3; Psychology Software Tools, Sharpsburg, PA). In most cases, patients reached with the forearm pronated and fingers flexed. Therefore, active infrared motion-capture markers were placed on the dorsum of the wrist at the midpoint between the radial and ulnar styloids, and were used to record the 3-D trajectory of the wrist and hand during reaching (Northern Digital Inc. (NDI) Optotrak Certus; Waterloo, Canada).
Data Analysis

Lesion-symptom mapping. Using the ROI toolbox in MRIcron (MRIcron; Columbia, SC), stroke lesion masks were drawn on each image slice (Rorden & Brett, 2000). Lesion masks and whole-brain images were oriented and normalized into Montreal Neurological Institute (MNI) standard stereotaxic space using FSL (FMRIB Software Laboratory). FSL procedures were adapted from the procedure developed by Riley et al. (2011). The BET brain extraction tool automated deletion of the skull and other non-brain tissue from the images (fractional intensity threshold set to 0.035). On some images, additional automated steps were taken for eye, optic nerve, and neck removal after BET extraction (Smith, 2002). Once only brain tissue was present in the image, brain images were aligned using FLIRT (FMRIB’s Linear Image Registration Tool) (Jenkinson & Smith, 2001; Jenkinson et al., 2002). Images were aligned with the MNI152 T1 1mm brain and the FLIRT transformation was then applied to the lesion map. In MRIcron, lesion masks were overlaid on the Automated Anatomical Labeling template and the Johns Hopkins University White Matter template (1 mm slice thickness) (Mori et al., 2005; Hua et al., 2008). For each patient, we analyzed three factors: First, whether or not the lesion occupied any part of a particular anatomical area. Then, how much of the area was occupied was determined both in absolute terms (i.e. the sum of lesioned voxels within each area) and relative to the total size of the area (i.e. percentage of the total anatomical area that is occupied by the lesion). We extracted these values from 11 areas associated with the lateral and medial motor cortices, CST, and thalamo-striatal-cortical networks (called key motor areas throughout this study) (Felten et al., 2015). The key motor areas are: middle frontal gyrus (MFG), pallidum, pars opercularis, postcentral gyrus, precentral gyrus, putamen, superior corona radiata (SCR), superior frontal
gyrus (SFG), supplementary motor area (SMA), and thalamus. The total volume of lesions in precentral gyrus and CST were calculated as the sum of voxels in precentral gyrus, superior corona radiata (SCR), and PLIC.

**Reaching measures.** For each patient, the median values of 20 repetitions of the reaching movement (excluding maximum reach) were included in subsequent analyses. Movement units were defined as the number of peaks and valleys in the x-y combined velocity profile as collected by motion capture sensors on the wrist. Maximum reach distance was defined as the greatest forward distance at which subjects could contact the response pads. Response time was defined as the time between the appearance of the ‘Go’ signal and first contact recorded by the response pad.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics Version 24 (Chicago, IL). The α-level was set to 0.05 for all statistical analyses and outliers were removed if they fell greater than two standard deviations from the mean.

In the primary analyses, we determined how lesion size and location differed between patients with and without distal impairment. Using independent t-tests, we determined the difference between Groups 1 and 2 in 1) total lesion volume, 2) total lesion volume in precentral gyrus and CST and 3) percentage of lesion overlap in key motor areas. A χ² test determined the differences in lesion location (expressed as a binary categorization of whether the brain region is or is not affected by the lesion) between severity levels (Groups 1 and 2).

In a secondary set of analyses, we examined how the presence or absence of a lesion in the four motor areas identified in the previous analysis related to performance on a proximal-arm
reaching task. Independent t-tests were used to test for differences in maximum reach distance, response time, and movement units in patients with and without lesions occupying pallidum, PLIC, putamen, and SCR.

2.3 Results

Participants

30 patients were included in these analyses (Table 1) aged 44-78 (62.03 ± 9.56), 13 females and 17 males, and an average of 53.3 months post stroke. All patients had a single hemispheric stroke. Patients were grouped into either Group 1 (positive) or Group 2 (negative) based on the presence or absence, respectively, of voluntary wrist and finger extension (Cho et al., 2007). Groups 1 and 2 differed in level of arm impairment but not in age, sex, time since stroke (months), or overall severity of stroke impairment (NIHSS).

Primary Analyses: Lesion Characteristics and Severity

Lesion size. The analysis of average lesion size revealed no difference in total average lesion volume between Group 1 and Group 2 (Group 1: 32.8 ± SE 14.4 cc, Group 2: 50.3 ± SE 15.9 cc; t(28) = -0.82, p = 0.42; Figure 1). Although average lesion size was higher, on average, in Group 2 than in Group 1, there was relatively high variability within both groups, and the difference was not statistically significant.

Next, we analyzed the difference in average total lesion volume in the precentral gyrus and CST (SCR and PLIC) between the two groups. Total average lesion volume also did not differ between Groups 1 and 2 (Group 1: 27.9 ± 14 cc, Group 2: 47.5 ± 14.1 cc; t(28) = -0.98; p = 0.36; Figure 2). Like total average lesion volume, average lesion volume in precentral gyrus
and CST was larger, on average, in Group 2 than in Group 1, but the difference was not statistically significant.

**Lesion location.** Next, we tested for differences in lesion location between patients in Group 1 vs. Group 2. The $\chi^2$ test revealed that, compared to Group 1, a significantly larger proportion of patients in Group 2 had lesions occupying PLIC: ($\chi^2 (1, N = 30) = 9.6, p = .002$) and SCR: $\chi^2 ((1, N = 30) = 4.6, p = .03)$). These results indicate that there is a statistically significant difference between severity and lesions occupying PLIC and SCR. There were no relationships found in other key motor areas (Table 2).

There were significant between-group differences in the average lesion overlap in the pallidum (Group 1: $6 \pm SE 3%$; Group 2: $23 \pm SE 6%$; $t(28) = -2.54, p = 0.02$), PLIC (Group 1: $4 \pm SE 2%$; Group 2: $19 \pm SE 4%$; $t(28) = -3.47, p = 0.002$), and putamen (Group 1: $6 \pm SE 2%$; Group 2: $43 \pm SE 9%$; $t(28) = -4.07, p < 0.001$). There was no significant between-group differences observed in the other designated motor areas (Figure 3; Table 3).

The results of this analysis provide preliminary evidence for greater CST and striatal damage in patients who lack distal arm function after stroke compared to those who retain or recover distal movement. Compared to patients with some distal motor function, significantly more patients who lacked distal movement had lesions within PLIC and SCR and the lesions occupied more of the area in pallidum, PLIC, and putamen.

**Secondary Analyses: The Influence of Lesion Motor Areas on Reaching Function**

Lesions in pallidum, PLIC, putamen and SCR all differed between patients with and without distal arm function. The previous analysis, by nature of our grouping criteria, examined the role of lesion characteristics in distal arm function (voluntary extension of the wrist and
fingers). In this section, we will examine how lesions in these areas affect proximal arm movement.

**Maximum reach distance.** The first comparison was between patients with lesions in pallidum, PLIC, putamen and SCR and the difference in distance achieved during maximum forward reach. Significant differences in maximum reach distance were observed in those with vs. without lesions involving PLIC (intact: 33.8 ± 3.3 cm; lesioned: 23.2 ± 3.0 cm; \( t(27) = 2.39, p = 0.03 \)). When patients had a lesion in PLIC, their maximum reach was significantly shorter. No significant differences in reaching distance were found between those with vs. without involvement of pallidum, putamen, or SCR (Figure 4a).

**Reaching response time.** Similarly, significant differences were observed in reaching response time in those with vs. without lesions involving PLIC (intact: 961 ± 83.4 ms; lesioned: 1217.8 ± 85.6 ms; \( t(24) = -2.15 \ p = 0.04 \)). Patients with lesions in PLIC were significantly slower during the reaction time task. No significant differences were found based on involvement of pallidum or SCR (Figure 4b).

**Movement units.** Finally, a significant difference was also observed in the smoothness (i.e. number of movement units) of reaching movements performed by those with vs. without lesions involving PLIC (intact: 1.05 ± 0.05 units; lesioned: 1.47 ± 0.16 units; \( t(27) = -2.47, p = 0.02 \)). Patients with lesions involving PLIC had significantly less smooth movement during the reaching task than those who did not. No significant differences were found in patients with lesions involving the pallidum, putamen, or SCR (Figure 4c).
2.4 Discussion

The primary aim of this study was to examine differences in lesion characteristics of patients with mild and severe arm impairment, or those who could and could not perform distal arm movements. We achieved this by comparing lesion location and size between these two groups of patients. Perhaps surprisingly, given the substantial difference in their motor abilities, there was no difference between groups in the total size of the lesion. Instead, more patients in the more severe group who lacked distal function had lesions involving PLIC or SCR and Group 2 lesions overlapped pallidum, PLIC, and putamen more than Group 1 lesions. In a subsequent analysis, we examined the role of pallidum, PLIC, putamen, and SCR in proximal arm reaching movements. We compared aspects of a reaching task between patients who did or did not have a lesion occupying one of the target areas. This analysis showed that only patients with lesions in PLIC had worse performance on all three aspects of reaching movement (distance, speed, and smoothness).

In the first set of analyses, the grouping criteria split the patients into those with and without voluntary extension of the wrist and fingers. Group 1 also had significantly higher UEFM scores. Voluntary extension of the wrist and fingers against gravity is a task that is unlikely to be achieved unless CST is intact after stroke. Cho et al. (2007) found that, in patients who presented with hand paralysis in the acute stage, 96.3% of patients who demonstrated DTI patterns of CST activation originating from perilesional motor, premotor, and supplementary areas regained finger extension against gravity as compared to 10% of patients in which the CST degenerated before the level of infarct. With the knowledge that voluntary extension of the wrist and fingers is unlikely when the CST is not intact, we can infer that lesion locations in patients
that cannot perform voluntary finger extension (in this group of patients: pallidum, PLIC, putamen, and SCR) are contributing to CST disruption, either through direct occlusion or through network effects.

The second analysis examined the role of lesion location relative to a proximal reaching task. Visually guided reaching tasks employ a broad range of cortical networks across the lesioned and nonlesioned hemispheres and, when supported against gravity with the shoulders restrained, can be performed to some degree by many patients with severe arm impairment (Harris-Love et al., 2012). In the present study, patients with lesions occupying PLIC had worse performance on all three aspects of the reaching task (speed, distance, and smoothness of movement). PLIC is largely composed of long motor neuron axons originating in M1 and surrounding motor areas (Dum & Strick, 2002). The grouping of axons becomes more compact as it descends inferiorly through SCR until they are tightly bundled at the level of PLIC. Lesions that occupy even small areas of PLIC could act as a bottleneck that hinders transmission between M1 and the contralateral upper-extremity. Future intervention studies may consider lesions in PLIC as a potential indication for enhancing activation and recruitment of nonlesioned hemisphere motor areas (di Pino et al., 2014).

The percent of putamen lesioned was also different between the two groups of patients. Group 1 patients had an average of 6% of putamen affected by the lesion. Lesion overlap in putamen in Group 2, however, was quite large with an average of 43% of the region affected by the lesion. It is worth considering that a lesion occupying the putamen could cause severe impairment after stroke. It has a role in voluntary movement and shares several features with M1: corticostriatal loops, neurons tuned to direction, and somatotopic representation of the limbs.
(Monchi et al., 2006; Scholtz et al., 2000; Alexander & DeLong, 1985). Misfiring of the striatum can cause hypokinesia and hyperkinesia and lesions in the putamen have been shown to result in an increase in spasticity (Cheung et al., 2016).

It is likely, however, that the significance of putamenal lesion overlap in Group 2 patients is potentially confounded. The putamen shares arterial supply (Cromwell et al. 1970; Donzelli et al., 1998), anatomical neighbors (Felten et al., 2015), and, in this study, patient commonality with PLIC. The putamen is located just to the anterior of PLIC and both areas are particularly vulnerable after ischemia in the lenticulostriate branches of the middle cerebral artery (Cromwell et al. 1970; Donzelli et al., 1998). In this analysis, lesions located in the putamen and PLIC were frequent in this data set and often occurred together. Of the 20 patients with lesions in putamen, 18 also had lesions in PLIC.

This exploratory study had several strengths. Group 1 and Group 2 were well matched in key factors outside of motor impairment, including age, time since stroke, total lesion volume, cognitive function, and overall stroke severity (NIHSS). These group similarities increase the likelihood that the differences seen in lesion characteristics and reaching functions were not confounded by other stroke or age-related factors. Other strengths include the wide spectrum of levels of motor impairment, high resolution MRI images for lesion mapping along with a standardized procedure for drawing the stroke masks, automated procedures for transforming the stroke masks into standardized space, and accurate templates for determining lesion location in white matter (Rorden & Brett, 2000; Riley et al., 2011; Smith, 2002; Jenkinson & Smith, 2001; Jenkinson et al., 2002; Mori et al., 2005; Hua et al., 2008). This preliminary evidence should be used to design a well-powered, prospective study. There were several limitations to this study.
We did not include cost-function weighting in our lesion transformations and this should be addressed in future studies to ensure that lesions do not warp transformations. Another limitation was the boundaries drawn by anatomical gray matter maps. Several important gray matter motor structures were not defined alone, but included in their respective gyri. A template with anatomical regions specific to M1 and PMd would provide a better analysis of the role of cortical strokes.

Summary

This retrospective analysis aimed to identify lesion characteristics in a small group of patients with and without control of distal hand movements after stroke. A secondary analysis examined the role of those lesion characteristics in performance of a proximal reaching task. These analyses could provide initial evidence for identifying the specific lesion characteristics that may necessitate recruitment of the nonlesioned hemisphere in paretic arm movement after stroke. Primary differences in lesion characteristics between these groups of patients included the presence or absence of a lesion in CST and the size of a lesion within the pallidum, PLIC, or putamen. Involvement of PLIC in a lesion resulted in worse performance in a number of aspects during a reaching task. Future, prospective studies should examine the contributions of these regions of interest to post-stroke arm motor performance.
Figure 2.1: Total lesion volume in Group 1 vs. Group 2.

Average total lesion volume of Group 1 and Group 2 patients. A t-test reveals no significant differences between lesion volume in patients with mild (M = 32.8 ± 14.4 cc) and severe (50.3 ± 15.9 cc) arm impairment; \( t(28) = -0.82, p = 0.42 \)
Figure 2.2: Total volume of lesions occupying the precentral gyrus and CST in Groups 1 and 2.

Average total volume of lesions in precentral gyrus and CST of Group 1 and Group 2 patients. A t-test reveals no significant differences between lesion volume in patients with mild (M = 27.9 ± 14 cc) and severe (M = 47.5 ±14.1 cc) arm impairment; $t(28) = -0.98$, $p = 0.36$. 
Figure 2.3: Percent lesion overlap with cortical and subcortical areas in Groups 1 and 2.

Average percent lesion overlap in Group 1 and Group 2. Independent sample t-test revealed significant differences between of area overlapped by the lesion in pallidum (M = 6% ± SE 3%) (M = 23% ±SE 6%); t (28) = -2.54, p = 0.02, PLIC (M = 4% ± SE 2%) (M = 19% ± SE 4%); t (28) = -3.47, p = 0.002, and putamen (M = 6% ± SE 2%) (M = 4% ± SE 9%); t (28) = -4.08, p < 0.001. No other comparisons reached significance.
Figure 2.4: Differences in reaching performance depending on lesion location.

Differences in reaching outcomes when pallidum, PLIC, putamen or SCR are (+) intact or (-) occupied by a lesion. Independent sample t-test revealed significant differences in maximum reach between patients with and without lesions in PLIC. Maximum reach: nonlesioned (M = 33.8 ± 3.32 cm) lesioned (M = 23.2 ± 3.0 cm); t(27) = 2.39, p = 0.03; response time: (M = 961.0 ± 83.4 ms) (M = 1217.8 ± 85.61 ms); t(24) = -2.15, p = 0.04.; and movement units: (M = 1.05 ± 0.05) (M = 1.47 ± 0.16); t(27) = -2.47, p = 0.02. No other comparisons reached significance.
Table 2.1
Demographic and clinical data

<table>
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<th>Demographics</th>
<th>Group 1</th>
<th>Group 2</th>
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<td>15</td>
<td></td>
</tr>
<tr>
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<td><strong>Age (years)</strong></td>
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<td>30.3</td>
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<td>3/12</td>
<td></td>
</tr>
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<td>2.3</td>
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<td>8.8</td>
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<td>50.3</td>
</tr>
<tr>
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<td>1277.6</td>
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<td>.3</td>
<td>1.6</td>
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*Note: * = p < .05  ** = p < .01  *** = p < .001
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<th></th>
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<td>Group 2</td>
<td>χ²</td>
<td>ϕ</td>
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<td>1 (-3.1)</td>
<td>9.6**</td>
<td>0.57**</td>
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<tr>
<td></td>
<td>6 (-3.1)</td>
<td>14 (3.1)</td>
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<tr>
<td>Superior corona radiata (SCR)</td>
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<td>1 (-2.2)</td>
<td>4.6*</td>
<td>0.39*</td>
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<td></td>
<td>9 (-2.2)</td>
<td>14 (2.2)</td>
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<td>6 (-1.5)</td>
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<td>0.14</td>
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<td>4 (-0.8)</td>
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<td>Postcentral gyrus</td>
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</tr>
<tr>
<td></td>
<td>4 (-.4)</td>
<td>5 (0.4)</td>
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<td>Group 2</td>
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<tr>
<td></td>
<td>(-0.4)</td>
<td>(0.4)</td>
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<tr>
<td>Putamen</td>
<td>(+)</td>
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<td>1.6</td>
</tr>
<tr>
<td></td>
<td>(1.3)</td>
<td>(-1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-)</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-1.3)</td>
<td>(1.3)</td>
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<tr>
<td>Supplementary motor area (SMA)</td>
<td>(+)</td>
<td>14</td>
<td>13</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>(.06)</td>
<td>(-.06)</td>
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<tr>
<td></td>
<td>(-)</td>
<td>1</td>
<td>2</td>
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<td></td>
<td>(-.06)</td>
<td>(.06)</td>
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<tr>
<td>Superior Frontal Gyrus (SFG)</td>
<td>(+)</td>
<td>13</td>
<td>13</td>
<td>†</td>
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<tr>
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<td>(-)</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Thalamus</td>
<td>(+)</td>
<td>12</td>
<td>12</td>
<td>†</td>
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<tr>
<td></td>
<td>(-)</td>
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</table>

Note: * = $p < .05$  ** = $p < .01$  *** = $p < .001$ †Too few participants had lesions within these regions to calculate $\chi^2$ Adjusted standardized residuals appear in parentheses below group frequencies. (+) indicates no lesion, (-) indicates lesion.
Table 2.3
Lesion overlap with the motor network in Group 1 vs. Group 2

<table>
<thead>
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<th>Area</th>
<th>Percent of area occupied</th>
<th>Group 1</th>
<th>Group 2</th>
<th>t-value, df(28)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Pallidum</td>
<td></td>
<td>6%</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Posterior limb of the internal capsule (PLIC)</td>
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<td>4%</td>
<td>8%</td>
<td>19%</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td>6%</td>
<td>7%</td>
<td>43%</td>
</tr>
<tr>
<td>Middle frontal gyrus (MFG)</td>
<td></td>
<td>4%</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Pars opercularis</td>
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<td>8%</td>
<td>26%</td>
<td>18%</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td></td>
<td>8%</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td></td>
<td>6%</td>
<td>18%</td>
<td>8%</td>
</tr>
<tr>
<td>Superior corona radiata (SCR)</td>
<td></td>
<td>12%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>Superior frontal gyrus (SFG)</td>
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<td>3%</td>
<td>4%</td>
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<td>Supplementary motor are (SMA)</td>
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</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
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</table>

Note: * = p < .05  ** = p < .01  *** = p < .001
3.1 BACKGROUND

Stroke affects 795,000 Americans per year (Mozaffarian et al., 2016). It is a leading cause of long-term disability and has extensive monetary and personal costs to quality of life and independence (Mozaffarian et al., 2016; Nichols-Larsen et al., 2005). Of patients who have had a stroke, 88% demonstrate some degree of hemiparesis upon initial assessment (Bonita & Beaglehole, 1988). Between three and six months after stroke, rapid recovery of motor function plateaus (Hendricks et al., 2002), leaving many patients with chronic impairment. Bonita & Beaglehole found that 62% of patients had some degree of arm hemiparesis at six months and that 24% of those patients had arm hemiparesis that was moderate or severe. Similar studies found that 11.6-14% of patients gained full recovery and 30-38% gained partial recovery at six months (Nakayama et al., 1994; Kwakkel et al., 2003). These studies indicate that of the almost one million Americans that have a stroke each year, ~60% have varying degrees of upper-extremity impairment and between 25-50% of those patients have moderate or severe impairment.

Large-scale longitudinal studies suggest that those with acute mild arm impairment are more likely to achieve pre-stroke baseline levels of functions than those with severe impairment. Nakayama et al. (1994) found that 79% of patients with mild impairment compared to 18% with severe arm impairment regained full function. Similar studies have shown that patients have a proportional recovery of 63% of function if their corticospinal tract (CST) is intact, but that recovery of patients with severe CST damage was not proportional to sub acute assessment.
(Stinear et al., 2017). Even with intervention, patients with severe stroke are less likely to recover (Nakayama et al., 1994) although these data are sparse as many clinical trials include only patients with mild to moderate hemiparesis.

During movement of the affected arm, functional imaging studies have found that more well-recovered patients have relatively lateralized activation centering around the motor areas of the lesioned hemisphere, while those with more severe impairment have bilateral activation of motor areas (Ward et al., 2003). This observation has often been interpreted as an indication that activation of the nonlesioned hemisphere is detrimental to post-stroke movement. The interhemispheric competition (IC) model suggests that the undamaged hemisphere inhibits activation of the damaged hemisphere through increased transcallosal inhibition, thus resulting in worse outcomes post-stroke (Perez & Cohen, 2009). This theory is supported by evidence that patients with mild arm impairment have an increase in inhibition from the nonlesioned hemisphere to the lesioned hemisphere as compared to controls (Murase et al., 2004) and that inhibition of the nonlesioned hemisphere in patients with mild impairment can improve performance in motor tasks post-stroke (Takeuchi et al., 2005). These studies, however, are often limited to primary motor cortex (M1) and most do not include more severely impaired patients. Di Pino et al., (2014) suggests that the IC model accounts only for patients who retain high levels of structural reserve, or enough perilesional tissue or CST fibers to assume function of the lesioned area. The Bimodal Balance Recovery model instead suggests that patients who lack structural reserve must recruit regions outside of the lesioned hemisphere motor areas or within the nonlesioned hemisphere to control movement. While promising, there is limited evidence to support the idea that the nonlesioned hemisphere contributes to ipsilateral post-stroke movement.
This study addresses this gap in the literature by examining the role of nonlesioned hemisphere motor areas, specifically of PMd in affected arm motor performance.

PMd has the ability to compensate for the lesioned hemisphere and to control ipsilateral paretic arm movement. Animal studies have shown that there are direct ipsilateral connections between the spinal cord and PMd as well as bilateral activation patterns in single unit recordings of unilateral reaching (Bucy, 1933; Cisek et al., 2003). O’Shea et al. (2007) performed a series of experiments examining the role of PMd in normal control subjects. The study found that patients had an increase in activation of the ipsilateral PMd during an fMRI action selection task after the contralateral PMd was downregulated with 1 Hz repetitive transcranial magnetic stimulation (rTMS) and that this activation was compensatory. Double-pulse TMS (DP-TMS) perturbation of the ipsilateral PMd had no effect on performance during the action selection task unless the contralateral PMd was inhibited with rTMS. Finally, Johansen-Berg et al. (2002) found that single-pulse TMS of ipsilateral PMd slowed response time in mildly impaired patients but not controls during a simple reaction time finger task. There was a strong correlation between patients who demonstrated a change in reaction time and patients who demonstrated less laterality during the same task in fMRI. None of these studies, however, have examined the role of PMd in patients with severe arm impairment.

In this study, we hypothesize that there is a role for movement control in the nonlesioned hemisphere of severely impaired patients. Specifically, we suggest that nonlesioned PMd can contribute to motor performance in patients with severe CST damage. We will first demonstrate that patients with mild and severe arm impairment differ in their recruitment of the lesioned and
nonlesioned hemispheres during a reaching movement. Then, we will show that only patients with severe impairment recruit nonlesioned PMd.

3.2 METHODS

Participants

The study cohort was recruited from MedStar National Rehabilitation Hospital and the surrounding community. MedStar Health Research Institute’s Institutional Review Board approved all protocols and recruitment procedures. Written informed consent was obtained from each patient. Patients were grouped into either mild or severely impaired upper extremity motor function based on high or low structural reserve, as measured by the presence or absence of voluntary wrist or finger extension and lesions within the posterior limb of the internal capsule as explained in Chapter 2. For inclusion, patients must have had a single stroke more than six months prior to study enrollment and the lesioned area could not include the brain stem or cerebellum. Patients must have been between the ages of 18 and 85 with no history of neurological disorder or orthopedic injury affecting the paretic limb at the time of testing. Patients were excluded if they were unable to perform the reaching tasks or had contraindications to MR imaging or transcranial magnetic stimulation procedures (pregnancy, history of craniotomy or epilepsy, or metallic objects implanted in the body). Patients were also excluded if they had lesions involving large areas of cortex that extended to or near the surface of the brain as this prevented DP-TMS to the ipsilesional hemisphere.

Clinical Measures

Clinical movement measures included the Upper Extremity Fugl-Meyer Assessment (UEFM; Fugl-Meyer et al., 1975; Gladstone et al., 2002; Page et al., 2012), the Modified
Ashworth Scale (MAS; Gregson et al., 1999), the National Institutes of Health Stroke Scale (NIHSS; NINDS 2011; Meyer et al., 2002) and the Mini Mental Status Exam (MMSE; Folstein et al. 1975). A physical therapist administered UEFM and MAS, a neurologist administered NIHSS, and a researcher administered MMSE. The neurologist also performed a brief exam to ensure that patients were healthy enough to participate in the study.

**Experimental Set-Up**

During data collection, patients were seated in an adjustable chair with the shoulders restrained by a 4-point seat belt. The chair was positioned in front of a table with a semi-circular cutout. The height of the chair was adjusted so that the table was just above the patient’s thighs and the front of the table was against their torso. Two 3 x 3 inch response pads were placed at 80% of the patient’s maximum reach distance with the paretic arm. Maximum reach distance (cm) was defined as the greatest forward distance at which patients could contact the response pads. The position of the chair and the position of the response pads were measured and reproduced for each subsequent data collection session.

Patients were familiarized with the behavioral reaching task prior to any data collection. For baseline data and each subsequent behavioral testing session, patients were asked to perform a choice reaction time task. Patients responded to a ‘Go’ signal by reaching as quickly as possible with their paretic arm from a designated starting position to the center of the response pad indicated by the signal. For each reaching movement they were asked to have their forearm pronated and fingers flexed. Timing of the ‘Go’ signal and response pad selection were randomized for each trial to prevent a learning effect. The amount of time between the appearance of the ‘Go’ signal and completion of the button tap was defined as the overall
response time, while the time between the onset of movement and completion of the button tap was defined as movement time, the primary outcome measure (Figure 1). Timing data of reach completion were collected with E-Prime 3 (Psychology Software Tools, Sharpsburg, PA) while onset of movement initiation was recorded with the Northern Digital Inc. (NDI) Optotrac Certus movement capture systems (Waterloo, Canada). During each behavioral task, kinematic sensors were placed on the dorsum of the wrist, at the midpoint between the radial and ulnar styloids. Movement of these sensors in the x, y, and z planes were recorded at a sampling frequency of 300 Hz.

Anatomical, T1-weighted, high-resolution Magnetic Resonance Imaging (MRI) brain scans for all patients were recorded without contrast at 1 mm slice thickness on either a Phillips CV Intera 1.5T MRI Centre (TE = 4.76 ms, TR = 1400 ms, 25° flip angle, NEX = 1, FOV = 250 x 250 cm) or a Siemens 3T Tim Trio (TE = 2.52 ms, TR = 1900 ms, 9° flip angle, NEX = 1, FOV = 250 x 250 cm). The DICOM images of each patient’s brain and skin were reconstructed in the Brainsight neuronavigation system (Rogue Research, Inc., Montreal, Canada). A set of fiducial markers attached to a pair of eyeglasses were tightly fitted to the patient’s head and the markers were localized to four landmarks from the patient’s skin reconstruction (the tip and bridge of the nose and the right and left tragus). A corresponding set of fiducial markers attached to a figure-of-eight TMS coil (MagPro C-B60) placed over the head allowed visualization of the immediate cortex underneath in the neuronavigation software.

Once the cortex was visualized, four sites were identified and marked for subsequent perturbation with a transcranial magnetic stimulator (MagProX100 with MagOption, MagVenture Inc., Atlanta, GA). M1 was identified anatomically near the hand knob of the
central sulcus (Yousry et al., 1997) and functionally by reliably eliciting motor evoked potentials (MEPs) from either the biceps or the triceps of the contralateral arm. This site was also used to identify the patient’s resting motor threshold (RMT) prior to each data collection session. RMT was defined as the minimum stimulator output that would elicit MEPs > 50 µV in 5 out of 10 trials in the biceps. If no MEPs were elicited after stimulation of the lesioned hemisphere, the site was identified by mirror image of the site selected within the nonlesioned hemisphere. Dorsal premotor cortex (PMd) of the nonlesioned and lesioned hemisphere were identified anatomically (the posterior third of the region between the middle and superior frontal gyrus) (Bestmann et al., 2005). In a typical subject, 70-80 samples of coil position data were collected for each site and accuracy was calculated in MNI space in the x, y, and z coordinates. After identification of the lesioned and nonlesioned PMd sites, a spreading test (10 iterations of DP-TMS at 120% RMT applied to PMd) was performed to ensure that no MEPs could be elicited from the contralateral arm, confirming that the targeted site was not within M1.

The behavioral task was performed in 4 sets of 10 blocks of 10 trials, over 2-4 visits (depending on patient severity). We used a randomization table to select the order of perturbation sites (nonlesioned or lesioned M1 or PMd) for each set. Within each block, the order of stimulation conditions applied was also randomized. Nine of the trials instructed the patient with the ‘Go’ signal to reach to one of the two response pads. Six of those trials were accompanied by DP-TMS perturbation of the designated site and three were not (termed no-TMS trials). In addition, one trial did not give the ‘Go’ command but was accompanied by DP-TMS perturbation (termed a catch trial). The catch trial was included as a control measure to ensure that patients were reaching in response to the ‘Go’ cue and not to the sound or feel of the DP-
TMS perturbation and to prevent learning effects. Average response time was monitored at the end of each block to ensure that patients were not tiring and a rest break was given per patient request or if their average response time declined by more than 25% between blocks. Pain levels were assessed at the beginning, middle and end of each block to determine if pain was affecting their performance on the behavioral task. No patients reported any pain at the beginning, middle, or end of any tested block. DP-TMS perturbation (interstimulus interval (ISI) 25 ms) was delivered at 120% of the patient’s RMT (Chouinard & Paus, 2010). These perturbations were randomized as a no-TMS trial, a catch trial, or trials with DP-TMS perturbation 150, 200, or 250 ms after the ‘Go’ signal.

The coil was placed on the scalp over the designated site for each trial with the handle pointed posteriorly, 45° between coronal and sagittal planes and the position of the coil was recorded in Brainsight for each stimulation (Brasil-Neto et al. 1992). Trials were rejected when the coil was more than 3mm from the targeted site. Trials were also rejected if the patient was distracted or failed to make contact with the response pad. The experiment was completed when each patient had completed 10 blocks of 10 trials, including rejected trials, with stimulation over each of the four sites: nonlesioned or lesioned M1 or PMd.

**Data Analysis**

The primary outcome measure of the behavioral task was percent change in movement time. Percent change was calculated for each participant as the difference between the median of the no-TMS trials and the median of the perturbation time point that had the greatest effect within each set. Movement time was calculated as the period from movement initiation to contact with the specified response pad (Figure 1).
Dependent measures were computed using Microsoft Excel (Microsoft, Redmond, WA) and a customized program written in Matlab (MathWorks, Natick, MA). Additional reliability measures (pain ratings and TMS coil placement reliability) were also calculated.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics Version 24 (Chicago, IL). The $\alpha$ level was set to 0.05 and percent change outliers were removed if they fell greater than two standard deviations from the mean. Separate mixed model ANOVAs were used to test for differences between stimulation site (within-subjects factor: M1, PMd) and group (between-subjects factor: mild, severe) for the lesioned and nonlesioned hemisphere. A priori, post-hoc independent t-tests were used to test for differences in percent change in movement time (dependent) between severity levels (independent) for each site.

**3.3 Results**

20 patients were included in this analysis aged 51-78 (62 ±7 years), 8 females and 12 males, and an average of 60.1 months post stroke. (Table 1, 2) Mild and severe groups differed in clinical reaching measures of arm impairment but not in age, sex, time since stroke, or overall stroke impairment (Table 3). No patient reported any pain during the reaching task.

**DP-TMS Perturbation of Lesioned and Nonlesioned Hemispheres**

For DP-TMS perturbation of the lesioned hemisphere, there was no Interaction effect of site x severity. There were no significant main effects of perturbation site or severity on movement time (Table 4). Within the mild group, perturbation of M1 and PMd resulted in a 12.1% ± 2.2% and 3.8% ± 2.3% slower movement time, respectively. Within the severe group,
perturbation of M1 resulted in a 7.1% change in movement time ± 3.9% and perturbation of PMd resulted in a 5.4% change in movement time ± 2.4% (Figure 2; Table 4).

There was no significant interaction effect for perturbation Site x Severity in the lesioned hemisphere: F(1,17) = 1.18, p = 0.29. For DP-TMS perturbation of the lesioned hemisphere, there were no significant main effects of perturbation Site: F(1, 17) = 2.7, p = 0.11 or Severity: F(1,17) = 0.28, p = 0.6 on percent change in movement time. Within the mild group, perturbation of M1 and PMd resulted in a 12.1% ± 2.2% and 3.8% ± 2.3% slower movement time, respectively. Within the severe group, perturbation of M1 resulted in a 7.1% change in movement time ± 3.9% and perturbation of PMd resulted in a 5.4% change in movement time ± 2.4% (Figure 2; Table 4).

Only the reaching movements of patients with severe arm impairment were affected after perturbation of the nonlesioned hemisphere and this effect was specific to PMd (Figure 3). There was a significant Interaction effect of site and severity: F(1,15) = 5.43, p = 0.03 and main effects of Site: F(1,15) = 7.45, p = 0.02, and of Severity: F(1,15) = 4.34, p = 0.05. Within the mild group, perturbation of M1 and PMd resulted in a 1.5% ± 2.2% and a 2.4% ± 3.6% slower movement time, respectively. Within the severe group, perturbation of M1 and PMd resulted in a 3.7% ± 2.1% and 14.6% ± 3.4% slower movement time, respectively (Figure 3; Table 4).

A priori post-hoc analyses showed that only perturbation of nonlesioned PMd was significantly different between levels of severity (t(18) = -2.29; p = 0.03) (Table 5).

3.4 DISCUSSION

The aim of this study was to determine if the nonlesioned hemisphere contributes to reaching in patients with severe hemiparesis. Previous research has indicated that recruitment of
the lesioned hemisphere for affected arm movement correlates with greater recovery of movement (Rehme et al., 2012; Ward et al., 2003). These studies, however, often sample a greater number of patients who retain voluntary hand function and do not examine the role of different sites within each hemisphere. The Bimodal Balance Recovery model suggests that for patients with low structural reserve, that is, for patients with more severe impairment, the nonlesioned hemisphere may contribute to movement. In order to design effective non-invasive brain stimulation (NIBS) protocols, it is necessary to determine if the nonlesioned hemisphere is adaptive or maladaptive in patients with severe arm impairment. In the present study, we identified site-specific differences in recruitment of lesioned and nonlesioned hemispheres in patients with and without voluntary hand function (i.e. “mild” and “severe” impairment, respectively).

Here, we found no difference in the contribution of lesioned hemisphere in patients with mild and severe impairment during the reaching task. The contribution of nonlesioned hemisphere to reaching movement, however, was greater in patients with severe arm impairment, and was specific to the PMd. These results add significantly to the literature. Here we have shown that in patients with mild impairment, activation of the lesioned hemisphere contributes to movement no differently than patients with severe impairment. Patients with severe impairment, however, are the only group that demonstrated nonlesioned hemisphere contribution to movement. Our results indicate that activation of nonlesioned hemisphere is contributing, and not maladaptive, to movement in patients with severe impairment.

Patients with severe post-stroke arm impairment are rarely studied. Here we have shown, at least in post-stroke neural recruitment, that patients with severe impairment significantly differ
from those with mild impairment. We believe that, due to a loss of enough perilesional tissue or corticospinal projections from the lesioned hemisphere, patients with severe arm impairment are partially unmasking latent abilities of structures in the nonlesioned hemisphere to control function in the paretic arm. Patients with more severe impairment lack the descending connections necessary to efficiently recruit the lesioned hemisphere and must additionally recruit areas within the nonlesioned hemisphere, such as PMd, that can contribute to arm function.

Our data at least partially support the Bimodal Balance Recovery Model by confirming that perilesional tissue within the lesioned hemisphere contributes most to reaching movements in patients with mild impairment, or high structural reserve, and that tissue within the nonlesioned hemisphere contributes most to reaching movements in patients with severe arm impairment. Following the model, patients with more mild impairment would benefit most from a NIBS protocol that would reduce interhemispheric inhibition (IHI) from the nonlesioned hemisphere and promote cortical activity in the lesioned hemisphere. Our results also have implications for NIBS design for patients with severe impairment. These patients would benefit from a NIBS protocol that promotes cortical excitability within the nonlesioned hemisphere. The role of specific sites within the nonlesioned hemisphere need to be further examined to determine which would be the best target for excitatory NIBS, specifically, as our data suggest, nonlesioned PMd.

This study had several strengths. The patients in the two groups were well matched in age, time since stroke, and overall stroke severity (NIHSS). Data collection was standardized and objective and conditions were replicated for each set of perturbation testing. DP-TMS targeting of neural sites was accurate and consistent. This study also had limitations. DP-TMS is an
excellent investigational tool, but it can only show changes in physiology after perturbation of specific regions within a network. Results are most likely indicative of the role of the perturbed neural region but they could potentially reflect network effects. We attempted to control for these network effects by perturbing two sites within each hemisphere that exist within the same motor network for normal reaching. Sham DP-TMS was not employed in this study, however we did control for some of the effect of TMS perturbation with the inclusion of multiple sites and interspersed ‘catch’ trials to avoid a startle effect to demonstrate that large changes in movement outcomes were not attributable to the presence of the TMS-coil alone. Additionally, examining a population of severely impaired patients can be difficult due to the high variability of their motor performance. To control for this limitation, we analyzed the data within each session, comparing the median of DP-TMS trials to randomly interspersed “no perturbation” trials. A final limitation of this study was an inability to induce MEPs from the lesioned hemisphere to identify the location of M1 in patients with more severe impairment. For these patients, we selected lesioned M1 by mirroring the location of nonlesioned M1 using anatomical landmarks. We hypothesize that with more power, there is a statistically significant difference in percent change in movement time after perturbation of lesioned hemisphere M1. A larger n will be recruited for this comparison in future studies.

3.6 Conclusion

Patients with mild and severe stroke-induced motor impairment have a demonstrated divergence in their ability to recover after stroke. These data suggest that the post-stroke neural patterns of the two groups may also be different and should be further examined, both in the lesioned and nonlesioned hemispheres, prior to designing NIBS trials. Future research should
examine the contribution of multiple sites within the nonlesioned hemisphere in patients with severe impairment to identify a neural target for NIBS. Lesion characteristics of both groups should be examined to determine if high and low structural reserve can be defined. With the promise of NIBS as an adjuvant to therapy in the future of rehabilitation, identifying brain regions within patients with the most severe impairment that contribute to motor control is imperative and this data demonstrates the nonlesioned PMd may serve as a possible target for enhancement.
Figure 3.1: Reaching task with DP-TMS perturbation.

Schematic of the reaching task. Patients reach to a visually guided target after a ‘Go’ signal. After the ‘Go’ signal but prior to the onset of movement, DP-TMS is applied to one of four sites. The main outcome measure of this study is movement time, defined as the time from movement onset to movement completion.
Figure 3.2: Average change in movement time after DP-TMS to the lesioned hemisphere.

Percent change in movement time after perturbation of M1 (Mild: 12.1% ± 2.2%) (Severe: 7.1% ± 3.9%) and PMd (Mild: 3.8% ± 2.3%) (Severe: 5.4% ± 2.4%) in the lesioned hemisphere. There was no effect of Site (F(1, 17) = 2.7, p = 0.11), Severity (F(1,17) = 0.28, p = 0.6) and no Interaction effect of site x group (F(1,17) = 1.18, p = 0.29).
Figure 3.3: Average change in movement time after DP-TMS to the nonlesioned hemisphere.

Percent change in movement time after perturbation of M1 (Mild: 1.5% ± 2.2%) (Severe: 3.7% ± 2.1%) and PMd (Mild: 2.4% ± 3.6%) (Severe: 14.6% ± 3.4%) in the nonlesioned hemisphere. There was a significant effect of Site (F(1,15) = 7.45 p = 0.02), Severity (F(1,15) = 4.34 p = 0.05) and an Interaction effect of site and severity (F(1,15) = 5.43 p = 0.03).
Table 3.1
Demographics and clinical data of patients with mild arm impairment

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<th>Affected Limb</th>
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Table 3.2

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### Table 3.3

Demographics and clinical data group averages

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<td><strong>UEFM</strong></td>
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<td>15.9</td>
<td>7.9</td>
<td>p &lt; 0.001***</td>
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<td><strong>Maximum Reach (cm)</strong></td>
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<td>12.9</td>
<td>p = 0.003**</td>
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*Note: * = p < .05 ** = p < .01 *** = p < .001
Table 3.4

Results of mixed-model repeated measures ANOVAs

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<td>$F(1,15) = 4.34$</td>
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</tr>
<tr>
<td>Site x Severity:</td>
<td>$F(1,15) = 5.43$</td>
<td>$p = 0.03^*$</td>
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*NOTE: * $p < .05$  ** $p < .01$  *** $p < .001$
Table 3.5

Results of post-hoc independent t-tests

<table>
<thead>
<tr>
<th>Perturbation site</th>
<th>Patient groups</th>
<th>t-value, df(28)</th>
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<tr>
<td></td>
<td>Mild arm impairment</td>
<td>Severe arm impairment</td>
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<tr>
<td>Lesioned M1</td>
<td>Mean 12.1% SD 12.7%</td>
<td>Mean 7.1% SD 10.2%</td>
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<tr>
<td>Lesioned PMd</td>
<td>Mean 3.8% SD 1.5%</td>
<td>Mean 4.3% SD 2.9%</td>
</tr>
<tr>
<td>Nonlesioned M1</td>
<td>Mean 1.5% SD 3.5%</td>
<td>Mean 3.7% SD 7.9%</td>
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<tr>
<td>Nonlesioned PMd</td>
<td>Mean 2.9% SD 4.7%</td>
<td>Mean 13.4% SD 12.9%</td>
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</tbody>
</table>

*Note:* * = p < .05  ** = p < .01  *** = p < .001
CHAPTER 4
THE CONTRIBUTION OF NONLESIONED HEMISPHERE DORSAL PREMOTOR CORTEX TO PARETIC ARM MOVEMENT AFTER SEVERE STROKE

4.1 BACKGROUND

Stroke is a common and leading cause of disability in the United States (Mozaffarian et al., 2016). Hemiparesis, or weakness, of the affected arm is a common result of stroke and hinders quality of life and independence (Nichols-Larsen et al., 2005). Of patients who have had a stroke, ~90% experience some degree of initial hemiparesis (Bonita & Beaglehole, 1988). After 3-6 months, spontaneous recovery plateaus (Hendricks et al., 2002). 11-30% of those patients will regain full function of the arm and 30-38% regain partial use of the arm (Bonita & Beaglehole, 1988; Nakayama et al., 1994; Kwakkel et al., 2003). The patients who do not regain use of the arm are often those with the most severe impairment upon initial admission. Stinear et al. (2017) found that most patients demonstrate a proportional recovery of 63% of post-stroke arm movement from 3 weeks to 3 months, but that this effect was not seen if the corticospinal tract (CST) was not intact. Similarly, Nakayama et al. (1994) found that of patients with mild impairment upon admission, 79% regained full motor function, while that number reduced to 18% in patients with more severe impairment.

Intervention for arm impairment is most effective in the first 3-6 months after stroke (Bonita & Beaglehole, 1988) although there is some evidence for limited improvement after six months (McIntyre et al., 2012). Patients with initially severe impairment have been shown to be less likely to recover function even after intervention (Nakayama et al., 1994). Many of the treatment validation studies exclude patients who cannot extend the wrist or fingers, or patients with the most severe impairment, and many of these treatments have not been shown to be
effective in patients with severe arm impairment (Hayward et al., 2011). This confluence leaves a large number of patients with limited improvement and, thus, permanent disability. It is unclear why patients with severe motor impairment are less responsive to intervention.

Various imaging studies have examined cortical activation during movement of the recovering arm and hand. Results of these studies demonstrate that those who are early in stroke recovery or who continue to experience severe impairment later in their recovery demonstrate less lateralization of activation to the lesioned hemisphere and instead show more bilateral activation of motor areas (Ward et al., 2003; Rehme et al., 2012). The effect of the nonlesioned hemisphere activation is unclear. Bilateral activation may be due to an imbalance in interhemispheric inhibition (IHI), with the nonlesioned hemisphere dampening cortical excitability of the lesioned hemisphere (Perez & Cohen, 2009). This is evidenced by an increase in transcallosal inhibition from the nonlesioned to the lesioned hemisphere (Murase et al., 2004) and improved motor performance after repetitive transcranial magnetic stimulation (rTMS) inhibition of the nonlesioned hemisphere in patients with mild stroke impairment (Takeushi et al., 2005).

The other possibility, however, is that activation of the nonlesioned hemisphere is compensating for areas within the lesioned hemisphere that, due to the extent of the lesion, lack connectivity with the affected arm. Recently, the Bimodal Balance Recovery model was proposed. This model suggests that the notion that the nonlesioned hemisphere inhibits the lesioned hemisphere in all patients is oversimplified (di Pino et al., 2014). Instead, the model proposes that there is a gradient of damage after stroke, termed structural reserve. Patients at each end of the gradient rely on different cortical and subcortical structures to control paretic arm
movement. As discussed in Chapter 2, previous lesion mapping studies have suggested that the differences between patients with mild and severe arm impairment result from individual lesion voxel thresholds in cortical and subcortical structures or a marked reduction in CST integrity (Chen et al., 2000; Burke Quinlan et al., 2015). Our data suggest that structural reserve is dependent on descending connections from the lesioned hemisphere, specifically lesions in the posterior limb of the internal capsule (PLIC). Patients who have greater structural reserve are subject to the IHI model, relying primarily on areas within the lesioned hemisphere that previously controlled movement. Patients who have low structural reserve must instead rely on the concept of vicariation. The vicariation framework (Finger, 2009) suggests that when certain regions of the brain are damaged, other areas previously not involved in a function can assume neural control. It is possible, then, that the nonlesioned hemisphere is playing a compensatory role in more severely impaired patients who lack the structural reserve to successfully relay signals from lesioned hemisphere motor areas to the lower motor neurons.

As we have demonstrated previously (Mohapatra et al., 2016), patients with severe arm impairment after stroke recruit motor areas within the nonlesioned hemisphere during reaching movements. One such area, the dorsal premotor cortex (PMd) is particularly well suited to aide in these movements. PMd has projections directly to the spinal cord; 30% of descending CST fibers originate in PMd (Martino & Strick, 1987) and a portion of those fibers terminate in ipsilateral spinal cord (Bucy, 1933; Kuypers & Brinkman, 1970). In animal studies, single-unit recordings from PMd show activation during planning and movement of both the ipsilateral and contralateral arm (Cisek et al., 2003). In humans, inhibitory rTMS of PMd results in activation of the homologous PMd during an action selection task. Further, rTMS inhibition of PMd followed
by double-pulse TMS (DP-TMS) perturbation of the homologous PMd slows reaction time during an action selection task demonstrating a compensatory role for ipsilateral PMd (O’Shea et al., 2007). In patients with mild impairment, single-pulse TMS perturbation of nonlesioned PMd slowed response time during a finger movement task and the response to TMS perturbation correlated with the fMRI laterality index of the same task (Johansen-Berg et al., 2002), demonstrating a functionally relevant role for the activation of nonlesioned PMd.

In this study, we used an online DP-TMS paradigm to examine the role of specific sites within the nonlesioned hemisphere during a reaching task performed with the paretic arm. We hypothesized that patients with severe arm impairment would recruit the nonlesioned hemisphere during a reaching movement and that that effect would be larger in PMd than control sites.

4.2 METHODS

Participants

The study cohort was recruited from MedStar National Rehabilitation Hospital and the surrounding community. The MedStar Health Research Institute’s Institutional Review Board approved all protocols and recruitment procedures and all patients provided written, informed consent. Inclusion criteria were as follows: patients must have been between the ages of 18-85, must have had a single stroke (or multiple strokes within the same vascular region). The stroke must have occurred at least six months prior to inclusion and could not occupy the cerebellum or the brain stem. To classify as severe, patients must have clear CST damage as demonstrated by a lack of voluntary extension of the wrist or fingers and lesions involving posterior limb of the internal capsule or superior corona radiata. Patients were not included if they had any history of neurological disorder, severe cognitive impairment, or orthopedic injury that affected arm
movements. Patients were also not included if they were unable to perform the reaching task or had contraindications for TMS or MRI (pregnancy, epilepsy, craniotomy, or MRI-incompatible metallic objects in the body).

**Clinical Measures**

Clinical movement measures included the Upper Extremity Fugl-Meyer Assessment (UEFM; Fugl-Meyer et al., 1975; Gladstone et al., 2002), the Modified Ashworth Scale (MAS; Gregson et al., 1999), the National Institutes of Health Stroke Scale (NIHSS; NINDS 2011; Meyer et al., 2002) and the Mini Mental Status Exam (MMSE; Folstein et al. 1975). A physical therapist administered UEFM and MAS, a neurologist administered NIHSS, and a researcher administered MMSE. The neurologist also performed a brief neurological exam to ensure that patients were healthy enough to participate in the study.

**Experimental Set-Up**

All experimental data were collected according to a standardized protocol. Patients were seated in front of the experimental space with their shoulders restrained. The chair was adjusted for each patient such that his or her thighs and torso were tight to the experimental plane. The position of the chair and table were recorded and reproduced for each subsequent experimental session. Each patient’s maximum forward reach (defined as the greatest forward distance the patients could contact the response pad with their shoulders restrained) was measured and two 3-x 3-inch response pads were placed at 80% of their maximum reach distance (cm).

For the behavioral reaching task, patients were seated with their affected hand in a designated start position. The patients responded to a visual ‘Go’ signal by reaching as quickly as possible with their paretic arm to one of the two response pads indicated. Patients were asked to
reach with their forearm pronated and fingers flexed. Timing of the ‘Go’ signal and response pad selection were randomized to prevent a learning effect (i.e. to prevent the patients from being able to predict/anticipate when and where the next reaching target would be). The amount of time between the appearance of the ‘Go’ signal and completion of the button tap was defined as the overall response time, while the time between the onset of movement and completion of the button tap was defined as movement time, the primary outcome measure. Timing data of reach completion were collected with E-Prime 3 (Psychology Software Tools, Sharpsburg, PA) while onset of movement initiation was recorded with the Northern Digital Inc. (NDI) Optotrac Certus movement capture system (Waterloo, Canada). During each behavioral task, kinematic sensors were placed on the dorsum of the wrist, at the midpoint between the radial and ulnar styloids. Movement of these sensors in the x, y, and z planes were recorded at a sampling frequency of 300 Hz.

Anatomical T1-weighted high-resolution MRI scans were recorded for all patients without contrast (Phillips CV Intera 1.5T MRI Centre; with the following parameters: repetition time = 1400 ms; echo time = 4.76 ms; flip angle = 25°; 172 contiguous 1 mm sagittal slices; field of view = 250 x 250 cm; voxel size = 1 x 1 x 1 mm; slice thickness = 1 mm; in 2 patients, Siemens 3T Tim Trio with the following parameters: repetition time = 1900 ms; echo time = 2.52 ms; flip angle = 9°; 160 contiguous 1 mm sagittal slices; field of view = 250 x 250 cm; voxel size = 1 x 1 x 1 mm; slice thickness = 1 mm). Images were reconstructed in theBrainsight neuronavigation system (Rogue Research, Inc. Montreal, Canada). A set of fiducial markers attached to eyeglasses were used to localize the position of the patient’s skull in space and a corresponding set of fiducial markers were attached to a figure-of-eight TMS coil (MagPro C-
The fiducial markers on the patient and on the coil allowed for visualization of the cortex immediately underneath.

Three sites were identified for subsequent stimulation: primary motor cortex (M1), PMd, and dorsolateral prefrontal cortex (DLPFC). Only 5 participants participated in DLPFC perturbation. M1 served as a motor control site for PMd. DLPFC served as a primarily non-motor control site, to determine whether patients were reacting solely to the sound and feel of TMS perturbation and not to the site specific perturbation. M1 was identified functionally as the site at which TMS reliably elicited motor evoked potentials (MEPs) from the biceps or the triceps of the contralateral arm. PMd and DLPFC were located anatomically as the posterior third of the superior frontal sulcus (Bestmann et al., 2005) and the anterior third of the middle frontal gyrus (Mylius et al., 2013), respectively. A stimulus-spreading test was performed over PMd to ensure that no MEPs could be elicited from the site. DP-TMS stimulation was delivered via a MagProX100 with MagOption (MagVenture Inc., Atlanta, GA). Resting motor threshold (RMT) was defined as the minimum stimulator output that would elicit MEPs > 50 µV in 5 out of 10 trials in biceps or triceps from M1.

The reaching task was performed in 4 sets of 10 blocks of 10 trials each, typically over several visits. One of the three perturbation sites (M1, PMd, or DLPFC) was randomly selected for each set. Within each block, timing of the ‘Go’ signal and stimulation were randomized. In nine of the trials, the ‘Go’ signal indicated that the patient should reach to one of the two response pads. Six of those trials were accompanied by DP-TMS perturbation of the designated site and three were not (termed no-TMS trials). In addition, in one trial per set the ‘Go’ command did not appear but was accompanied by DP-TMS perturbation (termed a “catch trial”).
The catch trial was included as a control measure to ensure that patients were initiating movement in response to the ‘Go’ cue and not to the sound or feel of the TMS perturbation. Average response time was monitored at the end of each block to ensure that patients were not tiring and a rest break was given upon patient request or if their average response time declined by more than 25% between blocks. Pain levels were assessed at the beginning, middle and end of each task to determine if pain was affecting their performance on the behavioral task. No patients reported any pain at the beginning, middle, or end of any tested block. DP-TMS perturbation (interstimulus interval (ISI) 25 ms) was delivered at 120% of the patient’s RMT (Chouinard & Paus, 2010). The coil was placed on the scalp over the designated site for each trial with the handle pointed posteriorly, 45° between coronal and sagittal planes and the position of the coil was recorded in Brainsight for each stimulation applied (Brasil-Neto et al., 1992). These perturbations were randomized as a no-TMS trial, a catch trial, or trials with DP-TMS perturbation 150, 200, or 250 ms after the ‘Go’ signal. The experiment was completed when each patient had completed 10 blocks of 10 trials with stimulation over each of the three sites, including excluded trials.

**Data Analysis**

The primary outcome measure of the behavioral task was percent change in movement time. Percent change was calculated for each participant as the difference between the median of the no-TMS trials and the median of the perturbation time point that had the greatest effect within each set. Movement time was calculated as the period from movement initiation to contact with the specified response pad. The secondary outcome measures were percent change in response time (time from the onset of the ‘Go’ signal to contact with the response pad), peak
velocity (m/s), movement units (number of peaks and valleys after reaction onset in the x-y combined velocity profile), and hand path length (total hand path length in x, y, and z directions). These kinematic measures were chosen as measures of speed, error, and movement quality.

Dependent measures were computed using Microsoft Excel (Microsoft, Richmond, WA) and a customized Matlab program (Mathworks, Natick, MA). Percent difference was calculated as the difference between the median of the no-TMS trials and the median value at each perturbation time point. Pain ratings and TMS coil placement values were also calculated. Reliability of the coil position was calculated within patients to ensure accuracy.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics Version 24 (Chicago, IL). To test for differences in percent change in movement time after perturbation of the two motor areas (M1 and PMd), paired sample t-tests were run with one factor (site). The α level was set to 0.05. Outliers in percent change were removed if they fell more than two standard deviations from the mean. To test for differences in percent change in movement time after perturbation of the two motor areas and the control site (percent change after perturbation of M1, PMd, and DLPFC), one-way repeated measures ANOVA were calculated with one within-subject factor (site). Post-hoc one sample t-tests were performed with the test value set to 0.

**4.3 Results**

16 patients were included in this analysis aged 44-78 (61.5 ± 9.2), 8 females and 8 males who were an average of 65.5 months post stroke (Table 1).
**Results of Primary and Secondary Outcome Measures**

After DP-TMS was delivered to M1 and PMd, there was a significant difference in percent change in movement time (or the time from the onset of movement to the completion of the reaching task). There was a percent change in movement time of 2.89 ± 1.81% and 11.1 ± 3.3%, respectively, \( t(14) = -2.55, p = 0.02 \), indicating that perturbation of PMd slowed the reaching movement more than perturbation of M1 (Figure 1).

Perturbation of PMd and not M1 resulted in a difference in response time, but not in reaction time (Figure 2). There was a significant difference in percent change in response time after DP-TMS of M1 vs. PMd. There was a percent change in response time of -1.96 % ± 1.64% and 2.29 ± 2.44%, respectively \( t(15) = -2.5, p = 0.05 \), indicating that perturbation of PMd slowed the overall response time more than perturbation of M1 did. There was no significant difference in percent change in reaction time after DP-TMS of M1 vs. PMd. There was a percent change in reaction time of -10.1± 2.35% and -9.2 ± 2.2%, respectively \( t(12) = -0.33 p = 0.75 \).

In addition to timing, we recorded changes in hand-path kinematics of the movements. There was a tendency, though not significant, for percent difference in peak velocity to differ after DP-TMS of M1 vs. PMd. There was a difference of 0.21 ± 1.72% vs. -5.54 ± 2.17%, respectively \( t(12) = 2.092 p = 0.06 \), indicating that peak velocity tended to decrease with perturbation of PMd (Figure 3). There was also a trend toward differences in the smoothness of the movement after DP-TMS of M1 vs. PMd, as measured by movement units (M1: -6.54 ± 3.5%; PMd: 13.33 ± 7.31%; \( t(14) = -2.03 p = 0.06 \), suggesting that the movement may also be less smooth after perturbation of PMd (Figure 4). Finally, there was no significant difference in percent change in hand path length after DP-TMS of M1 vs. PMd. With perturbation of M1 vs.
PMd, there was a insignificant difference in hand path length of .51 ± 1.27% and 6.59 ± 3.74% ($t(13) = -1.43 \ p = 0.17$), respectively, indicating that the movement was numerically less direct after perturbation of PMd (Figure 4).

**Results of Control Condition**

These data were collected for all three sites (M1, PMd, and DLPFC) in 5 of the 16 patients. On average, TMS perturbation of M1, PMd and DLPFC induced a percent change in movement time of -1.5 ± 7.7%, 11.3 ± 5.8%, and -0.41 ± 3%, respectively. ANOVA revealed a significant effect of site (PMd) ($F(2,10)=9.22, \ p = 0.005$) (Figure 5). These results show preliminary evidence that the PMd response shown in the above results is due to more than the presence or absence of TMS stimulation.

**4.4 DISCUSSION**

This study demonstrates a functionally relevant role for nonlesioned hemisphere PMd in a paretic-arm reaching task in patients with severe arm impairment after stroke. Here we analyzed two potential sites within the nonlesioned hemisphere, M1 and PMd, with additional analysis of a non-motor control site (DLPFC), using DP-TMS to momentarily perturb one of these sites prior to a reaching task. After perturbation of PMd, but not M1, reaching movements were slower and trended toward having a lower peak velocity, were less smooth, and less direct.

In a normal, visually guided reaching movement in the intact system, areas of the motor system of the contralateral hemisphere work hierarchically to plan and execute the movement. Cells within M1 are tuned to specific aspects of a movement, such as joint posture, muscle force, and direction, while neurons within PMd are less specified (Cisek et al., 2003; Georgopoulos, et al., 1992). In fact, many of the secondary motor areas within the contralateral hemisphere can
have a redundant role in a reaching movement and are often recruited in patients with more mild impairment after stroke (Ward et al., 2003). In patients who lack structural reserve, the CST cannot effectively relay signals to the contralateral arm. These patients appear to recruit nonlesioned hemisphere PMd, a motor region with a more broad function in the motor system that has demonstrated bilateral activation and connectivity (Bucy, 1933; Kuypers & Brinkman, 1970; Cisek et al., 2003).

In this study, we found that perturbation of PMd significantly slowed movement time as compared to perturbation of M1 or DLPFC. For response time, the effect of perturbation of nonlesioned PMd requires further interpretation. Response time improved slightly after perturbation of M1, while it worsened after PMd. A post-hoc one-sample t-test showed that percent change in response time after perturbation of PMd was significantly different from 0 but not after perturbation of M1. This demonstrates that M1 served as an adequate control site in this condition and the effects of change in response time can be interpreted as specific to a response to perturbation of PMd. Kinematic measures of speed, error, and quality of movement trended toward greater change after perturbation of PMd and not M1, but the differences were not significant. We cannot determine from these data which kinematic aspect of reaching movement is contributing to the slower movement.

The strengths of this study include the standardized, objective procedure in which these data were gathered. Conditions for each perturbation set could be replicated each visit and the use of neuronavigation ensured DP-TMS targeting was consistent within patients for each site. The greatest limitation of this study is the small number of patients from which these data were gathered from the second control site, DLPFC. Similarly, more power is needed to successfully
interpret kinematic variables. While we do not use a sham DP-TMS paradigm, we control for the presence of TMS stimulation with the non-motor control site, DLPFC. We also employed a choice reaction time task and ‘catch trials’ to avoid a startle or learning effect. In a heterogeneous group, such as patients with severe stroke impairment, there is a large degree of between-subject variability in movement parameters. By expressing values recorded during perturbation trials relative to those recorded from trials with no perturbation that were randomly intermixed within the same block, we can accurately compare these movements despite the variability between patients.

4.6 Conclusion

Patients with severe motor impairment after stroke recruit a specific site within the nonlesioned hemisphere, PMd, during the performance of reaching movements. Perturbation of this area prior to the reaching movement results in a slower and less exact execution of the task. These results are important, as PMd may be a potential stimulation target for non-invasive brain stimulation in patients with severe arm impairment after stroke.
Comparison of percent change in movement time after perturbation of M1 (2.9 ± 1.8) and PMd (11.1 ± 3.3). Perturbation of PMd had a greater effect on movement time than perturbation of M1 $t(14) = -2.55, p = 0.02$. 

Figure 4.1: Average change in movement time after perturbation of M1 and PMd.
Comparison of percent change in reaction time and response time after perturbation of M1 and PMd. Perturbation of PMd (2.3% ± 2.4%) had a greater effect on response time than perturbation of M1 (-2% ± 1.6%) \((t(15) = -2.5, p = 0.05)\). There were no significant differences between perturbation sites (M1: -10.1% ± 2.3%) (PMd: -9.2% ± 2.2%) for reaction time \((t(12) = -0.33, p = 0.75)\). Post-hoc one sample t-test shows that change in response time after PMd perturbation is significantly different from 0 \((t(15) = 3.38, p = 0.004)\) but that it is not statistically significant after M1 perturbation \((t(14) = 1.4, p = 0.14)\).
Figure 4.3: Average change in peak velocity after perturbation of M1 and PMd.

Comparison of percent change in peak velocity after perturbation of M1 (2 ± 1.7) and PMd (-5.5 ± 2.2) (t(12) = 2.092, p = 0.06). Though not significant, perturbation of PMd had a greater effect on change in peak velocity than perturbation of M1. Post-hoc one sample t-test shows that change in peak velocity after PMd perturbation is significantly different from 0 (t(15) = -2.54, p = 0.02) but not after M1 perturbation (t(12) = 0.12, p = 0.9)
Figure 4.4: Average change in movement units and hand path length after perturbation of M1 and PMd.

Comparison of percent change in movement units and hand path length after perturbation of M1 and PMd. Though not significant, perturbation of PMd (MU: -13.3 ± 7.3) (HPL: 6.6 ± 3.7) had a greater effect on change in movement units and hand path length than perturbation of M1 (MU: -6.6 ± 3.5) (HPL: 0.5 ± 1.3) (movement units: \(t(14) = -2.03 \ p = 0.06\); hand path length: \(t(13) = -1.43 \ p = 0.17\) ).
Figure 4.5: Control condition: Average change in movement time after perturbation of M1, PMd, and DLPFC.

Comparison of change in movement time after perturbation of M1 (-1.5 ± 3.9), PMd (11.3 ± 3.8), and DLPFC (-0.4 ± 3.6). An ANOVA reveals a significant main effect of site: F(2,10)=9.22, p = 0.005. *within subject error detailed in legend and shown in figure.
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CHAPTER 5
DISCUSSION

5.1 CONCLUSIONS

Our overall research goal is to design a non-invasive brain stimulation (NIBS) paradigm for patients with severe arm impairment after stroke. To achieve this goal, we needed to understand which brain areas are most often affected by the lesion in this group and which of the remaining nonlesioned areas may be able to support movement of the affected arm. The objectives of this dissertation were to 1) examine differences in lesion characteristics between patients with mild vs. severe arm impairment, 2) understand differences between patients with mild and severe arm impairment in the contributions of the lesioned and nonlesioned hemispheres to affected arm movements, and 3) compare the contributions of different nonlesioned hemisphere motor areas to reaching movements in patients with severe arm impairment.

First, we hypothesized that patients with lesions occupying the corticospinal tract (CST) would have more severe impairment than those with little or no involvement of the CST. Second, we hypothesized that the nonlesioned hemisphere would contribute to reaching movements in patients with severe arm impairment but not in those with mild arm impairment. Finally, we hypothesized that the nonlesioned hemisphere dorsal premotor cortex (PMd) would contribute more than primary motor cortex (M1) or a control site to the reaching movements of patients with severe arm impairment. We found that the greatest difference between patients with and without distal arm function was lesions in posterior limb of the internal capsule (PLIC) and that patients with lesions in PLIC performed worse on a proximal arm-reaching task as well. Second, we found that the nonlesioned hemisphere contributed to reaching movement in patients with
severe but not mild arm impairment. Finally, we found that PMd, but not the other nonlesioned hemisphere sites, contributed to reaching movement in patients with severe arm impairment.

5.2 Broader impact

The results of this research show that there are a number of factors that need to be considered in order to design effective interventions for patients with severe arm impairment after stroke. Even in the case of relatively small strokes, patients with lesions occupying PLIC may be unable to successfully use lesioned-hemisphere areas for motor control of the paretic arm. If the remaining CST projections from the lesioned hemisphere are insufficient to allow perilesional areas to control paretic arm movement, sites within the nonlesioned hemisphere may be considered as targets for excitatory intervention. Here we have shown that the nonlesioned hemisphere PMd has a functionally relevant role in paretic arm reaching movements in patients with severe arm impairment.

The results of this work provide evidence that supports and expands upon the Bimodal Balance Recovery model. As previously discussed, the Bimodal Balance Recovery model reconciles the Interhemispheric Competition model with theories of vicariation to the nonlesioned hemisphere by incorporating a gradient of different levels of “structural reserve” (di Pino et al., 2014). In our data, patients with chronic, severe arm impairment demonstrated significantly more recruitment of the nonlesioned hemisphere than did patients with mild arm impairment. This would suggest that patients with mild arm impairment, or those who presumably retain high levels of structural reserve, are demonstrating patterns of cortical reorganization consistent with the Interhemispheric Competition model. Conversely, patients with severe arm impairment, or those with presumably low structural reserve, are demonstrating
patterns of cortical reorganization consistent with models of vicariation to the nonlesioned hemisphere. From these results, we can infer that the lesion characteristics that differ between these patients are likely elements of the structural reserve gradient. These results would suggest that we should further investigate lesions in PLIC as an element in recruitment of nonlesioned hemisphere motor areas.

The larger implications of this research are that we cannot use a one-size-fits-all approach to designing interventions for the paretic arm. Interventions that improve function for patients with mild impairment, or those who retain enough perilesional tissue and CST axons to rely on motor areas within the lesioned hemisphere for paretic arm movement, are unlikely to translate to patients with more severe impairment who must rely on the nonlesioned hemisphere for motor control. This is an implication not just for design of NIBS interventions but for therapeutic rehabilitation as well. Interventions that are designed to limit activation of the nonlesioned hemisphere, such as constraint-induced movement therapy, may not be optimal for patients who rely on the nonlesioned hemisphere for motor control (Corbetta et al., 2010). These results may help to explain why few interventions have been validated for patients with severe arm impairment (Hayward et al., 2010).

These results also have several implications for the design of NIBS interventions for paretic arm movement after stroke. Patients should be stratified into different treatment groups based on whether or not they retain enough perilesional tissue and CST axons to successfully relay signals from the lesioned hemisphere to the paretic arm. Making this distinction could be as simple as eliciting contralateral motor-evoked potentials with stimulation of lesioned M1 or as complex as white matter tractography. For patients that do not have adequate projections from
the lesioned hemisphere, we should consider NIBS paradigms that increase cortical excitability in the nonlesioned hemisphere, specifically over PMd. While more research is needed to understand the relationship between the structural reserve gradient and motor control, we should begin to examine how upregulation of nonlesioned PMd affects paretic arm motor function.

5.3 STRENGTHS AND LIMITATIONS

The results of this work are novel and important for future study design and intervention for patients with severe arm impairment after stroke. We have provided evidence supporting the need to tailor NIBS paradigms based on remaining CST relay ability and recruitment of the lesioned or nonlesioned hemisphere. Our groups in Chapters 2 and 3 were well matched in key factors outside of motor impairment, including age, time since stroke, total lesion volume, cognitive function, and overall stroke severity (NIHSS), increasing the likelihood that the differences seen in lesion characteristics and perturbation effects were not confounded by other factors. There was very little subjectivity in our data collection. In Chapter 2, stroke lesion masks were traced, transformed, and analyzed according to standardized and/or automated procedures to reduce the chance of human error. In Chapters 3 and 4, double-pulse transcranial magnetic stimulation (DP-TMS) perturbation was randomized and a customized program determined the timing of stimulus delivery that was used in all trials. Consistent conditions were carefully reproduced before each subsequent testing session and neuronavigation was used to ensure that stimulation of DP-TMS was consistent for each site. With the exception of Chapter 2 and the control condition in Chapter 4, our comparisons were well powered and there was statistical significance to support our hypotheses. DP-TMS is an excellent investigational tool for determining recruitment of specific cortical areas for motor behaviors.
Despite these strengths, there were several limitations to these studies. Conclusions from our examination of lesion characteristics would have been significantly bolstered by a prospective study of specific lesion locations and CST integrity. Because this was a retrospective study, we were limited to analyzing lesions in structural scans when diffusion tensor imaging and measures of fractional anisotropy would have been a better measure for analyzing CST integrity. While voluntary extension of the wrist and fingers is a good marker of CST function, we could have made a stronger conclusion about CST integrity with the inclusion of a test of motor-evoked potentials from the lesioned hemisphere. Similarly, our inference about the potential relationship between lesions in PLIC and recruitment of nonlesioned hemisphere would have been stronger with a comparison between lesion characteristics and change in movement time after DP-TMS of PMd.

There are also limitations to consider in the perturbation studies. Clinical populations are dynamic, particularly patients who have had a stroke, and the data for this study has been collected over a period of years. As the experiments evolved, we added additional data collection measures to the procedures (such as the pain rating scale and the control site in Chapter 4). Many patients who participated early in the study were unable to return for additional data collection due to new stroke, changes in medical condition, relocation to other states, and lack of transportation. As such, our control condition in Chapter 4, which was added later in the study, had fewer participants than our other comparisons. In Chapter 3, we stimulated sites in both the nonlesioned and lesioned hemispheres. Due to risk of seizure from TMS (Rossi et al., 2009), we did not stimulate the lesioned hemispheres of patients with large lesions that extended to the surface of the cortex in the motor areas. As a result, we could not perform the comparison
between the lesioned and nonlesioned hemisphere in all of the patients for Chapter 3 and the groups for Chapter 3 and Chapter 4 are composed of slightly different patients.

All studies employing TMS perturbation have inherent limitations. Deep cortical structures are inaccessible with a standard figure-of-eight coil, which limits our ability to directly examine the role of subcortical areas in post-stroke movement. Controlling for a placebo effect can be difficult in these studies. DP-TMS has a distinct feel and sound that can be recreated with sham TMS to some degree of success, but sham TMS feels noticeably different from real TMS and cannot control for other non-specific effects such as contraction of facial muscles or MEPs from perturbation of nonlesioned M1 (Chouinard & Paus, 2010; Duecker & Sack, 2015). In these studies, we did not employ sham TMS. Instead, we included multiple sites and conditions within reaching trials without stimulation. Finally, we cannot be sure that the effects of DP-TMS are specific to the area tested. Spreading tests between PMd and M1 controlled for direct stimulation of an unintended target, but cannot control for network effects. It is possible that the effects of DP-TMS seen here are a result of perturbation of a network, and are not necessarily specific to PMd. The induction of network effects is, however, less likely with a short-lasting perturbation such as that used here than with the more sustained effects of inhibitory rTMS that is also sometimes used to induce a “virtual lesion” effect.

5.4 Future directions

Despite these limitations, the results provide an important foundation for future research. The preliminary evidence gathered regarding the role of lesions in PLIC in severity of paretic arm function detailed in Chapter 2 should be subjected to a well powered, prospective study. The Bimodal Balance Recovery model suggests that recruitment of perilesional areas versus areas
previously uninvolved in a function vary on a gradient of remaining structural reserve (di Pino et al., 2014). In future studies, we should analyze how lesions occupy specific cortical areas. CST occupies only a portion of PLIC and, much like the motor cortices, is organized somatotopically (Holodny et al., 2005). Future lesion analyses should further divide the structure of PLIC into areas that contain CST fibers and their somatotopic organization and examine the extent of damage to longitudinal subsections of CST (Riley et al., 2011). These results, as well as fractional anisotropy values of CST integrity in SCR and PLIC, should be compared to the beneficial recruitment of nonlesioned hemisphere PMd to further define the gradient of structural reserve described in the Bimodal Balance Recovery Model.

In this research, we found that nonlesioned hemisphere PMd can contribute to paretic arm reaching in patients with severe post-stroke arm impairment. Futures studies should apply these results to determine the extent to which excitatory NIBS of nonlesioned hemisphere PMd can enhance the effects of reaching performance and practice. Ultimately, if excitatory NIBS applied to nonlesioned PMd is successful in enhancing the effects of practice in patients with chronic, severe impairment, there will be exciting implications for application of this paradigm in the subacute clinical population. Rehabilitation in the subacute phase after stroke is inherently time limited; spontaneous plastic recovery occurs primarily during the first several months after stroke (Hendricks et al., 2002) and patients can receive as little as four hours of physical therapy a week during this time (Sunderland et al., 1992). Enhancing the results of therapeutic intervention and practice during this period could have significant effects on long-term outcomes.

These results also have implications for aspects of post-stroke impairment other than visually guided reaching. The role of nonlesioned PMd demonstrated thus far has been specific
to proximal arm reaching tasks. Future studies should examine if and how other nonlesioned hemisphere areas may contribute to motor control in the case of severe disruption of the affected hemisphere networks. Outside of the motor system, these results provoke questions about whether a similar dichotomy between recruitment of perilesional areas versus areas previously uninvolved in a function exists in other post-stroke impairments such as sensory disturbances, aphasia, cognition, and neglect. The identification of nonlesioned hemisphere sites that could be facilitated with NIBS in other post-stroke impairments could play a crucial role in improving rehabilitation for patients with severe impairment.

5.5 Summary

In this work, we aimed to explore the role of lesion characteristics and nonlesioned hemisphere PMd in paretic arm reaching movements in patients with severe arm impairment after stroke. We compared lesion characteristics between a group of patients with mild and severe arm impairment and found that the proportion of lesions in PLIC were different between the two groups of patients. Using a DP-TMS perturbation paradigm applied to cortical motor areas in the nonlesioned hemisphere during a reaching task, we determined that the nonlesioned hemisphere can contribute to reaching movements in patients with severe arm impairment and that this effect is specific to PMd. Future studies will expand upon these finding by directly examining the impact of lesions involving specific subsections of PLIC in nonlesioned hemisphere recruitment for paretic arm movement with lesion mapping and diffusion tensor imaging. We will also investigate if excitatory NIBS of nonlesioned PMd can enhance the effects of practice in the visually guided reaching of patients with severe arm impairment. The
results of this research have broad implications for patient inclusion and site selection in future NIBS trials.
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