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Identifying altered sensorimotor pathways and their role in motor impairment post-stroke

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ABSTRACT

Identifying altered sensorimotor pathways and their role in motor impairment post-stroke

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Stroke is the leading cause of permanent adult disability. Subcortical unilateral (hemiparetic) stroke affecting the internal capsule or basal ganglia is the most common of all strokes and usually results in hemiparesis of the contralateral arm and leg. About 80% of the individuals with a moderate to severe hemiparetic stroke suffer from upper limb motor impairment, particularly in the wrist and fingers, as the most disabling, which limits the basic activities of daily life like dressing, eating, and grooming. The wrist/finger weakness in these individuals is greater for extensors than flexors, causing difficulty in hand opening, and leading to a dysfunctional wrist/fingers flexed posture.

Previous neuroimaging studies of hemiparetic stroke over the past two decades, trying to understand the underlying neural mechanism of hand impairment, have frequently reported increased neural activity in motor cortices of both lesioned and non-lesioned hemispheres in individuals with stroke, during their attempt to move their affected upper extremity. It is also known that the more severe the stroke, the greater activity in the contralesional (non-lesioned) hemisphere than ipsilesional (lesioned) hemisphere. However, it is still unclear what descending motor pathways allow the non-lesioned hemisphere to control the ipsilateral paretic arm, although

one proposed idea from animal studies suggests the brainstem ipsilaterally projecting motor pathways to play this role.

Damage to the corticospinal tract and its role in motor impairment post unilateral subcortical stroke is widely studied, however less is known about changes to other sensorimotor pathways. One reason for this lack of knowledge is that a majority of previous studies have only investigated the morphological changes in the brain, where the main descending and ascending brain pathways (e.g. corticospinal, cortico-bulbospinal, dorsal column medial lemniscal tracts) mostly overlap and are not distinguishable with currently available imaging techniques. Sensorimotor pathways, in fact, delineate from each other in the brainstem and continue travelling through separate regions in the spinal cord.

To this end, the goal of this dissertation is to use a combination of advanced anatomical and functional MRI methods to identify all altered sensorimotor pathways and their role in motor impairment post stroke. More specifically, we first used high resolution and advanced structural MRI of brainstem and cervical spinal cord to identify sensorimotor pathways with microstructural changes in individuals with stroke compared to controls. Furthermore, we used functional MRI (fMRI) of the brainstem to examine the activity in nuclei of brainstem descending motor pathways in individuals with chronic stroke and age-match gender-match controls, while they attempt to close their paretic hand.

The results from our morphological investigations in brainstem and cervical spinal cord indicated a significant decrease of white matter integrity in corticospinal tract, lateral and medial reticulospinal tracts, descending medial longitudinal fasciculus, tectospinal tract and cuneate and

gracile fasciculi related to the lesioned hemisphere. Furthermore, the results from brainstem and cervical spinal cord DTI analyses indicate a significant increase in the white matter integrity of medial reticulospinal tract at the side of contralesional hemisphere which projects ipsilaterally to the paretic (contralesional) limbs. When testing the correlation between these morphological changes and impairment severity in individuals with stroke, we found the decreased white matter integrity of ipsi-lesional corticospinal tract and increased white matter integrity of contra-lesional medial reticulospinal tract are correlated with upper limb impairment severity in these stroke participants.

The results of our investigation of functional activity in brainstem during squeezing a pressure ball indicated significant activity in medial reticulospinal tract nuclei in all severely and moderately impaired individuals with stroke, as well as, a less intense activity in lateral reticulospinal tract nuclei, medial vestibulospinal tract nuclei, and pontine nuclei of motor cortex-ponto-cerebellum pathway in some individuals with stroke. Interestingly, mildly impaired stroke subjects, as well as, healthy controls did not show any activation in nuclei of brainstem descending pathways, suggesting that they continue to use the main motor pathway - corticospinal tract - during the hand closing task.

These results for the first time identify all altered sensorimotor pathways post unilateral subcortical stroke and their correlation with upper extremity motor impairment in these individuals. Furthermore, this work directly suggests the brainstem ipsilaterally projecting pathways to facilitate the hand closing post stroke. It is also noteworthy to mention that these results demonstrate a correlation between impairment severity and greater reliance on reticulospinal tract, but not a causation. These findings suggest that the excessive flexor hypertonicity in elbow, wrist

and fingers, as well as, the flexion synergy impairment observed in individuals post stroke to be a result of increased reliance on reticulospinal tract post stroke (due to flexor-biased nature of this pathway). However, it still remains unclear that what the impact of these alternative pathways projecting from non-lesioned hemisphere is during motor recovery in severely impaired individuals and how much movement control they could gain without the help of these alternative motor pathways. Further longitudinal investigations with targeted interventions in a large group of individuals with acute stroke should help us better understand how these pathways affect recovery after stroke. This will allow us to optimize rehabilitation strategies that take into account the innate capabilities of these pathways.

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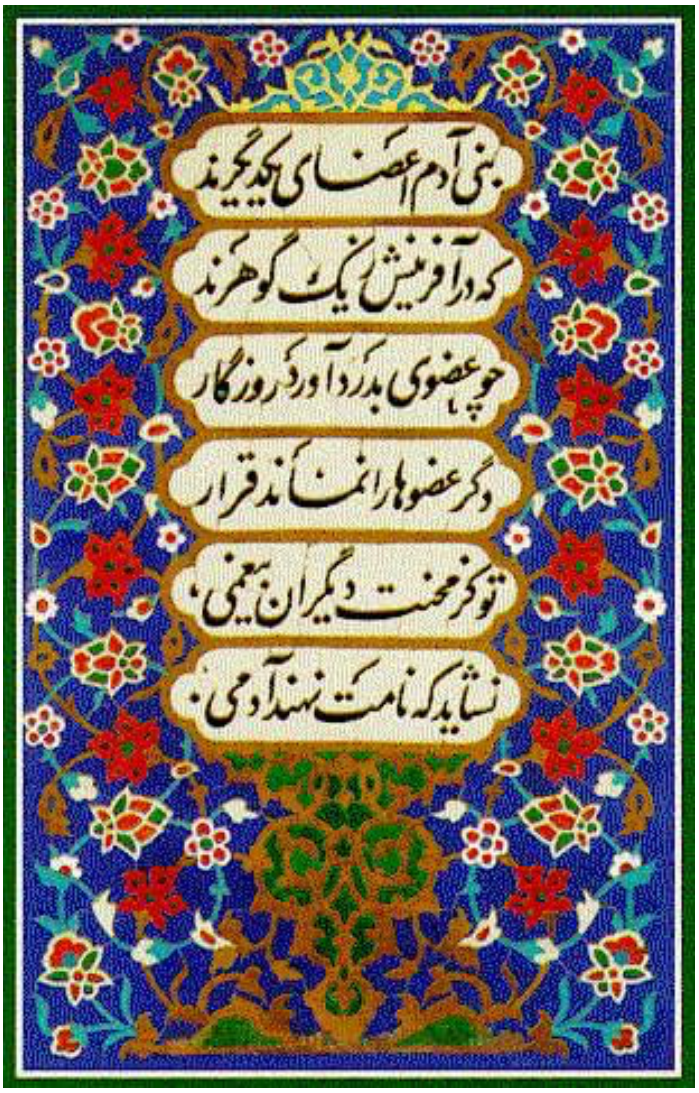

All human beings are in truth, like body parts,

akin; All in creation share one origin and essence.

When fate allots a member pangs and pains,

no ease for other members then remains.

If you have no sympathy for human pain,

the name of human you cannot retain.

Saadi Shirazi (Persian poet of the medieval period), 1184-1292

LIST OF ABBREVIATIONS

ARAT	Action Research Arm Test
CBT	Corticobulbar Tract
CST	Corticospinal Tract
DCML	Dorsal Column Medial Lemniscus
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalography
FA	Fractional Anisotropy
FCu	Cuneate Fasciculus
FGr	Gracile Fasciculus
fMRI	Functional Magnetic Resonance Imaging
FMA	Fugl-Meyer Assessment
GM	Gray Matter
HD-EEG	High Density Electroencephalography
LRST	Lateral Reticulospinal Tract
MLF	Medial Longitudinal Fasciculus
MRI	Magnetic Resonance Imaging
MRST	Medial Reticulospinal Tract
PMC	Premotor Cortex
RST	Reticulospinal Tract
SMA	Supplementary Motor Area
SMC	Sensorimotor Cortices

SPM	Statistical Parametric Mapping
TBSS	Tract-Based Spatial Statistics
TST	Tectospinal Tract
VST	Vestibulospinal Tract
WM	White Matter

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1. INTRODUCTION

Problem Statement

Stroke is the leading cause of permanent adult disability and the 5th cause of death in the US, affecting more than 800,000 people per year (Rosamond 2007, Members, Roger et al. 2012, Go, Mozaffarian et al. 2014, Benjamin, Blaha et al. 2017). Sadly, the damage to the brain tissue caused by a stroke leads to the death of approximately 21 percent of individuals with stroke within a year. Stroke survivors can experience different long-lasting impairments depend on the location of the lesion, such as trouble with speaking or understanding spoken or written language, cognitive and memory deficits, or loss of control or sensation of the face, arm or leg. (Members, Roger et al. 2012, Mozaffarian, Benjamin et al. 2015, Benjamin, Blaha et al. 2017). Throughout this research and dissertation, I focus on individuals with subcortical unilateral stroke, which is the most common type of stroke, affecting the internal capsule or basal ganglia and usually resulting in hemiparesis of the contralateral arm and leg.

About 80% of individuals with a moderate to severe hemiparetic stroke report upper limb motor impairment, particularly in the wrist and fingers, as the most disabling, which limits the most basic activities of daily life like dressing, eating, and grooming (Pryor 1981, Parker, Wade et al. 1986, Members, Roger et al. 2012). The wrist/finger weakness in these individuals is greater for extensors than flexors (Kamper, Harvey et al. 2003, Cruz 2005), causing difficulty in hand opening, and leading to a dysfunctional wrist/fingers flexed posture. Furthermore, more severely impaired individuals involuntarily close the hand when attempting to open it (Yiyun Lan 2017).

Numerous functional neuroimaging studies of hemiparetic stroke have reported increased neural activity in motor cortices of both ipsilesional and contralesional hemispheres in individuals with

stroke, during their attempt to move their affected upper extremity (Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Cao, Olhaberriague et al. 1998, Carey, Kimberley et al. 2002, Johansen-Berg, Rushworth et al. 2002, Ward, Brown et al. 2003, Grefkes, Nowak et al. 2008, Rehme, Fink et al. 2011, Rehme, Eickhoff et al. 2012, McPherson, Chen et al. 2018). Furthermore, the more severe the stroke, the greater activity in the contralesional hemisphere compared to the ipsilesional (i.e. a shift of activity to non-lesioned hemisphere).(Cramer, Nelles et al. 1997, Cao, Olhaberriague et al. 1998, Johansen-Berg, Rushworth et al. 2002, Rehme, Fink et al. 2011).

However, it is still unclear what descending motor pathway allows the non-lesioned hemisphere to control the ipsilateral paretic arm. One proposed idea from animal studies suggests the ipsilaterally projecting motor pathways (i.e. reticulospinal tract or vestibulospinal tract) may play this role (Baker, Zaaimi et al. 2015, Herbert, Powell et al. 2015). Moreover, previous reports on flexor-biased role of reticulospinal tract in primates and cat (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson, Buford et al. 2004, Davidson and Buford 2006) and relatively preserved ability for wrist/fingers flexion, compared to extension, in individuals with stroke further suggest the possible role of ipsilaterally projecting brainstem pathways post stroke.

Damage to the corticospinal tract is widely studied following unilateral subcortical stroke, whereas less is known about changes to other sensorimotor pathways. (Werring, Toosy et al. 2000, Thomalla, Glauche et al. 2004, Ward, Newton et al. 2006, Lindenberg, Renga et al. 2010). One reason for this lack of knowledge is that majority of previous studies have only investigated the morphological changes in the brain, where the main descending and ascending brain pathways (e.g. corticospinal tract, cortico-bulbospinal tracts, dorsal column medial lemniscus) mostly

overlap and are not distinguishable with currently available imaging techniques. Sensorimotor pathways, in fact, delineate from each other in the brainstem.(Haines 2004, Mai and Paxinos 2011, Vanderah and Gould 2015, Gray, Standring et al. 2016) Moreover, these tracts continue travelling through separate regions in the spinal cord.(Haines 2004, Gray, Standring et al. 2016)

Research Goals

The goal of this dissertation is, therefore, to use advanced brainstem and spinal cord MRI methods to identify altered sensorimotor pathways and their role in motor impairment post stroke. More specifically, I will use high resolution and advanced structural MRI of brainstem and cervical spinal cord to identify sensorimotor pathways with microstructural changes in individuals with stroke compared to controls. Moreover, I will use functional MRI (fMRI) of brainstem to examine the activity in nuclei of brainstem descending motor pathways in individuals with chronic hemiparetic stroke, while they attempt to close their paretic hand.

Research Aims

Following research aims will facilitate the accomplishment of the research goal stated above:

Aim 1: Identify the morphological changes in sensorimotor pathways in both brainstem and cervical spinal cord and test their correlation with motor impairment post-stroke.

Aim 1a: *Determine the morphological changes in sensorimotor pathways in brainstem and their correlation with motor impairment post-stroke.*

Aim 1b: *Determine the morphological changes in sensorimotor pathways in cervical spinal cord and their correlation with motor impairment post-stroke.*

Aim 2: Investigate the activity in nuclei of brainstem descending motor pathways during the hand closing task post stroke.

Significance

This work, for the first time, combines high resolution anatomical MRI and DTI of brainstem and cervical spinal cord with functional MRI of brainstem to identify both morphological and functional changes in sensorimotor pathways post stroke, and also test the correlation between these changes and the upper extremity motor impairment in these individuals.

Dissertation Outline

The remaining chapters of this dissertation will provide you with a background on previous research, and then discuss in depth the experimental design, methodology and results of each of research aims stated above. Chapter 2 will provide background information on the etiology of stroke, upper extremity motor impairments post stroke, previous neuroimaging studies on cortical activity post stroke, and main descending and ascending brain pathways. Chapter 3 uses high resolution structural MRI of both brainstem and cervical spinal cord and advanced analysis methods to identify sensorimotor pathways with morphological changes in brainstem and spinal cord post stroke. Chapter 4 uses functional MRI of the brainstem and a task-dependent fMRI design to investigate the activity in brainstem nuclei during hand closing task in individuals with chronic hemiparetic stroke. Chapter 5 will provide a discussion of the results, future directions and conclusions of the thesis.

2. BACKGROUND

Etiology of Stroke

Stroke is the leading cause of permanent adult disability and the 5th cause of death in the US, affecting more than 800,000 people per year (Rosamond 2007, Members, Roger et al. 2012, Go, Mozaffarian et al. 2014, Benjamin, Blaha et al. 2017). A stroke is a cardiovascular accident that occurs when there is a sudden interruption in the oxygen-rich-blood supply to a region of the brain, causing the brain cells in that region to die within minutes due to lack of oxygen and nutrients. There are two types of stroke: Ischemic stroke, which is caused by a blockage of arteries leading to the brain; and Hemorrhagic stroke, which is caused by a blood vessel rupture and bleeding into brain tissue. Ischemic strokes are the most prevalent type of stroke and account for about 87%, while hemorrhagic strokes account for about 13% of all strokes (Benjamin, Blaha et al. 2017). This damage to the brain tissue sadly leads to the death of approximately one fifth of individuals with stroke within a year after stroke. Stroke survivors often experience impairments such as trouble with speaking or understanding spoken or written language, loss of control or sensation of the face, arm or leg, or cognitive and memory deficits (Benjamin, Blaha et al. 2017). Throughout this research and dissertation, I will focus on individuals with subcortical unilateral stroke, which leads to the hemiparesis of contralateral arm and leg. About 80% of these individuals with a moderate to severe hemiparetic stroke report upper limb motor impairment, particularly in the wrist and fingers, as the most disabling, limiting the most basic activities of daily life like dressing, eating, and grooming (Pryor 1981, Parker, Wade et al. 1986, Members, Roger et al. 2012).

Upper Extremity Motor Impairments Post Stroke

There are three main motor impairments observed following hemiparetic subcortical stroke:

a) **Muscle weakness**

Muscle weakness in individuals with stroke is the inability to fully activate a muscle and therefore move the limb. It is, in fact, the result of damage to corticospinal and corticobulbar tracts in the lesioned hemisphere after stroke.

The muscle weakness in upper extremity after stroke is greater distally, particularly in wrist and fingers, than proximally (Garmirian, Acosta et al. 2018), which limits the most basic activities of daily life like dressing, eating and grooming in these individuals(Pryor 1981, Parker, Wade et al. 1986).

The wrist and finger weakness in these individuals is greater for extensors than flexors (Kamper, Harvey et al. 2003, Cruz, Waldinger et al. 2005, Conrad and Kamper 2012), causing difficulty in hand opening and leading to a dysfunctional wrist/fingers flexed posture. Furthermore, more severely impaired individuals involuntarily close the hand when attempting to open it. This might be due to the fact that corticospinal tract is likely the main motor pathway which innervates distal muscles and can cause wrist and finger extension. Although there are some evidences for reticulospinal tract projecting to upper extremity as well (Davidson, Buford et al. 2004, Davidson and Buford 2006), previous primate and cat studies have suggested the stimulation of reticulospinal tract nuclei in the brainstem to be associated with a flexion in the elbow, wrist and fingers (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson, Buford et al. 2004, Davidson and Buford 2006).

Moreover, the brain imaging MRI studies have also reported the damage to the corticospinal tract to be associated with impairment severity and a greater weakness. (Watanabe, Honda et al. 2001, Thomalla, Glauche et al. 2005, Moller, Frandsen et al. 2007, Puig, Pedraza et al. 2010).

b) Loss of independent joint control (limb synergies)

Loss of independent joint control or limb synergies is the inability to voluntarily move segments of the limb independently of each other(Brunnstrom 1970). This deficit is especially evident in individuals with hemiparetic stroke in the upper extremity, where there is an increased abnormal flexion of the elbow, wrist and fingers as an individual attempts to lift their paretic arm (i.e., shoulder abduction), and is described as the flexion synergy (Brunnstrom 1970, Sawner, LaVigne et al. 1992, Dewald, Pope et al. 1995, Dewald, Sheshadri et al. 2001, Hu, Tong et al. 2006, Sukal, Ellis et al. 2007, Miller and Dewald 2012). This loss of independent joint control leads to a reduction in reaching ability and hand opening ability, which makes many daily life activities difficult or impossible for these individuals.

It is noteworthy to mention that there can also be extension synergy in upper extremity in individuals post stroke, although it is less common than flexion synergy. In case of extension synergy, shoulder adduction is associated with extension in elbow but still flexion in wrist and fingers(McPherson and Dewald 2019, O'Sullivan, Schmitz et al. 2019).

The flexion synergy observed in individuals with a hemiparetic stroke might, in fact, be a result of damage to corticospinal tract and a higher reliance on ipsilaterally projecting motor pathways. It has been shown that increasing shoulder abduction load which leads to the expression of the flexion synergy in these individuals results in an increased reliance on the contralesional hemisphere (McPherson, Chen et al. 2018). Considering the evidence from primates and cat studies indicating the stimulation of reticulospinal tract nuclei to be associated with flexion in elbow, wrist and fingers (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson, Buford et al. 2004, Davidson and Buford 2006), the excessive muscle flexion observed post stroke and also the increase in this flexion with shoulder abduction might be the result of a higher reliance on ipsilaterally projecting motor pathways.

c) Excessive muscle tone and spasticity

Excessive muscle tone, also known as hypertonicity, might be a result of increase in monoaminergic signaling to the spinal cord from brainstem nuclei (Heckman, Johnson et al. 2008, McPherson, Ellis et al. 2008, Johnson and Heckman 2014, McPherson, Stienen et al. 2018). In other words, the higher reliance on contralesional hemisphere and possibly descending bulbospinal tracts after stroke can lead to increased metabotropic input using monoamines, such as serotonin and norepinephrine, released by these indirect motor pathways to alpha motoneurons in spinal cord (McPherson, Ellis et al. 2018). As a result of the increased release of monoamines at the spinal cord, motoneurons become more excitable resulting in hyperactive stretch reflexes or spasticity, that appears as abnormal resistance of the muscle to passive elongation or stretch (McPherson, Ellis et al. 2008, Francisco and McGuire 2012, Li and Francisco 2015, McPherson, Stienen et al. 2018).

Some studies also investigated this upregulation of the reticulospinal tract by measuring the acoustic startle reflex in individuals with stroke. They have found that this cohort generated a greater acoustic startle reflex in their paretic than in their non-paretic limb in individuals with stroke (Jankelowitz and Colebatch 2004, Honeycutt and Perreault 2012, Honeycutt and Perreault 2014).

Previous Neuroimaging Studies on Cortical Activity Post Stroke

Previous human fMRI studies in individuals with hemiparetic stroke have frequently reported increased neural activity in motor cortices of both the lesioned and contralesional (non-lesioned) hemisphere during movement of upper extremity post stroke (Carey, Kimberley et al. 2002, Johansen-Berg, Rushworth et al. 2002, Rehme, Fink et al. 2011, Rehme, Eickhoff et al. 2012). For instance, in an fMRI study of 10 individuals with chronic stroke, Carey et al. reported a bilateral activity in both ipsilesional and contralesional hemispheres during a finger tracking experiment (**Figure 2.1**) (Carey, Kimberley et al. 2002).

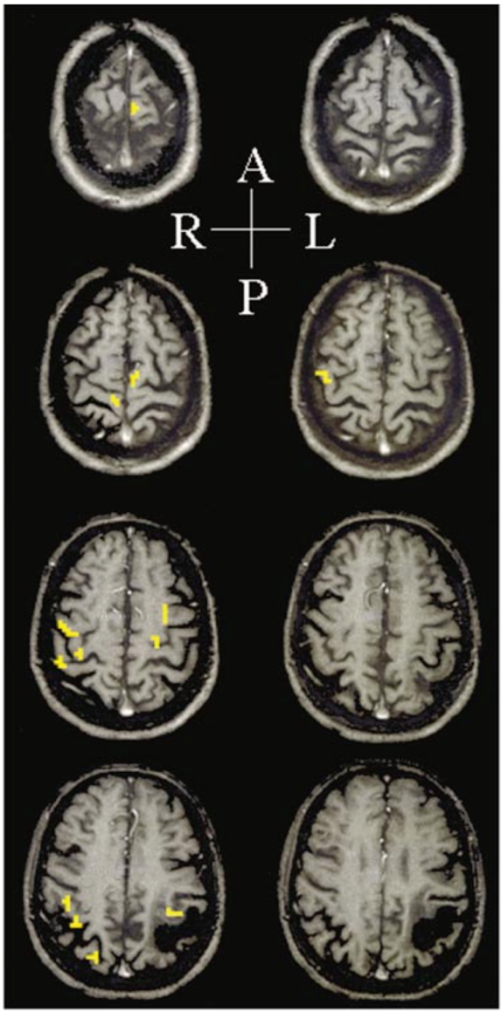

Figure 2.1. Brain activity in both ipsilesional and contralesional hemispheres during finger movement task in individuals with chronic stroke. Adapted from James R Carey et al. 2002

The same study also investigated the laterality index in primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), primary sensory area (S1), and sensorimotor cortices (SMC) in individuals with stroke and compared it to elderly healthy controls. The laterality index is defined as the number of active voxels in a specific region in the contralateral hemisphere (C), minus the number of active voxels in a specific region in the ipsilateral hemisphere (I), divided to sum of them. In other words, the Laterality Index = (C – I) / (C + I).

As shown in **Figure 2.2**, the individuals with stroke demonstrated a negative laterality index in SMC, M1, S1, PMC, and SMA, while the elderly controls with no stroke had negative laterality index only in SMA. In other words, individuals with chronic stroke were using the ipsilateral (contralesional) hemisphere more than contralateral hemisphere during the finger movement task, while the elderly healthy controls continued to use their contralateral hemisphere during the finger movement task.

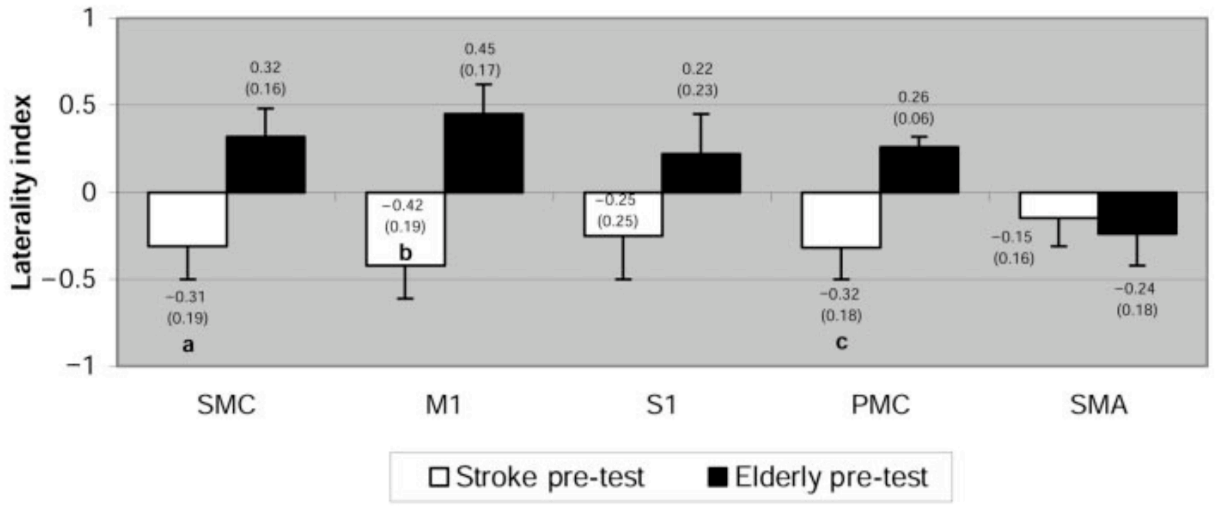

Figure 2.2. Laterality index during the finger tracking task in individuals with chronic stroke compared to elderly healthy controls. Individuals with stroke have a negative laterality index in SMC, M1, S1 and PMC, which indicates their greater use of ipsilateral hemisphere than contralateral after stroke, while healthy controls continue using their contralateral hemisphere in these brain regions. Figure is adapted from James R Carey et al. 2002.

Similarly, in a meta-analysis study of 54 fMRI stroke studies (472 patients), Rehme et al. reported bilateral activity in both lesioned and non-lesioned hemispheres during upper limb movement in individuals with stroke (**Figure 2.3. section A**). When comparing this brain activity in patients with healthy controls, they found that individuals with stroke have a greater activity in contralesional hemisphere than controls (**Figure 2.3. Section B, orange color**) (Rehme, Eickhoff et al. 2012).

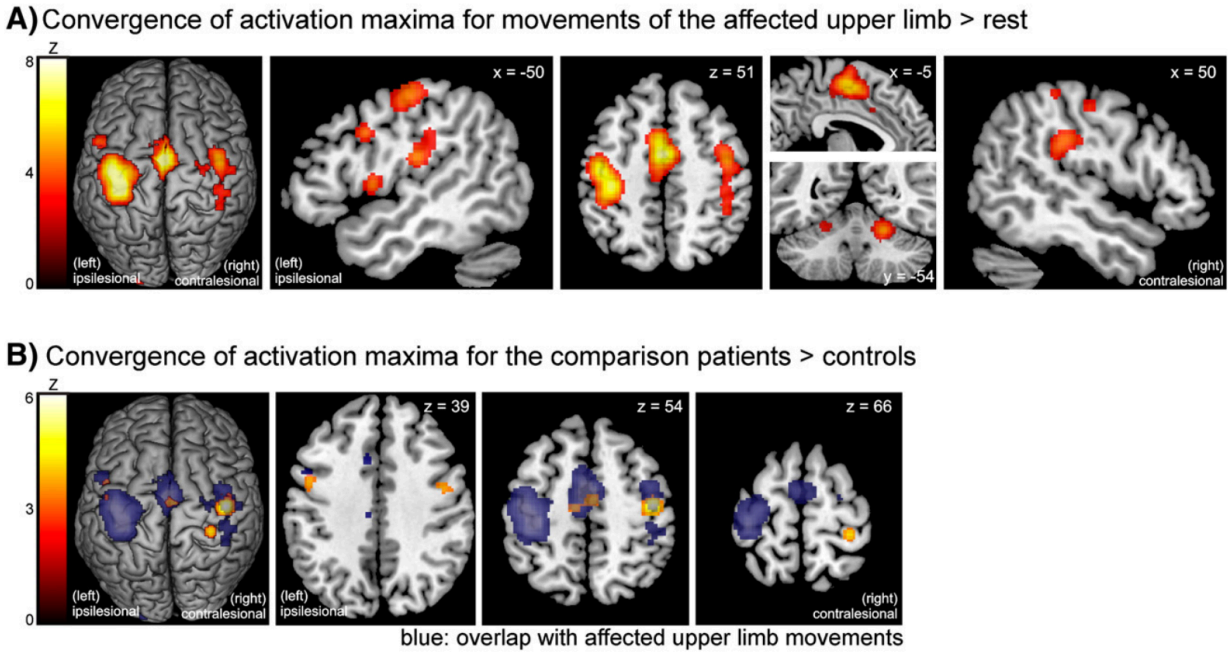

Figure 2.3. Brain activity in individuals with stroke and healthy controls during movements of the affected upper limb. (A) brain activity in individuals with stroke during upper limb movement. These patients show bilateral activity in both ipsilesional and contralesional hemispheres during affected limb movement. **(B)** Blue color shows the activity in individuals with stroke during affected limb movement. Yellow/orange color presents the clusters/regions in which individuals with stroke have a greater activity than healthy controls. These clusters are mainly in contralesional hemisphere. Figure is adapted from Rehme et al. 2012.

In a longitudinal study of 11 acute stroke patients, Rehme et al. investigated the brain cortical activity in about 2 days, 5 days and 10 days after stroke, while the participants tried to move their affected and unaffected hand during separate fMRI task. They found that individuals with stroke were using their lesioned (contralateral) hemisphere, just like control subjects, in 2 days after stroke. However, in just 10 days after stroke, the patients developed hyperactivity in both contralateral and ipsilateral hemispheres during movement of their affected hand. (**Figure 2.4, first row, sections A and B**)(Rehme, Fink et al. 2011). When testing the brain activity during movement of non-paretic hand, they found that stroke participants continued using their contralateral motor cortices like control subjects. (**Figure 2.4, second row, sections A and B**).(Rehme, Fink et al. 2011)

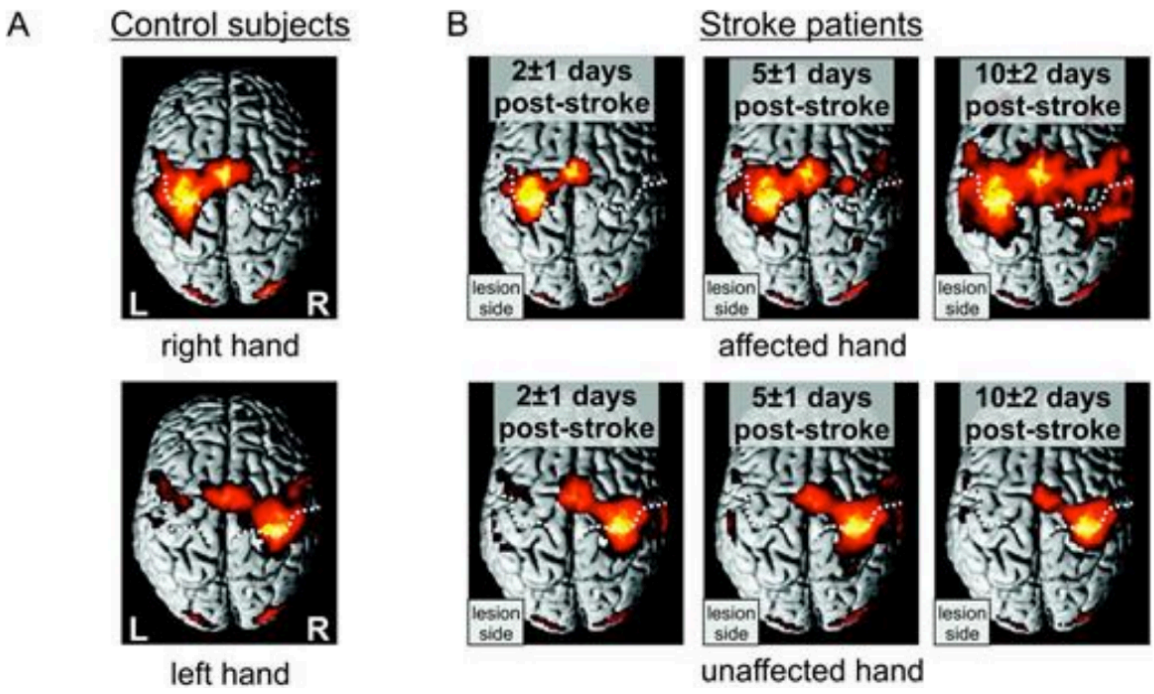

Figure 2.4. Brain activity in healthy controls and individuals with stroke during movement of affected hand in 2 days, 5 days and 10 days after stroke. (A) brain activity in control subjects during right hand and left hand movements. Control subjects continue using their contralateral motor cortices. **(B)** brain activity in stroke patients in 2, 5 and 10 days after stroke. Patients develop a hyperactivity in both lesioned and nonlesioned hemispheres when trying to move their affected

hand. However, they continue using their contralateral motor cortices when moving their unaffected hand. Figure is adapted from Rehme et al. 2011.

In the same study, Rehme et al. found this hyperactivity and cortical shift of activity to the non-lesioned hemisphere in individuals with stroke to be correlated with their impairment severity. For this investigation, they divided the patients into two groups based on their impairment severity (ARAT score; Individuals with ARAT score 0-38: Severely impaired; ARAT score 43-55: Mildly impaired). As shown in **Figure 2.5**, mildly impaired stroke patients continued to use their lesioned hemisphere while trying to move their affected hand in 2 days, 5 days and 10 days after stroke. However, the severely impaired patients developed a hyperactivity in both lesioned and non-lesioned hemisphere while trying to move their affected hand over the 10 days post stroke. (**Figure 2.5**)(Rehme, Fink et al. 2011).

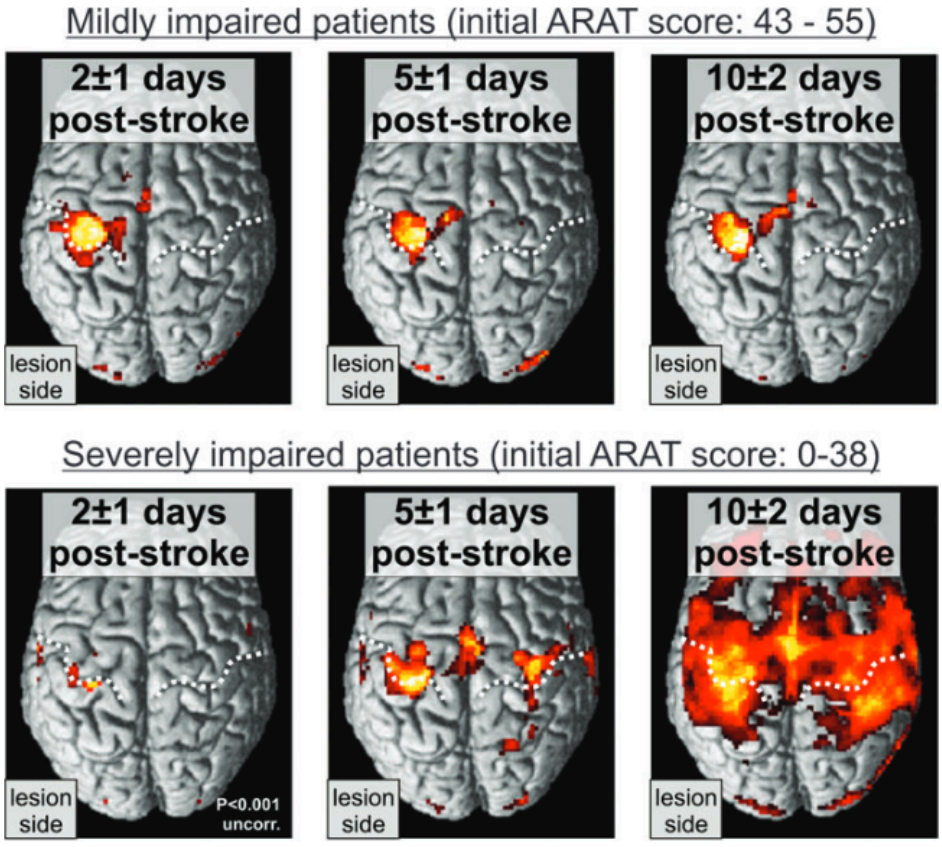

Figure 2.5. Brain activity in mildly impaired and severely impaired individuals with stroke during movement of affected hand in 2 days, 5 days and 10 days after stroke. Mildly impaired stroke patients continued using their lesioned hemisphere in 10 days post stroke. However, severely impaired stroke patients developed a hyperactivity in both lesioned and non-lesioned hemisphere in just 10 days post stroke, while trying to move their paretic hand. Adapted from Rehme et al. 2011.

Similarly, in a brain imaging study of individuals with stroke, Johansen-Berg research group found the bilateral motor cortex activity during a reaction time task was most common in more impaired individuals, while the contralateral activation was most common in less impaired individuals with stroke. (**Figure 2.6**)(Johansen-Berg, Rushworth et al. 2002). They also reported that decreased M1 laterality indices in these individuals were significantly correlated with their impairment severity (**Figure 2.6, right side**)(Johansen-Berg, Rushworth et al. 2002).

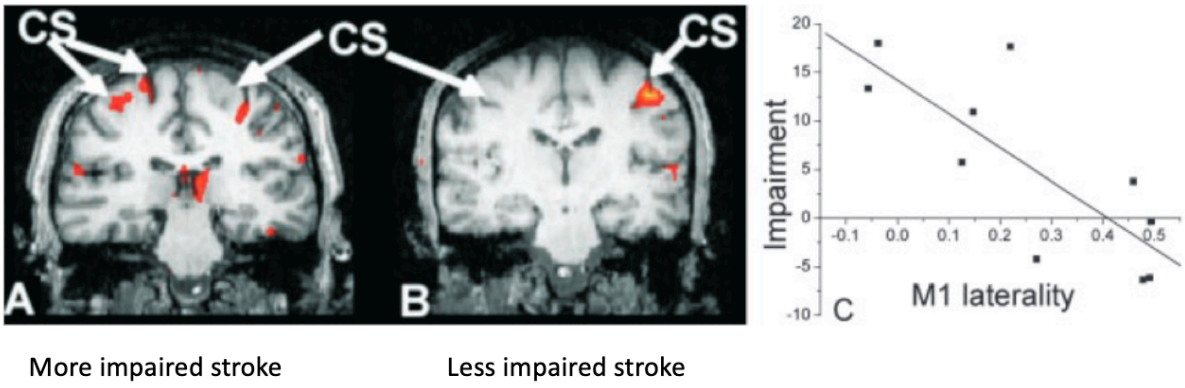

Figure 2.6. Brain activity during a reaction time task in individuals with stroke and its correlation with M1 laterality index. (Left Panel) The bilateral activity in motor cortex was present in more impaired stroke patient, while the less impaired individual continued using the contralateral motor cortex. Lesioned hemisphere is on the right. (**Right Panel)** The correlation between M1 laterality index and the impairment severity in individuals with stroke. Figure is adapted from Johansen-Berg et al., 2002.

Finally, in a high density electroencephalography (HD-EEG) study of 10 moderately to severely impaired individuals with stroke, McPherson et al. reported that a progressive increase of shoulder abduction load, which is associated with the expression of the flexion synergy, leads to a progressive increase in contralateral activity.(McPherson, Chen et al. 2018)

Main Descending and Ascending Brain Pathways

This section reviews the major descending and ascending brain pathways, which are essential in better understanding the research findings presented in the subsequent chapters.

Corticospinal tract

Corticospinal fibers originate predominantly from M1, but also from the premotor area, supplementary motor area, and somatosensory cortex (Dum and Strick 2002), They descend through internal capsule, pass through crus cerebri in the midbrain, and continue traveling through anterior portion of pons and medulla (pyramids) in brainstem (**Figure 2.7** and **Figure 2.8**). About 85% of the tract then crosses to the other side in the decussation of pyramids and makes the lateral corticospinal tract, which continues traveling contralaterally through lateral and posterior part of spinal cord and project to motoneurons and spinal interneurons to control the contralateral limb (**Figure 2.7** and **Figure 2.9**). (Haines 2004, Gray, Standring et al. 2016, Ebbesen and Brecht 2017).

About 15% of the corticospinal tract, which does not cross in the pyramidal decussation, projects ipsilaterally through medial and ventral portion of the spinal cord and makes the ventral corticospinal tract (**Figure 2.7** and **Figure 2.9**) (Haines 2004, Gray, Standring et al. 2016). Ventral corticospinal tract is believed to primarily innervate axial muscles (Zaaimi, Soteropoulos et al. 2018).

It is noteworthy to mention that although all the current anatomical atlases agree on this division of corticospinal tract (about 85% lateral corticospinal and 15% ventral corticospinal), a detailed investigation of termination of these tracts in spinal cord in rhesus monkeys has found a different pattern of projections. (Rosenzweig, Brock et al. 2009). Tracing the corticospinal tracts in cervical

spinal cord in monkeys, Rosenzweig et al. has reported the 87% of this tract to decussate and descend through the contralateral dorsolateral spinal cord. However, 11% of CST axons projected through the dorsolateral spinal cord ipsilaterally, and only 2% projected through the ipsilateral ventromedial CST.

Corticospinal tract is the primary voluntary descending motor tract with the fastest conduction velocity time, and synapses directly onto alpha motor neurons that drive muscle activation. However, it is noteworthy to mention that majority of corticospinal tract neurons which initiate from motor cortices do not synapse directly on motoneurons, but to spinal cord interneurons which have inhibitory projections to motoneurons (Ebbesen and Brecht 2017)

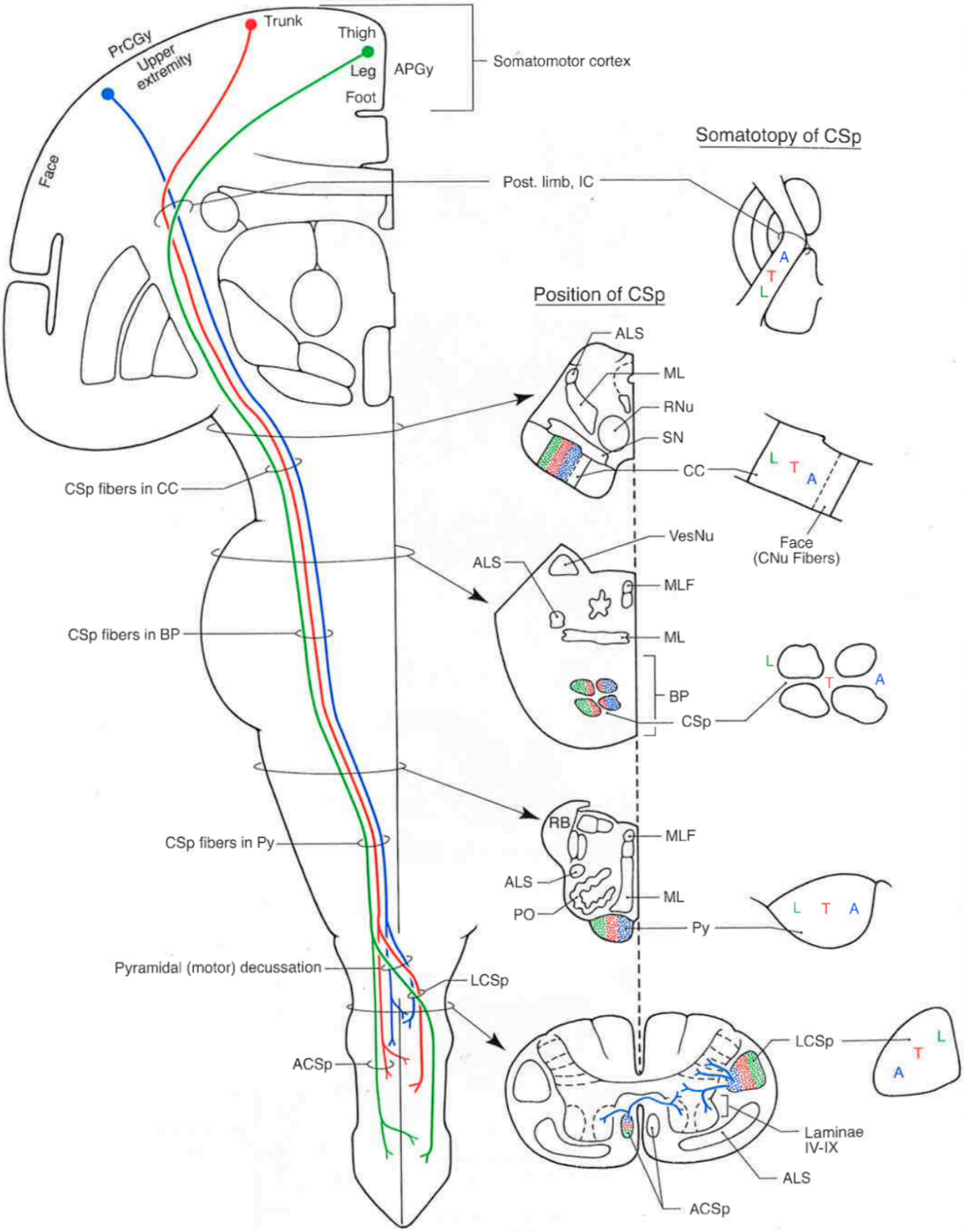

Figure 2.7. Corticospinal pathway in brain and brainstem. Figure adapted from Duane Haines' Anatomy, 7th edition.

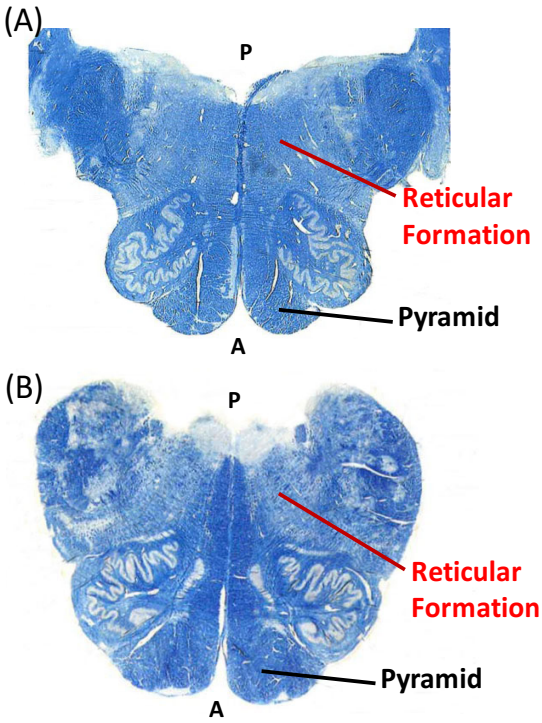

Figure 2.8. Location of Pyramids and Reticular nuclei on pontomedullary junction of brainstem (A) and medulla (B). Figure adapted from Gray's anatomy, 2016, Chapter 21, with modification to only show the location of pyramids and reticular formation.

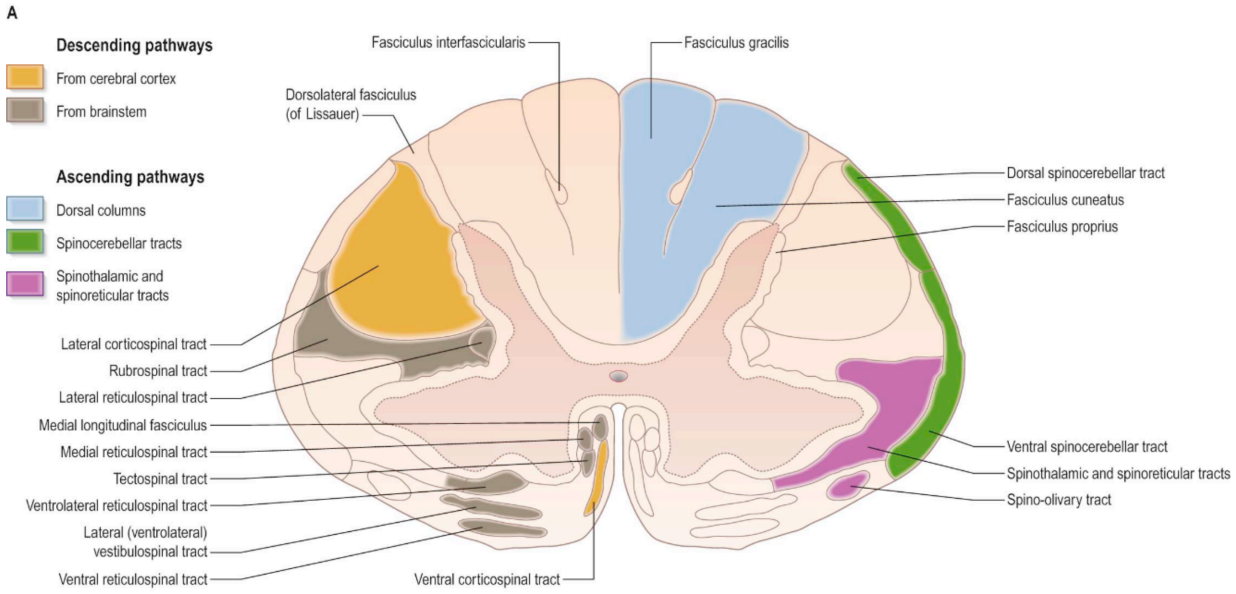

Figure 2.9. Atlas of spinal cord pathways. The approximate positions of fiber tracts in spinal cord at mid-cervical level. Figure adapted from Grays' Anatomy, 2016, Chapter 20.

Cortico-reticulospinal tract

The cortico-reticulospinal tract also originates from the motor cortices (M1, Premotor area, supplementary motor area), descends through internal capsule, and passes through crus cerebri in the midbrain. These fibers then project in the reticular formations in medial and posterior section of pons and medulla. (**Figure 2.10** and **Figure 2.8**). From there, three nuclei of reticular formation in the pons (Oral pontine reticular nucleus, Pontine tegmental reticular nucleus, and Caudal pontine reticular nucleus) are the source of the medial reticulospinal tract and project largely ipsilaterally through medial and ventral portion of spinal cord. (**Figure 2.10**, **Figure 2.9**, **Figure 2.11**). (Haines 2004, Paxinos, Xu-Feng et al. 2012, Gray, Standring et al. 2016).

However, the Gigantocellular nucleus of reticular formation, located in the pontomedullary junction, is believed to be the source of the lateral reticulospinal tract, which descends bilaterally through lateral portion of spinal cord. (**Figure 2.10**, **Figure 2.9**, **Figure 2.11**). (Fukushima, Peterson et al. 1979, Haines 2004, Paxinos, Xu-Feng et al. 2012, Gray, Standring et al. 2016).

As shown in the **Figure 2.11**, the reticular formation is a collection of 14 nuclei in the brainstem, divided on the basis of cytoarchitecture, chemoarchitectonic and functional criteria into three bilateral longitudinal columns: median; medial, containing mostly large reticular neurons; lateral, containing mostly small to intermediate neurons. The nuclei of the reticulospinal tracts belong to the medial column of reticular formation (shown in purple color in **Figure 2.11**).

It is noteworthy to mention that cortico-reticular tracts project bilaterally from motor cortices to the reticular formation. A recent study in monkeys has shown that corticobulbar projections from premotor area and supplementary motor area tend to end mainly ipsilaterally in reticular nuclei,

while the corticobulbar projections from motor cortex (M1) end contralaterally in reticular nuclei (Fregosi, Contestabile et al. 2017).

Although reticulospinal tracts are mainly involved with postural control and projecting into proximal muscles, they are shown to project to upper extremity through monosynaptic and disynaptic connections as well (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson, Buford et al. 2004, Davidson and Buford 2006, Riddle, Edgley et al. 2009, Baker 2011). The reticulospinal tract connections are reported to be much weaker than corticospinal tract connections (Riddle, Edgley et al. 2009, Baker 2011), and these tracts tend to have a longer latency and a higher threshold in response to TMS than the corticospinal tract.

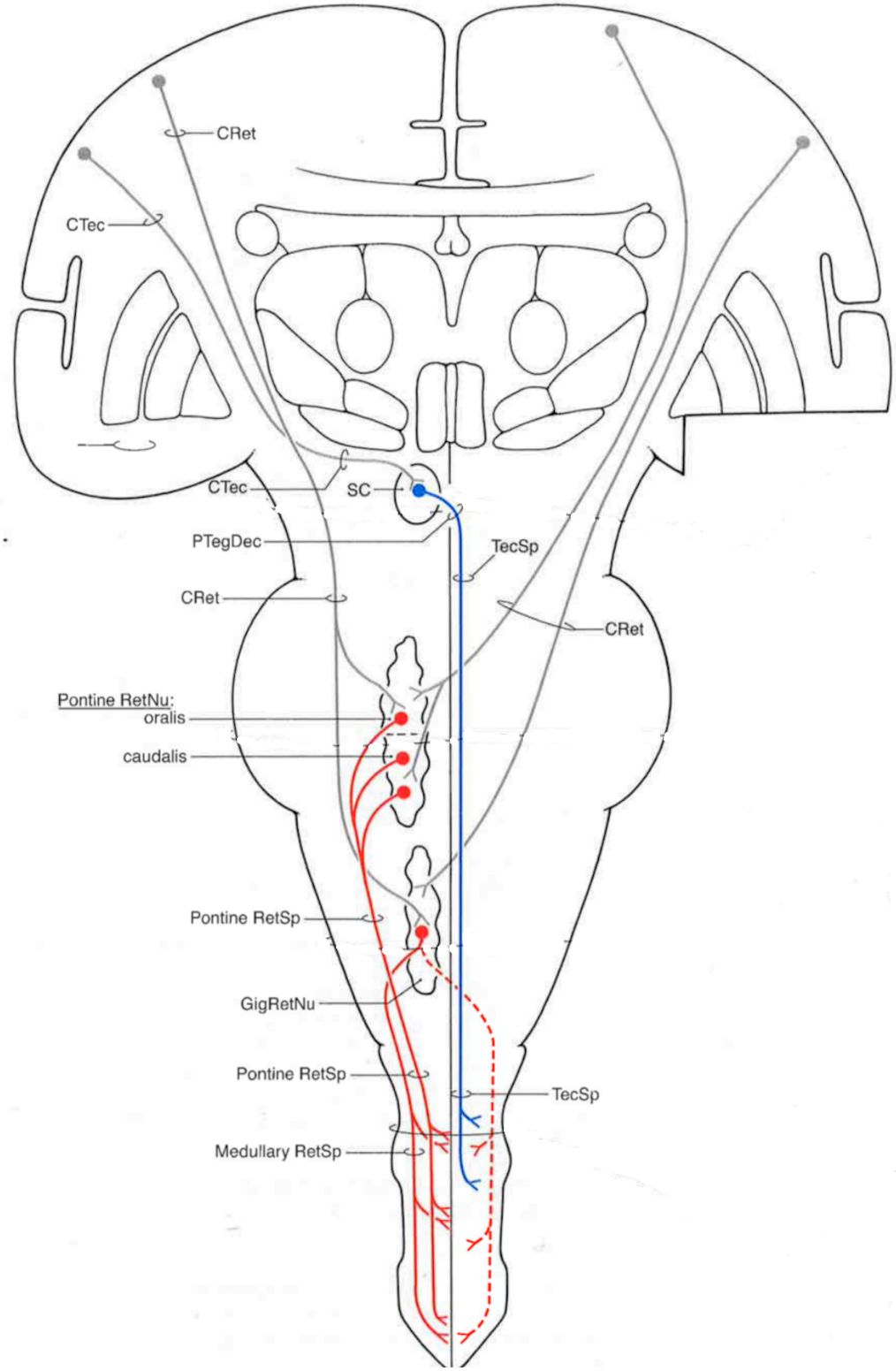

Figure 2.10. Cortico-reticulospinal and Tectospinal pathways in brain and brainstem. Figure adapted from Duane Haines' Anatomy, 7th edition.

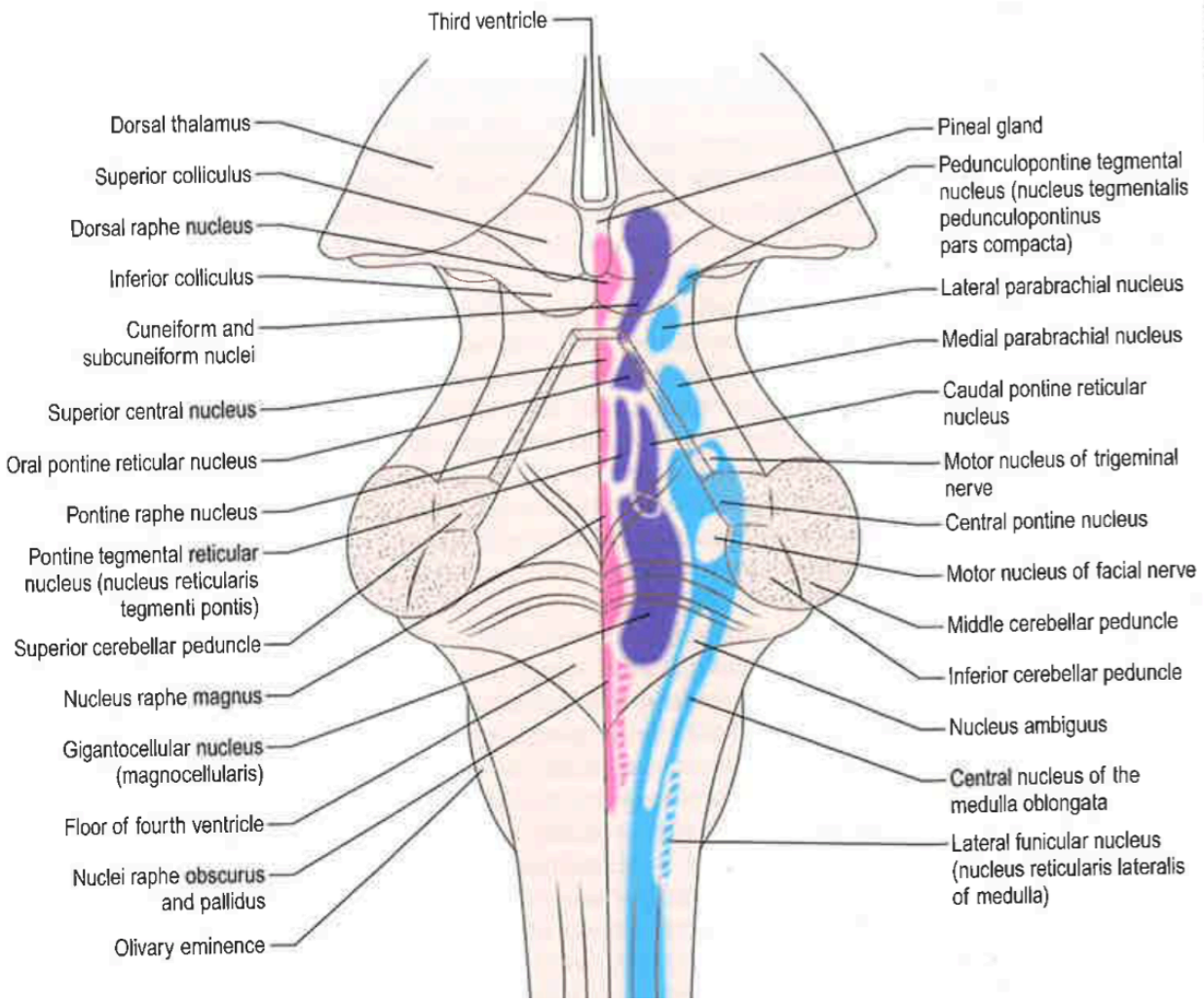

Figure 2.11. Reticular Formation Nuclei. Approximate location of nuclei of the reticular formation. Nuclei of the median and paramedian column shown in pink, the medial column shown in purple, and lateral column nuclei shown in blue. Figure adapted from Henry Gray's Anatomy, 2016.

Tectospinal tract

Also shown in **Figure 2.10**, Tectospinal track originates from neurons in the deeper layer of superior colliculi (Tectum) and descends ventral to the medial longitudinal fasciculus throughout the brainstem, crosses in the posterior (dorsal) tegmental decussation, and descends to the cervical segments in the ventral and medial part of spinal cord (**Figures 2.10** and **Figure 2.9**). Superior colliculus receives projections from several regions of cerebral cortex, including frontal, parietal and temporal cortices, but the most highly organized corticotectal projections arise from the visual cortex. Part of these corticotectal projections pass through internal capsule (**Figure 2.10**). (Haines 2004, Gray, Standring et al. 2016).

Rubrospinal tract

Rubrospinal fibers originate from red nucleus in the midbrain. They cross in the anterior (ventral) tegmental decussation and distribute to all spinal levels but mostly cervical levels (**Figure 2.12**). Rubrospinal tract passes through posterior and medial part of spinal cord (**Figure 2.9** and **Figure 2.12**). (Haines 2004, Gray, Standring et al. 2016).

Corticorubral fibers initiate from motor cortex, cross through internal capsule and project to red nucleus. Cells in the dorsomedial regions of the red nucleus receive input from upper extremity areas of the motor cortex and project to cervical spinal cord, but the cells in ventrolateral areas of the nucleus receive some fibers from lower extremity areas of the motor cortex and are believed to be projecting in spare numbers to lumbosacral levels. (Haines 2004, Gray, Standring et al. 2016).

Vestibulospinal tract

As shown in **Figure 2.12**, medial and lateral vestibulospinal tracts originate from medial and lateral vestibular nuclei, respectively. Medial vestibulospinal tract is a part of descending medial longitudinal fasciculus, and projects to medial and ventral part of cervical spinal cord, primarily ipsilaterally. Lateral vestibulospinal tract projects ipsilaterally to lumbar levels of ventral spinal cord (**Figure 2.12** and **Figure 2.9**) (Haines 2004, Gray, Standring et al. 2016). Both vestibulospinal tracts are involved in maintaining balance with postural adjustment and head movements. (Iwamoto, Perlmutter et al. 1996, Perlmutter, Iwamoto et al. 1998).

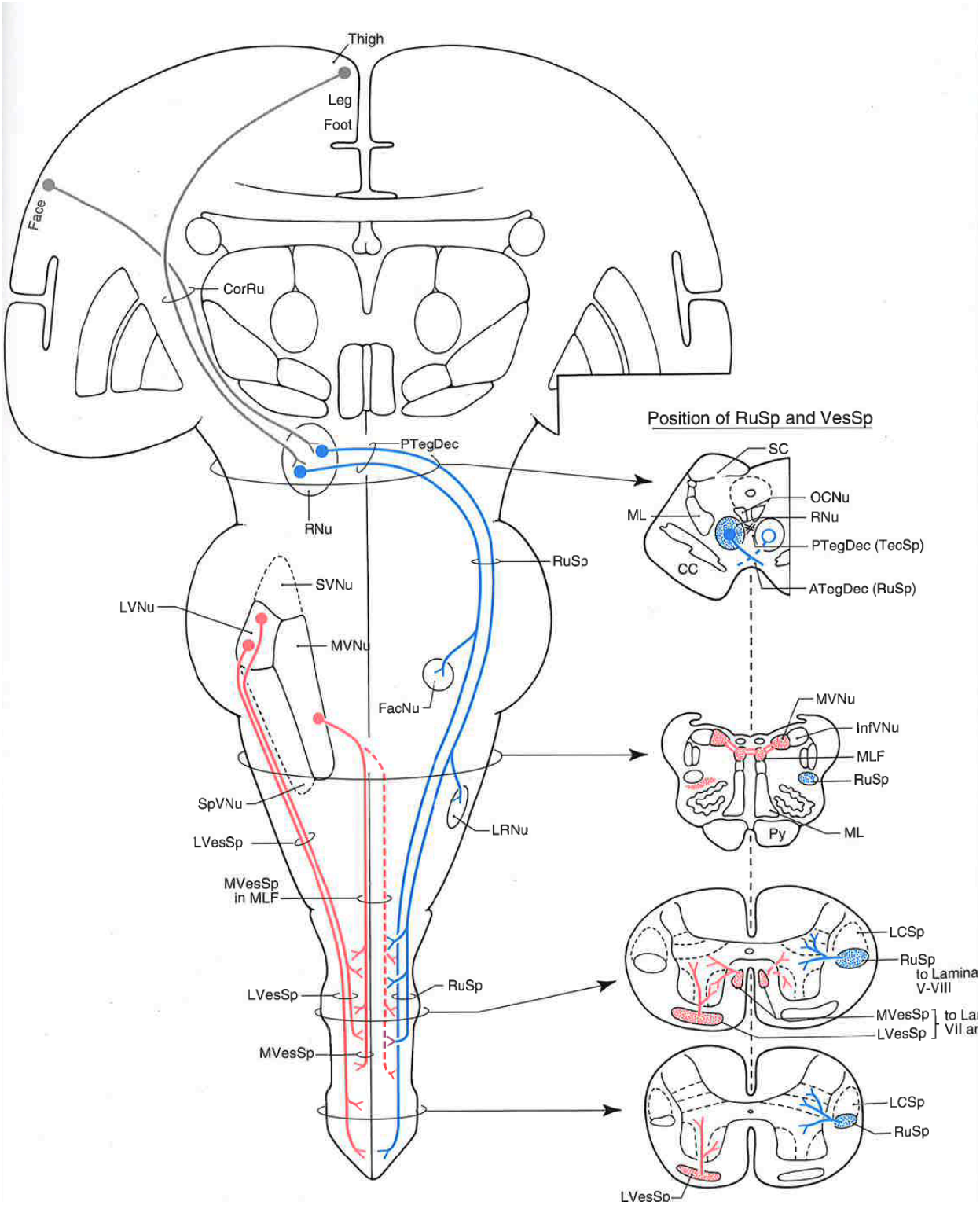

Figure 2.12. Rubrospinal and Vestibulospinal pathways in brainstem. Figure adapted from Duane Haines' Anatomy,7th edition.

Dorsal Column Medial Lemniscus pathway

Dorsal column medial lemniscus (DCML) is an ascending pathway which transfers sensory (touch and proprioception) information from body to somatosensory cortex. Cuneate fasciculus and gracile fasciculus pass through posterior portion of spinal cord and project to cuneate nucleus and gracile nucleus in lowest part of medulla. From there, the medial lemniscus continues ascending from medulla rostrally toward mesencephalic-diencephalic junction and projects to thalamus. The pathway continues ascending and projecting from the thalamus to the somatosensory cortex. (**Figure 2.9**, **Figure 2.13**) (Haines 2004, Gray, Standring et al. 2016).

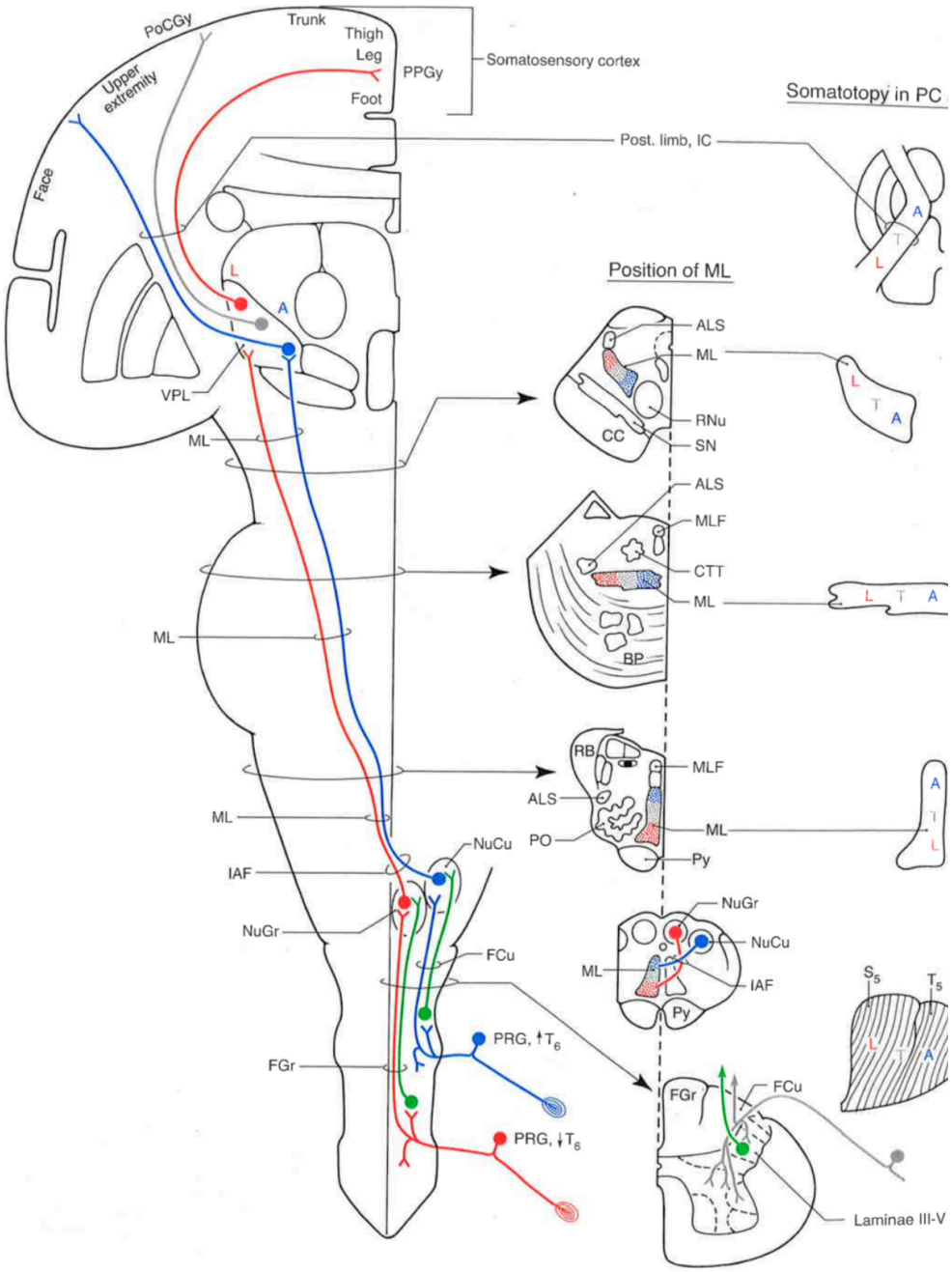

Figure 2.13. Dorsal Column Medial Lemniscus pathway in brain and spinal cord. Figure adapted from Duane Haines' Anatomy,7th edition.

3. BRAINSTEM AND SPINAL CORD STRUCTURAL MRI IDENTIFIES ALTERED SENSORIMOTOR PATHWAYS POST-STROKE

This chapter has previously been published.

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Abstract

Damage to the corticospinal tract is widely studied following unilateral subcortical stroke, whereas less is known about changes to other sensorimotor pathways. This may be due to the fact that many studies investigated morphological changes in the brain, where the majority of descending and ascending brain pathways are overlapping, and did not investigate the brainstem where they separate. Moreover, these pathways continue passing through separate regions in the spinal cord. Here, using a high-resolution structural MRI of both the brainstem and the cervical spinal cord, we were able to identify a number of microstructurally altered pathways, in addition to the corticospinal tract, post stroke. Moreover, decreases in ipsi-lesional corticospinal tract integrity and increases in contra-lesional medial reticulospinal tract integrity were correlated with motor impairment severity in individuals with stroke.

Introduction

Subcortical unilateral strokes affecting the internal capsule or basal ganglia are the most common of all strokes and usually result in hemiparesis of the contralateral arm and leg. Previous human brain imaging studies of unilateral subcortical stroke have frequently reported damage to the corticospinal tract.(Werring, Toosy et al. 2000, Thomalla, Glauche et al. 2004, Ward, Newton et al. 2006, Lindenberg, Renga et al. 2010) Cross-sectional studies also reported this damage to be associated with greater motor deficits, as well as, worse motor recovery in these individuals.(Watanabe, Honda et al. 2001, Thomalla, Glauche et al. 2005, Moller, Frandsen et al. 2007, Puig, Pedraza et al. 2010) However, less is known about other altered sensorimotor pathways post unilateral stroke and their role in motor impairments. An important reason for this lack of knowledge is that previous studies have only investigated the morphological changes in the brain, where the majority of descending and ascending brain pathways (e.g. corticospinal tract, cortico-bulbospinal tracts, dorsal column medial lemniscus) mostly overlap and are not distinguishable with currently available imaging techniques. Sensorimotor pathways, in fact, delineate from each other in the brainstem.(Haines 2004, Mai and Paxinos 2011, Vanderah and Gould 2015, Gray, Standring et al. 2016) Moreover, these tracts continue travelling through separate regions in the spinal cord.(Haines 2004, Gray, Standring et al. 2016)

It is also noteworthy to mention that numerous functional neuroimaging studies of stroke have reported increased neural activity in motor cortices of both lesioned and non-lesioned hemisphere during hand/arm movement.(Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Ward, Brown et al. 2003, Grefkes, Nowak et al. 2008) They have also reported that the more severe the impairment, the greater the activity in the contralesional hemisphere compared to the ipsilesional (i.e. a shift of activity to non-lesioned hemisphere).(Cramer, Nelles et al. 1997, Cao, Olhaberriague

et al. 1998, Cramer, Finklestein et al. 1999, Cramer, Moore et al. 2000, Marshall, Perera et al. 2000, Carey, Kimberley et al. 2002, McPherson, Chen et al. 2018) However, it is still unclear what descending motor pathway allows the contralesional motor cortex to control the ipsilateral paretic arm, although one proposed idea from human and animal studies suggests(Dewald, Pope et al. 1995, Schwerin, Dewald et al. 2008, Baker, Zaaimi et al. 2015, Herbert, Powell et al. 2015, Zaaimi, Soteropoulos et al. 2018) brainstem ipsilaterally projecting motor pathways (i.e. reticulospinal tracts or vestibulospinal tracts) may play this role.

Based on magnetic resonance imaging (MRI), diffusion Tensor Imaging (DTI) can probe white matter microstructure by providing information on the direction and degree of water diffusivity in white matter tracts.(Mukherjee, Berman et al. 2008) The degree of anisotropy (fractional anisotropy: FA) of water in the white matter tracts reflects their level of integrity.(Virta, Barnett et al. 1999, Pierpaoli, Barnett et al. 2001) Evidence from human brain imaging studies suggests that white matter integrity could change with experience. For example, damage or degeneration to a tract is shown to be associated with a decrease in its white matter integrity (fractional anisotropy).(Werring, Toosy et al. 2000, Thomalla, Glauche et al. 2004, Ward, Newton et al. 2006, Kraus, Susmaras et al. 2007, Vernooij, de Groot et al. 2008, Heise, Filippini et al. 2011) Likewise, training-induced or experience-dependent increases in white matter integrity have also been reported in humans.(Bengtsson, Nagy et al. 2005, Scholz, Klein et al. 2009, Lövdén, Bodammer et al. 2010) Moreover, recent developments in MRI of the spinal cord have opened new doors to further studies of the human nervous system.(Renoux, Facon et al. 2006, Cohen-Adad, El Mendili et al. 2011, Martin, Aleksanderek et al. 2016) High resolution DTI of cervical spinal cord and novel analyses approaches provide means of investigating the spinal cord white matter tracts. DTI's ability to determine long-term changes in white matter structure and its recent developments

in the cervical spinal cord(Renoux, Facon et al. 2006, Cohen-Adad, El Mendili et al. 2011, Martin, Aleksanderek et al. 2016) makes this an excellent method for investigating altered sensorimotor pathways in the brainstem and spinal cord in individuals with chronic stroke.

To this end, we used high resolution structural MRI of the brainstem and cervical spinal cord and unbiased voxel-wise analyses to identify all altered sensorimotor pathways post unilateral subcortical stroke. Subsequently, the link between microstructural changes in pathways and paretic upper limb motor impairments (Fugl-Meyer Assessment) was examined in the stroke participants. It was hypothesized that individuals with stroke would show reduced white matter integrity in a number of sensorimotor pathways travelling through subcortical regions of lesioned hemisphere, in addition to the corticospinal tract. Furthermore, an increased white matter integrity in some brainstem ipsilaterally projecting pathways from the non-lesioned hemisphere was expected. Our results indicate a significant decrease of white matter integrity in corticospinal tract, lateral and medial reticulospinal tracts, descending medial longitudinal fasciculus, tectospinal tract and cuneate and gracile fasciculi related to the lesioned hemisphere. Furthermore, the results from brainstem and cervical spinal cord DTI analyses indicate a significant increase in the white matter integrity of medial reticulospinal tract at the side of contralesional hemisphere which projects ipsilaterally to the paretic (contralesional) limbs. The decreased white matter integrity of ipsi-lesional corticospinal tract and increased white matter integrity of contra-lesional medial reticulospinal tract are correlated with upper limb impairment severity in individuals with stroke.

Methods

Participants

36 individuals with chronic hemiparetic unilateral stroke in internal capsule (ischemic or hemorrhagic) and 32 age-matched gender-matched healthy controls with no neurological or movement disorder were recruited to participate in this study. Stroke subjects were mildly to severely impaired and all sustained a unilateral brain lesion at least 3 years prior to participation in the study. Individuals with stroke were recruited through the Northwestern Clinical Neuroscience Research Registry, Ischemic Stroke Registry and approved flyers. This study was approved by the Institutional Review Board of Northwestern University, and all subjects provided written informed consent prior to participation.

Clinical Assessment

For each stroke individual, upper extremity motor assessment (Fugl-Meyer Assessment: FMA(Fugl-Meyer, Jaasko et al. 1975)) was performed by a licensed physical therapist. FMA is a performance-based impairment index assessing motor functioning, joint functioning, sensation and balance in upper limb. Higher values indicate higher motor abilities (less impairment) in these individuals.

Scanning parameters

Brainstem and cervical spinal cord (C2-C5) MRI scans were acquired at Northwestern University Center for Translational Imaging on a 3T Siemens Prisma scanner with a 64-channel head coil. Brainstem T1-weighted anatomical scans were acquired using an MPRAGE sequence with voxel size = 0.8 × 0.8 × 0.8 mm, repetition time = 9.9 ms, echo time = 4.7 ms, flip angle = 2°, field of view = 256 mm. Brainstem diffusion weighted images (DWI) were collected using spin-echo echo-

planner imaging with the following parameters: voxel size = 1.5 isotropic, TR = 3620 ms, TE = 68.4 ms, matrix size = 150 × 150, FOV = 222 × 222 mm^2, slice thickness = 1.5 mm, interslice gap = 0 mm, and number of slices covering whole brain and brainstem = 108. The sequence consisted of diffusion weighting of 1,000 s/mm^2 in 60 different directions and 8 scans with no diffusion weighting (b = 0 s/mm^2).

Cervical spinal cord T2-weighted anatomical scans were collected with the resolution = 0.8 × 0.8 × 0.8, TR = 1500 ms, TE = 100 ms, FOV = 256 × 256 mm^2, number of slices = 64, and scan duration = 4:35 min. Cervical spinal cord DWI scans were collected from level C2-C5 with 4 acquisitions averaged offline with the following parameters: in-plane resolution = 0.8 x 0.8, TR = ~ 600 ms (depend on heart-beat), TE = 61 ms, slice thickness = 5 mm, interslice gap = 0 mm, FOV = 86 mm^2, number of slices = 15, b-value = 1000 in 30 directions, 4 images with b = 0, and scan duration = 6:35 min. For a better gray matter - white matter segmentation of spinal cord, we also collected a T2*-weighted scan that used multi-echo recombined gradient echo with 3 echoes at 5, 10 20 ms, TR = 769 ms, in-plane resolution = 0.4 x 0.4 mm^2, slice thickness = 5 mm, number of slices = 15, and the scan duration = 5:11 min.

Brainstem DTI data preprocessing

The DWIs were pre-processed using the FMRIB Software Library version 5.0.11 (FSL: Oxford Centre for Functional MRI of the Brain, UK; http://www.fmrib.ox.ac.uk/fsl/).(Behrens, Woolrich et al. 2003, Smith, Jenkinson et al. 2004, Woolrich, Jbabdi et al. 2009, Jenkinson, Beckmann et al. 2012) Raw DTI data were corrected for eddy current distortions using the Eddy Current Correction (ECC) tool and for motion using McFlirt Motion Correction tool. The FMRIB Brain Extraction Tool (BET(Smith 2002)) was then used for skull stripping. Diffusion tensors were fitted at each

voxel and fractional anisotropy (FA) images were created using the DTIFIT tool of FMRIB FDT toolbox-version 5.0.(Behrens, Woolrich et al. 2003)

Brainstem Tract-based spatial statistics analysis

Majority of stroke participants had lesion in the left hemisphere. For those individuals with lesions in the right hemisphere, FA maps were flipped so that all subjects had lesions in the left hemisphere for group analysis. Voxel-wise statistical analysis of the DTI FA images was carried out using Tract-Based Spatial Statistics (TBSS(Smith, Jenkinson et al. 2006, Andersson, Jenkinson et al. 2007, Andersson, Jenkinson et al. 2007)) in FSL. First, all subjects' FA images were aligned to the standard 1x1x1 mm MNI152 template in FSL, using the non-linear registration tool (FNIRT). Next, the mean FA image was created and thinned to create a mean FA skeleton representing the centers of all tracts, using a threshold of 0.25. Each subject's aligned FA map was then projected onto this skeleton resulting in each subject's skeletonised FA image, and then masked by brainstem standard template to limit the analysis to the brainstem.

Group differences in voxel-wise FA were examined by entering each subjects' brainstem skeletonised FA into a general linear model (two-sample t-test) design matrix with non-parametric permutation testing, using the Randomize tool in FSL (50,000 permutations). The results were thresholded at p=0.05 (corrected), using the threshold-free cluster enhancement (TFCE) option to find clusters without setting an initial cluster level.(Smith and Nichols 2009)

To further test any association between these group differences and motor impairment in individuals with stroke, we ran a within-group voxel-wise correlation between stroke participants' brainstem skeletonized FA masked by group differences and each subject's clinical assessment of

performance. Results were corrected at p = 0.05 using the threshold-free cluster enhancement option to find the clusters with significant positive or negative correlation with motor impairment level in stroke individuals.

Spinal cord data preprocessing

All spinal cord images were visually inspected and excluded if motion, low signal, or artifacts were present. Data preprocessing was done using spinal cord toolbox version 3.2.2 (SCT; https://www.nitrc.org/projects/sct/).(De Leener, Levy et al. 2017) Automatic spinal cord segmentation was performed on T2WI, T2*WI, and DWI scans.(De Leener, Kadoury et al. 2014) Images were nonlinearly registered to the MNI-Poly-AMU template/atlas in SCT.(Levy, Benhamou et al. 2015) T2*WI image, which has a strong contrast between gray matter (GM) and white matter (WM), was further analyzed with automatic segmentation of GM and WM, and was used to refine the registrations to the template.

DTI data were corrected for motion and registered to the template. Fractional anisotropy (FA) maps were then created for each subject and registered to the template, using the same refined registration matrix.

Spinal cord DTI voxel-wise statistical analyses

For those individuals with lesions in the right hemisphere (left paretic side), spinal cord FA maps were flipped so that all subjects included in the group analysis had the paretic side presented on right. Statistical analysis of spinal cord DTI data was conducted using SPM12 (Statistical Parametric Mapping; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software on Matlab 2018a (https://www.mathworks.com/products/matlab.html). Statistical analysis was done by entering the individual subject FA maps into between group two-sample t-test analyses. Since

some subjects had a lower SNR at the vertebral level C5, the between group analysis was limited to the C2-C4 level. Voxel-wise p = 0.005 was applied and the cluster-level corrected at p = 0.05.

Results

Demographics

Of the subjects recruited, 5 stroke participants and 1 healthy control were excluded from the study due to brainstem, bilateral or cortical lesions, or poor-quality image. Therefore, the final sample consisted of 31 individuals with stroke and 31 healthy controls. Demographics of two groups are presented in **Table 3.1.** The stroke group had more African American participants than the controls group ($x^2 = 8.72$, p = 0.01). The two groups were well-matched on age and gender.

Table 3.1. Demographic Characteristics

Variable	Controls		Stroke		x^2	df	p
N	31		31				
Gender (male:female)	18:13		20:11		0.27	1	0.602
Ethnicity (White:AA:Other)	26:4:1		15:13:3		8.72	4	0.012
Affected Side of Body (Left:Right)	--		15:16		--	1	--
	Mean	**SD**	**Mean**	**SD**	**t**	**df**	**p**
Age	61.61	9.45	59.83	8.97	0.76	60	0.452
Years Since Onset	--	--	11.48	7.65	--	30	--
Fugl Meyer *	--	--	31.00	15.78	--	29	--

* Fugl Meyer score of one individual with stroke is missing.

Brainstem white matter integrity in stroke

Tracts with significant white matter integrity changes in the brainstem of individuals with stroke compared to controls are presented in **Figure 3.1** (threshold-free cluster enhancement p = 0.05). In the brainstem at the side of lesioned hemisphere, we observed decreased white matter integrity in corticospinal and bulbospinal tracts, including medial reticulospinal, lateral reticulospinal, and

medial longitudinal fasciculus (i.e. descending medial vestibulospinal tract) in individuals with stroke compared to controls (**Figure 3.1,** tracts in red-yellow color). Consistent with our hypotheses, at the side of the non-lesioned hemisphere, an increased white matter integrity in individuals with stroke was found in the medial reticulospinal tract, which receives projections from non-lesioned motor cortices (**Figure 3.1,** tracts in blue-light blue color). The locations of sensorimotor tracts in the brainstem were determined with the help of Gray's anatomy(Gray, Standring et al. 2016), Haines' neuroanatomy(Haines 2004), and Paxinos' brainstem anatomy.(Mai and Paxinos 2011, Paxinos, Xu-Feng et al. 2012) **Figure 3.1b** shows the location of tracts on the brainstem atlas, focusing on the sensorimotor pathways under investigation, for simplicity.

We then tested for any associations between these white matter alterations and clinical motor assessments in the paretic upper limb (Fugl-Meyer Motor Assessment score). **Figure 3.2** illustrates the tracts with significant correlation between white matter integrity changes and motor impairment in individuals with stroke. Decreases in corticospinal tract integrity at the lesioned hemisphere and increases in medial reticulospinal tract integrity at the non-lesioned hemisphere in individuals with stroke were showed to be significantly correlated with their motor impairment severity (**Figure 3.2**).

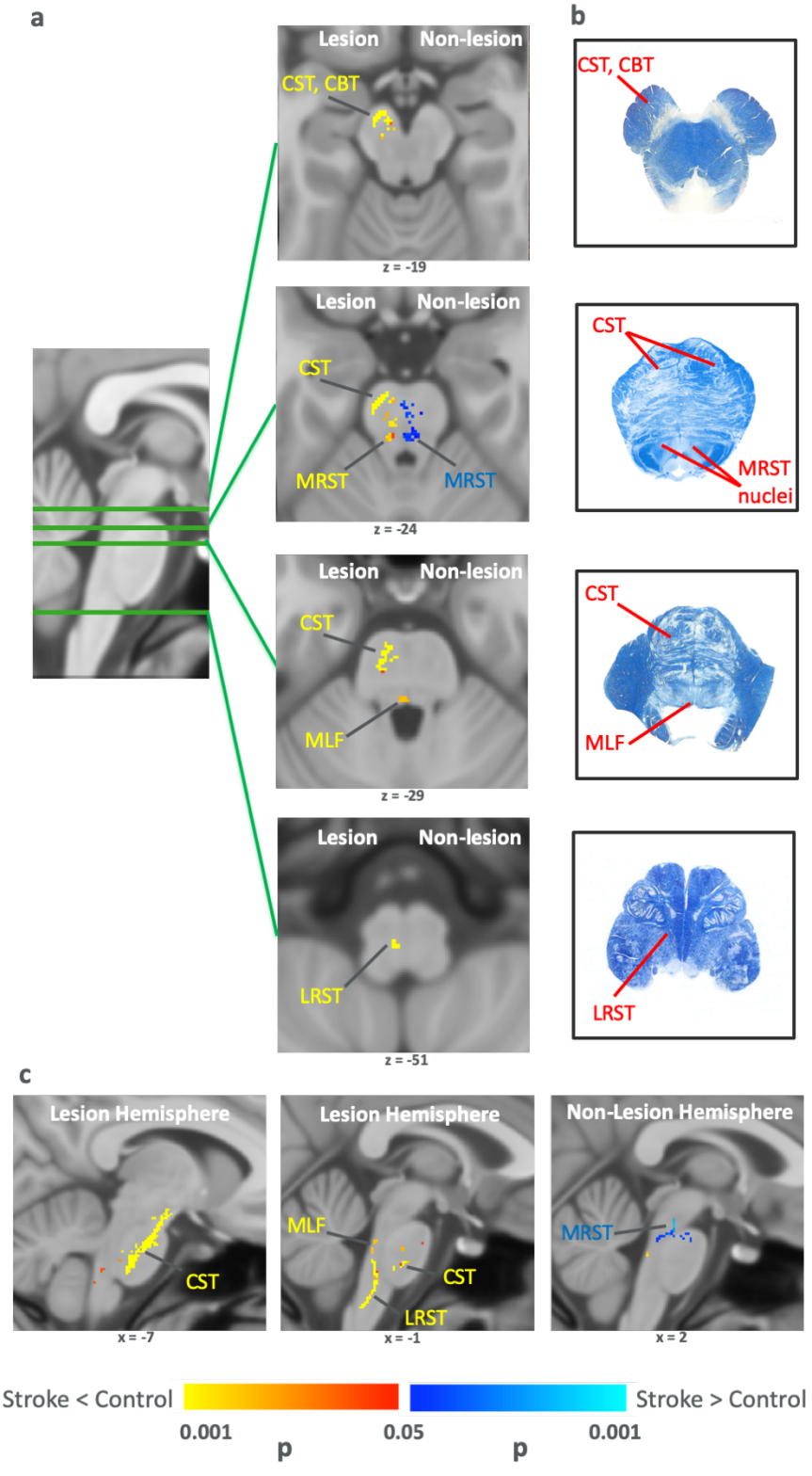

Figure 3.1. Tracts with white matter integrity changes in brainstem in individuals with stroke compared to controls. **(a)** Axial view of the tracts with significant decrease (red-yellow) or increase (blue) in white matter integrity in individuals with stroke compared to controls. corticospinal tract (CST), corticobulbar tract (CBT), medical reticulospinal tract (MRST), lateral reticulospinal tract (LRST), and medial longitudinal fasciculus (MLF) of the lesioned hemisphere showed significant decreased white matter integrity in individuals with stroke. Medial reticulospinal tract (MRST) of non-lesioned hemisphere showed significant increased white matter integrity in individuals with stroke compared to controls. **(b)** Brainstem atlas adapted from Gray's anatomy and Haines' neuroanatomy with modification for simplicity, showing the location of tracts. **(c)** Sagittal view of the tracts with significant decrease (red-yellow) or increase (blue). (statistical test: two-sample t-test with non-parametric 50,000 permutation. Using the threshold-free cluster enhancement with corrected $p<0.05$). Figure adapted from Karbasforoushan et al., 2019

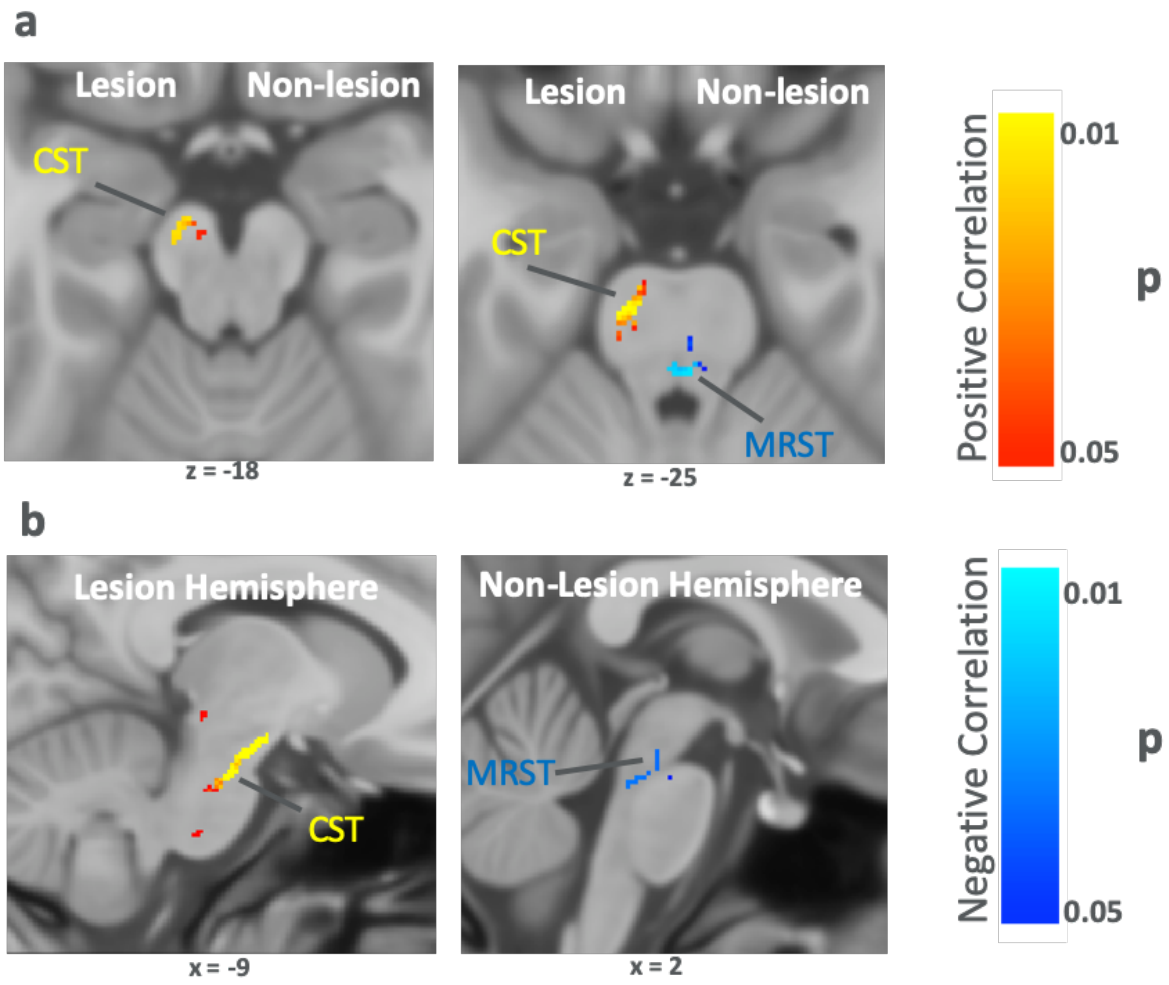

Figure 3.2. Tracts with significant correlation between white matter integrity changes and motor impairment. (a) Axial view of the tract with positive correlation (red-yellow) and negative correlation (blue) between white matter integrity and motor impairment (Fugl-Meyer assessment, FMA) in individuals with stroke. Corticospinal tract (CST) of the lesion hemisphere showed significant positive correlation with impaired motor performance in individuals with stroke. Medial reticulospinal tract (MRST) at the side of non-lesioned hemisphere showed significant negative correlation with impaired motor performance in individuals with stroke. **(b)** Sagittal view of the tracts with significant positive (red-yellow) or negative (blue) correlation between white matter integrity and impaired motor performance in individuals with stroke. (Statistical test: within-group voxel-wise correlation analysis, using the threshold-free cluster enhancement and $p< 0.05$). Figure adapted from Karbasforoushan et al., 2019.

Spinal cord white matter integrity in stroke

Figure 3.3 shows the tracts with significant white matter integrity changes in cervical spinal cord in individuals with stroke compared to the controls. The results from the cervical spinal cord analysis indicated a significant decrease in white matter integrity of lateral corticospinal tract, tectospinal tract, and cuneate and gracile fasciculi at the paretic (contralesional) side in individuals with stroke. The stroke participants also demonstrated a significantly decreased white matter integrity in a few smaller clusters, which, to our current knowledge of spinal cord pathways locations, appear to belong to the medial reticulospinal tract, medial longitudinal fasciculus, and medial corticospinal tract at the non-paretic side of body. Of note, these pathways project ipsilaterally from the lesioned hemisphere (**Figure 3.3A**, in red-yellow color). Consistent with results from the brainstem analyses, patients showed a significant increase in white matter integrity in a small cluster that, to our current knowledge of spinal cord pathways, belongs to the medial reticulospinal tract on paretic (contralesional) side, which projects ipsilaterally from the non-lesioned hemisphere (**Figure 3.3B**, in blue-light blue color). All resulted tracts are thresholded with a voxel-wise p value of 0.005 and corrected for cluster-size with a p value of 0.05. **Figure 3.3C** illustrates the high-resolution spinal cord white matter atlas derived from the Gray's anatomy atlas, adapted from Levy et al, 2015. (Levy, Benhamou et al. 2015)

Testing for any associations between these white matter differences in cervical spinal cord and clinical assessments of motor impairment in individuals with stroke, we found that the decreased white matter integrity of lateral corticospinal tract and increased white matter integrity of medial reticulospinal tract were correlated with motor impairment severity in these individuals (**Figure 3.3D**). In other words, a greater severity of motor impairment was correlated with a lower white

matter integrity of the lesioned lateral corticospinal tract and higher white matter integrity of the contra-lesional medial reticulospinal tract.

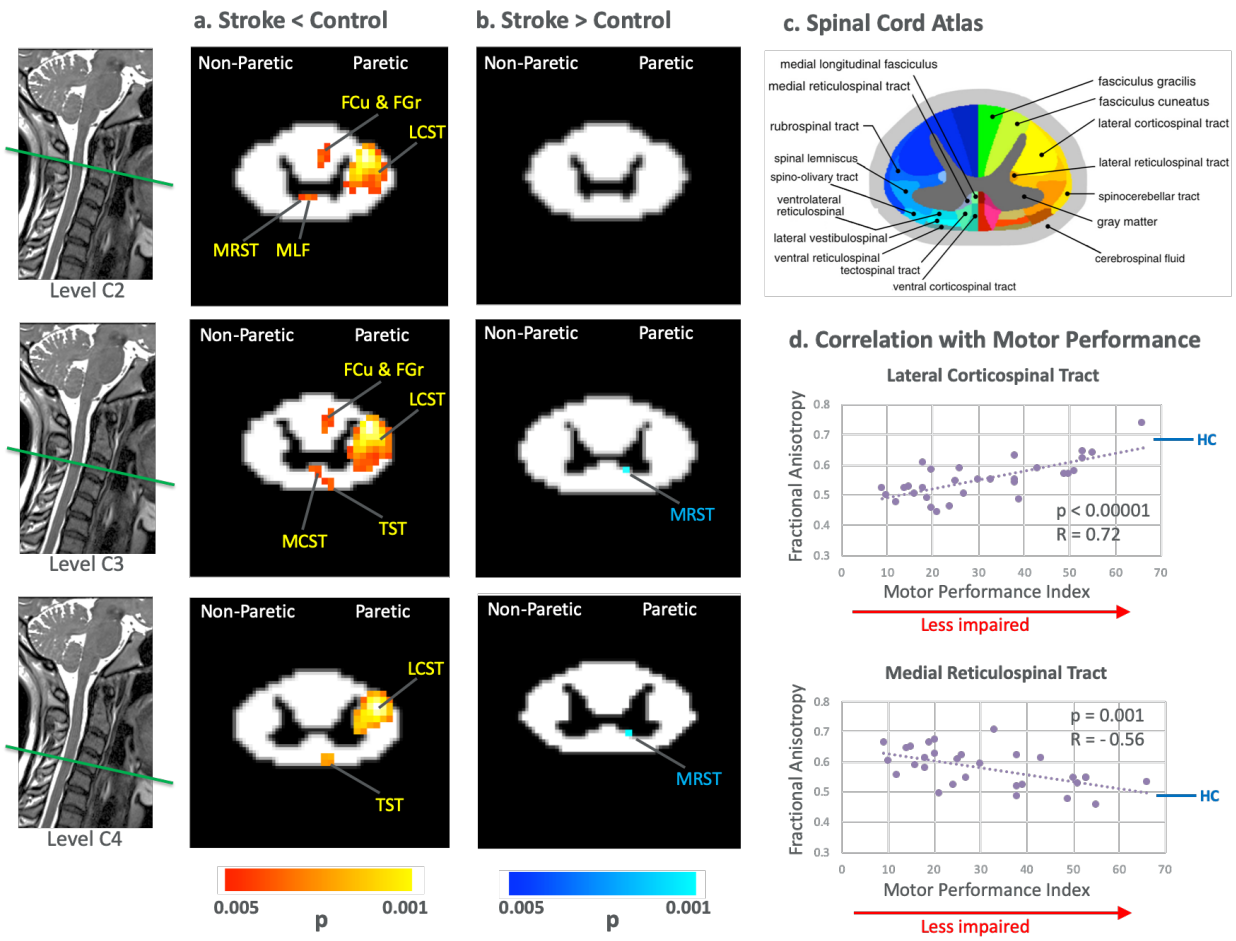

Figure 3.3. White matter integrity changes in spinal cord of individuals with stroke compared to controls. (a) Tracts with significant decrease (red-yellow) in white matter integrity (fractional anisotropy). When compared to controls, individuals with stroke had significant decrease in white matter integrity of lateral corticospinal tract (LCST), cuneate fasciculus (FCu), Gracile Fascicule (FGr) and tectospinal tract (TST) of the paretic side. These individuals also showed decrease white matter integrity in medial reticulospinal tract (MRST), medial longitudinal fasciculus (MLF) and medial corticospinal tract (MCST) of non-paretic side, which project ipsilaterally from the lesioned hemisphere. **(b)** Tracts with significant increase (blue) in white matter integrity. Medial reticulospinal tract of paretic side, which projects from non-lesioned motor cortices, had significant increased white matter integrity in individuals with stroke compared to controls. (Statistical test: between group two-sample t-test. Voxel-wise $p < 0.005$ was applied and the cluster-level corrected at $p = 0.05$). **(c)** High resolution spinal cord white matter atlas derived from the Gray's Anatomy atlas. **(d)** Correlation of significant white matter integrity changes in individuals with stroke with their motor impairment level. Decreases in lateral corticospinal tract in individuals with stroke had significant positive correlation with their impaired

motor performance. Increased in medial reticulospinal tract in individuals with stroke showed a negative correlation with their impaired motor performance. Paretic refers to the side of non-lesioned hemisphere (contralesional). Blue line with abbreviation HC indicates the mean of FA value in healthy controls for Lateral Corticospinal Tract (equal to 0.68) and Medial Reticulospinal Tract (equal to 0.49). FMA score is missing for one participant. Source data are provided as a Source Data file. Figure adapted from Karbasforoushan et al., 2019.

Discussion

Previous human brain imaging studies of unilateral subcortical stroke have frequently reported the damage to the corticospinal tract and its link with greater motor impairment.(Werring, Toosy et al. 2000, Watanabe, Honda et al. 2001, Thomalla, Glauche et al. 2004, Thomalla, Glauche et al. 2005, Ward, Newton et al. 2006, Moller, Frandsen et al. 2007, Lindenberg, Renga et al. 2010, Puig, Pedraza et al. 2010) While there are some other sensorimotor pathways passing through lesioned subcortical regions as well, less is known about other altered sensorimotor tracts post unilateral stroke and their role in motor impairment. An important reason for this lack of knowledge is that main descending and ascending brain pathways mostly overlap in the brain and delineate from each other in the brainstem(Haines 2004, Mai and Paxinos 2011, Vanderah and Gould 2015, Gray, Standring et al. 2016), while the previous studies have only investigated the morphological changes in the brain. Additionally, these tracts also continue to pass through separate regions in the spinal cord.(Haines 2004, Gray, Standring et al. 2016)

In this study, we used high resolution structural MRI (diffusion tensor imaging) of the brainstem and cervical spinal cord and unbiased voxel-wise analyses that, to the best of our knowledge, constitutes the only approach to identify all the sensorimotor pathways with white matter changes after unilateral subcortical stroke. Our results from the brainstem analyses show that the corticospinal and bulbospinal tracts (i.e. medial and lateral reticulospinal tracts and descending medial vestibulospinal tracts) at the side of lesioned hemisphere had decreased white matter

integrity in individuals with stroke compared to controls. It is worth noting that these corticospinal and cortico-bulbospinal pathways that pass together through the internal capsule – the lesioned region.

Our findings from spinal cord analyses further revealed decreased white matter integrity in cuneate fasciculus, gracile fasciculus and tectospinal tract of paretic (contralesional) side, which are also linked with the lesioned hemisphere. Decreased white matter integrity of gracile and cuneate fasciculi clearly provides support to previous studies that indicate impairments in tactile and proprioceptive sensations post unilateral stroke.(Carey 1995, Kim and ChoiKwon 1996, Tyson, Hanley et al. 2008, Dukelow, Herter et al. 2010)

Last but not least, the results from both brainstem and cervical spinal cord analyses indicated increased white matter integrity of the medial reticulospinal tract, which gets cortico-bulbar projections from non-lesioned hemisphere motor cortices and projects ipsilaterally from reticular nuclei to spinal cord. (Haines 2004, Mai and Paxinos 2011, Vanderah and Gould 2015, Gray, Standring et al. 2016) The combination of decreased white matter integrity in a number of sensorimotor pathways of the lesioned hemisphere and increased white matter integrity of the medial reticulospinal tract of the non-lesioned hemisphere is the most striking aspect of our results. This may provide an explanation for a large number of previous studies reporting an increase in activation of motor cortices on non-lesioned hemisphere during use of paretic arm in individuals with stroke.(Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Grefkes, Nowak et al. 2008) More interestingly, we found that decreases in corticospinal tract integrity at the lesioned hemisphere and increases in medial reticulospinal tract integrity at the non-lesioned hemisphere in stroke individuals were significantly correlated with their motor impairment. These results imply

that motor impairments post unilateral stroke are associated with the damage to the corticospinal tract of lesioned hemisphere and also with increased reliance on the medial reticulospinal tract of non-lesion hemisphere. The positive correlation between increased white matter integrity of contra-lesional medial reticulospinal tract and impairment severity in these individuals is consistent with previous reports of correlation between impairment severity and greater shift of activity to contra-lesional hemisphere.(Cramer, Nelles et al. 1997, Cao, Olhaberriague et al. 1998, Cramer, Finklestein et al. 1999, Cramer, Moore et al. 2000, Marshall, Perera et al. 2000, Carey, Kimberley et al. 2002, McPherson, Chen et al. 2018) These results have implications for rehabilitation interventions post unilateral stroke. Next, we need to further investigate the role of medial reticulospinal tract in motor control through functional experiments; this knowledge will help us optimize the rehabilitation strategies to work with the innate capabilities of this pathway.

There are a couple of limitations of the current investigation that merit consideration when interpreting the results. First, with regard to the spinal cord MRI spatial resolution, although our acquisition setup is comprised of the current state-of-the-art in the field of neuroimaging, there is still room for its improvement with the next generation of MRI scanners with better gradient systems. Second, even though we have taken a great care using the most detailed currently-known maps of the brainstem and spinal cord tracts from a number of atlases, future improvement in imaging approaches may further inform the correctness of the location of pathways in the human brainstem and spinal cord(Duval, Saliani et al. 2019). Follow-up investigations in the next decades with more advanced MRI scanners and improved knowledge of maps of brainstem and spinal cord tracts may further help refine the anatomical specificity of white matter tracts affected post unilateral stroke.

4. BRAINSTEM FUNCTIONAL MRI ACTIVITY DURING HAND MOVEMENT POST-STROKE

Abstract

Previous fMRI studies trying to understand the underlying neural mechanisms of hand impairment using neuroimaging techniques, have frequently reported increased neural activity in motor cortices of both lesioned and non-lesioned hemispheres in individuals with stroke during their attempt to move their affected hand. They have also reported that the more severe the impairment, the greater activity in the contralesional hemisphere compared to the ipsilesional. However, it is still unclear what descending motor pathway allows the nonlesioned hemisphere to control the ipsilateral paretic arm. The results of my first aim on morphological changes in descending and ascending brain pathways indicated an increase in white matter integrity of the medial reticulospinal tract from non-lesioned hemisphere post stroke. Given the fact that brain morphological changes are the result of functional changes over the time, white matter integrity increases in ipsilaterally descending motor pathways post stroke is most likely associated with greater activity in these pathways' nuclei in the brainstem. To this end, the goal of this project was to use high resolution fMRI of the brainstem to investigate the activation in brainstem nuclei in individuals with chronic hemiparetic stroke, while they try to squeeze a pressure ball with their paretic hand. Our findings demonstrate significant activation in nuclei of a number of ipsilaterally projecting motor pathways including medial reticulospinal tract, lateral reticulospinal tract, medial vestibulospinal tract, as well as, pontine nuclei of motor cortex-ponto-cerebellum pathway in moderately and severely impaired stroke subjects. The current findings also suggest that the medial reticulospinal tract is the most commonly used pathway in more impaired individuals with chronic hemiparetic stroke. There was no activation in brainstem nuclei in mildly impaired stroke patients

or healthy controls, suggesting their continuing use of corticospinal tract as the primary motor pathway.

Introduction

About 80% of individuals with a moderate to severe subcortical stroke report upper limb motor impairment, particularly in the wrist and fingers, as the most disabling. (Ince 1980, Parker, Wade et al. 1986). Previous fMRI studies trying to understand the underlying neural mechanisms of hand impairment using neuroimaging techniques have frequently reported increased neural activity in motor cortices of both ipsilesional and contralesional hemispheres in individuals with stroke, while trying to move their affected upper extremity (Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Cao, Olhaberriague et al. 1998, Carey, Kimberley et al. 2002, Johansen-Berg, Rushworth et al. 2002, Ward, Brown et al. 2003, Grefkes, Nowak et al. 2008, Rehme, Fink et al. 2011, Rehme, Eickhoff et al. 2012, McPherson, Chen et al. 2018). It is also reported that the more severe the stroke, the greater activity in the contralesional hemisphere compared to the ipsilesional (i.e. a shift of activity to non-lesioned hemisphere.(Cramer, Nelles et al. 1997, Cao, Olhaberriague et al. 1998, Johansen-Berg, Rushworth et al. 2002, Rehme, Fink et al. 2011)

However, it is still unclear what descending motor pathway allows the non-lesioned hemisphere to control the ipsilateral paretic arm. One proposed idea from human and animal studies suggests the ipsilaterally projecting motor pathways (i.e. reticulospinal tract or vestibulospinal tract) may play this role (Schwerin, Dewald et al. 2008, Baker, Zaaimi et al. 2015, Herbert, Powell et al. 2015). Moreover, previous reports on flexor-biased role of reticulospinal tract in primates and cat (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson,

Buford et al. 2004, Davidson and Buford 2006) and relatively preserved ability for wrist/fingers flexion, compared to extension, post stroke, further highlights the possible role of ipsilaterally projecting brainstem pathways post stroke.

The results of the morphological (microstructural) investigation of descending and ascending brain pathways in first aim of this dissertation (previous chapter) indicated increased white matter integrity of ipsilateral medial reticulospinal tract post stroke (Karbasforoushan, Cohen-Adad et al. 2019). In other words, the higher reliance on non-lesioned hemisphere post stroke might be led to higher use of ipsilaterally projecting medial reticulospinal tract in these patients. Given the fact that brain morphological changes are the result of changes in functional activity over time (Puig, Pedraza et al. 2010), white matter integrity increases in ipsilaterally descending motor pathways post stroke is likely to be the result of greater activity in nuclei of these pathways in the brainstem.

To this end, the goal of this project was to use high resolution fMRI of brainstem and a task-dependent fMRI design to investigate the activation in brainstem nuclei in individuals with chronic hemiparetic stroke, while they try to squeeze a pressure ball with their paretic hand. It was hypothesized that individuals with stroke would show functional activation in reticular nuclei in the brainstem while trying to close their hand and squeeze the ball.

Our results based on the activity pattern in brainstem nuclei in 9 individuals with stroke indicated that all severely and moderately impaired individuals had some activity in medial reticulospinal tract nuclei during the fMRI task. Moreover, some patients showed a less intense activity in lateral reticulospinal tract and medial vestibulospinal tract as well. Also, there were some activities observed in pontine nuclei, in the area where cortical projections from motor cortex (M1) synapse

to, which suggests the role of cortico-ponto-cerebellum and possibly greater reliance on cerebellum after stroke. Interestingly, mildly impaired stroke subjects, as well as, healthy controls did not show any activation in ipsilaterally projecting descending motor pathways nuclei in brainstem, suggesting they continue using the corticospinal tract.

These findings point to a greater reliance on ipsilaterally projecting motor pathways, including medial reticulospinal tract, lateral reticulospinal tract, medial vestibulospinal tract, as well as, motor cortex-ponto-cerebellum pathway post stroke, and suggest the medial reticulospinal tract as the most commonly used pathway in individuals with chronic hemiparetic stroke. Further investigation with a larger sample size may help demonstrate the activity pattern in brainstem nuclei as a group as opposed to individual level.

Methods

Participants

9 individuals with chronic hemiparetic unilateral stroke in internal capsule (ischemic or hemorrhagic) and 3 healthy controls with no neurological or movement disorder were recruited to participate in this study. Three stroke participants were severely impaired, three moderately impaired, and three mildly impaired (based on FMA of upper extremity), and all sustained a unilateral brain lesion at least 3 years prior to participation in the study. Individuals with stroke were recruited through the Northwestern Clinical Neuroscience Research Registry, Ischemic Stroke Registry and approved flyers. This study was approved by the Institutional Review Board of Northwestern University, and all study participants provided written informed consent prior to participation.

Clinical Assessment

For each stroke individual, upper extremity motor assessment (Fugl-Meyer Assessment: FMA (Fugl-Meyer, Jaasko et al. 1975)) was performed by a licensed physical therapist. FMA is an impairment-based motor assessment score that includes joint individuation, sensation and stretch reflex excitability in upper limb. Higher values indicate higher motor abilities (less impairment) in these individuals.

fMRI Task

Participants were set up inside a 3T Siemens Prisma scanner with a 64-channel head coil. Pillows and padding were used around the head to minimize the motion and keep the head in a comfortable position. The test arm (paretic arm in individuals with stroke; right arm in controls) was abducted by supporting it with some pillows/cushion, so that the hand could rest above the subject's stomach without making any contact to the body during hand movement. (See **Figure 4.1**). The elbow was flexed to about 110° with 180° being full extension.

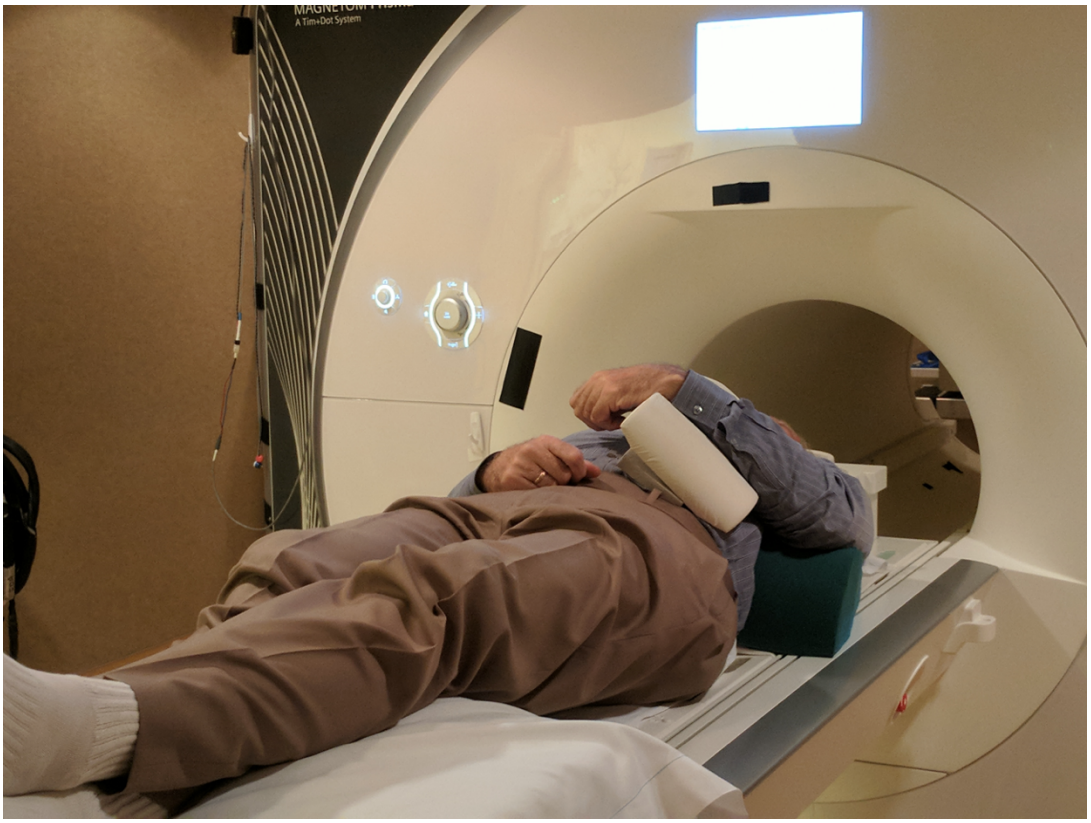

Figure 4.1. The subject's set-up inside the MRI scanner for fMRI data collection.

During the fMRI scan, the participants were instructed via commands on a screen to quickly squeeze a pressure ball, which was attached to the palm of their hand, in accordance with a green circle flashing on the screen with a 1 Hz frequency. The fMRI task included a block design, and each trial consisted of 5 blocks. As shown in **Figure 4.2**, each block included 30 seconds of the task (squeezing the pressure ball with 1Hz frequency), and 30 seconds of rest. There were two runs of task-dependent fMRI scans collected for each participant.

Figure 4.2. The fMRI task design. The block design consisted of 5 blocks. Each block consisted of 30 seconds of squeezing a pressure ball with frequency of 1Hz, and 30 seconds of rest.

MRI Scanning parameters

Whole brain and brainstem anatomical and fMRI scans were acquired at Northwestern University Center for Translational Imaging on a 3T Siemens Prisma scanner with a 64-channel head coil. T1-weighted anatomical scans were acquired using an MPRAGE sequence with voxel size = 0.8 × 0.8 × 0.8 mm, repetition time = 9.9 ms, echo time = 4.7 ms, flip angle = 2°, field of view = 256 mm. fMRI scans consisted of the following parameters: 72 axial slices, in-pane resolution = 2.0 mm x 2.0 mm, slice thickness = 2.0 mm, TR = 613 ms, TE = 22 ms, and scan duration of 5 minutes and 30 seconds.

Imaging Data Preprocessing and Statistical Analyses

MRI data was preprocessed and analyzed using Statistical Parametric Mapping 12 (SPM12) software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) (Friston, Holmes et al. 1994, Friston 2003, Flandin and Friston 2008, Penny, Friston et al. 2011) on MATLAB 2018a (https://www.mathworks.com/products/matlab.html). The functional images were corrected for slice timing and head motion and co-registered to the subject's structural image. Each subject's T1 structural scan was segmented into gray matter, white matter and CSF tissues, and normalized to the a-priori Montreal Neurological Institute (MNI) template tissues. Functional images were then normalized to MNI template using normalization parameters derived from structural data normalization step. Normalized functional images were then smoothed with a Gaussian kernel of $3mm^3$ FWHM. A majority of individuals with stroke had the unilateral lesion in the left hemisphere. For individuals with the unilateral lesion in the right hemisphere, the preprocessed functional activity maps were flipped, so that all subjects' activity maps included in the group analyses would have the lesion on the left hemisphere.

Voxel-wise statistical analysis proceeded by modeling each subject's time series functional data as a boxcar function, with "squeeze" condition as a predictor in first level analysis. Resulted activity maps for each subject were then put in a one-sample t-test or two-sample t-test for a within group or between groups analyses of stroke participants and controls.

Results

Group Analyses Results

As shown in **Figure 4.3**, individuals with stroke did not show any higher significant activity in brainstem nuclei during the squeeze task, when compared to controls. Also, using within-group analysis, no significant activity in brainstem nuclei for individuals with stroke during the squeeze task was found. In other words, no cluster in the brainstem passed the significance threshold level for the group analyses. This can be due to small sample size used in the group analyses or some individual differences in brain activity. I, therefore, continued my investigation by looking at the brainstem activity maps for each individual.

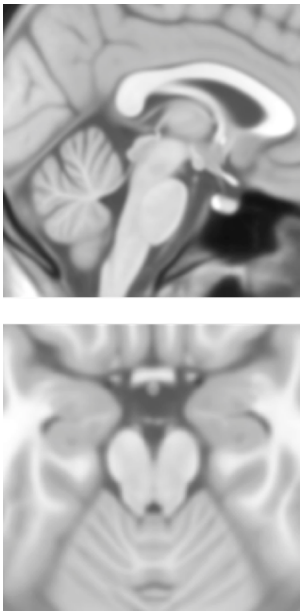

Figure 4.3. Results of between group analysis. Individuals with stroke, compared to healthy controls, had no significant increased activity in brainstem nuclei during the fMRI squeeze task.

Brainstem Activity in Each Individual

For subject-specific analysis, the processed activity maps are thresholded with conservative t value>4, and the cluster size is also corrected with $p < 0.05$. In this section, the activity pattern in each individual (from the most severely to most mildly impaired stroke participants) will be

presented. The lesioned hemisphere is the left hemisphere for all figures (i.e. paretic arm is on the right side).

Stroke Subject 1

As shown in **Figure 4.4**, the most severely impaired participant had a significant activity in nuclei of right medial reticulospinal tract (oral pontine reticular nucleus) while squeezing the pressure ball. This finding is consistent with the results of my previous findings of microstructural changes post-stroke (Karbasforoushan, Cohen-Adad et al. 2019).

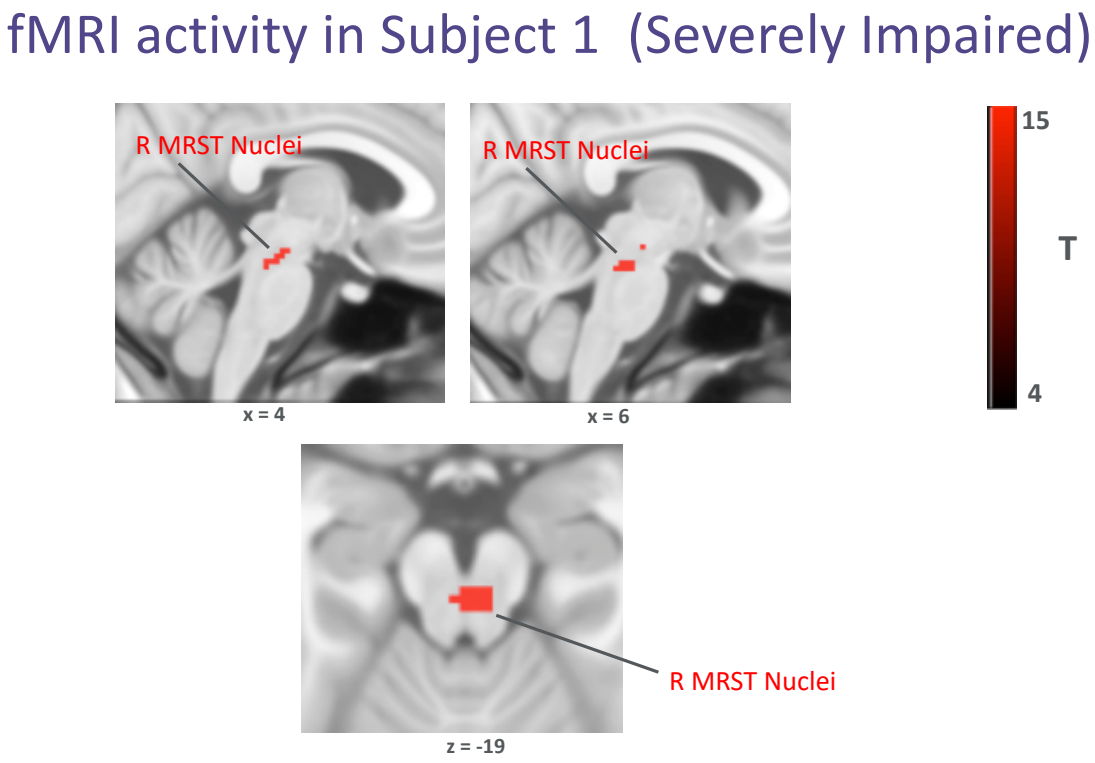

Figure 4.4. Brain activity in brainstem during the fMRI task in stroke subject 1. There is significant activity in nuclei of right medial reticulospinal tract in this individual with stroke during the fMRI task.

Stroke Subject 2

The second severely impaired individual with stroke showed a significant activity in right medial reticulospinal tract nuclei and small part of left medial reticulospinal tract nuclei, as well as, in bilateral medial vestibular nuclei during the fMRI task of squeezing the ball. (**Figure 4.5**).

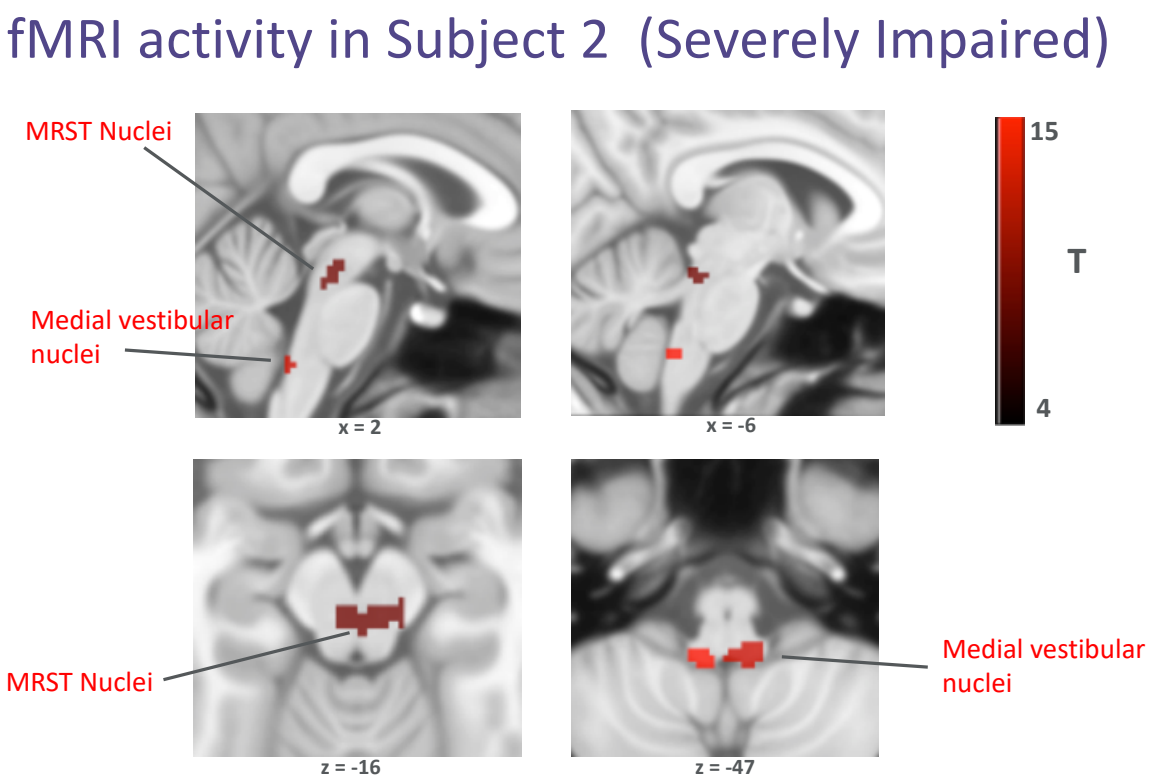

Figure 4.5. Brain activity in brainstem during the fMRI task in stroke subject 2. There is significant activity in nuclei of right medial reticulospinal tract, small part of left medial reticulospinal tract, and bilateral medial vestibulospinal tracts in this individual with stroke during the fMRI task.

Stroke Subject 3

As shown in **Figure 4.6**, the third severely impaired participant had a significant activity in nuclei of bilateral medial reticulospinal tract (oral pontine reticular nucleus, tegmental pontine reticular nucleus, and caudal pontine reticular nucleus), vestibulospinal tact, right lateral reticulospinal tract, as well as, pontine nuclei receiving input from motor cortex and projecting to cerebellum.

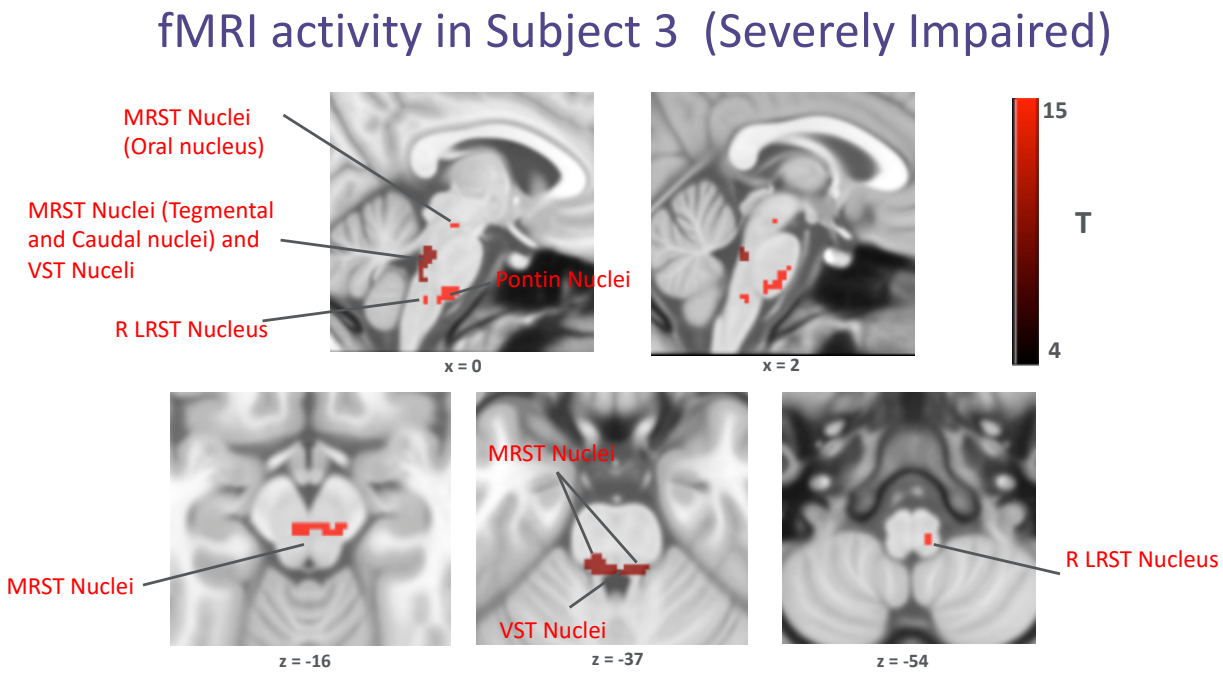

Figure 4.6. Brain activity in brainstem during the fMRI task in stroke subject 3. There is significant activity in bilateral medial reticulospinal tract, right lateral reticulospinal tract, and pontine nuclei projecting to cerebellum in this severely impaired individual with stroke during the fMRI task.

Stroke Subject 4

Stroke subject 4, who was moderately impaired, showed a significant activity in right medial reticulospinal tract nuclei (oral pontine reticular nucleus and caudal/tegmental pontine reticular nuclei) and right lateral reticulospinal tract nucleus during the squeeze task (**Figure 4.7**).

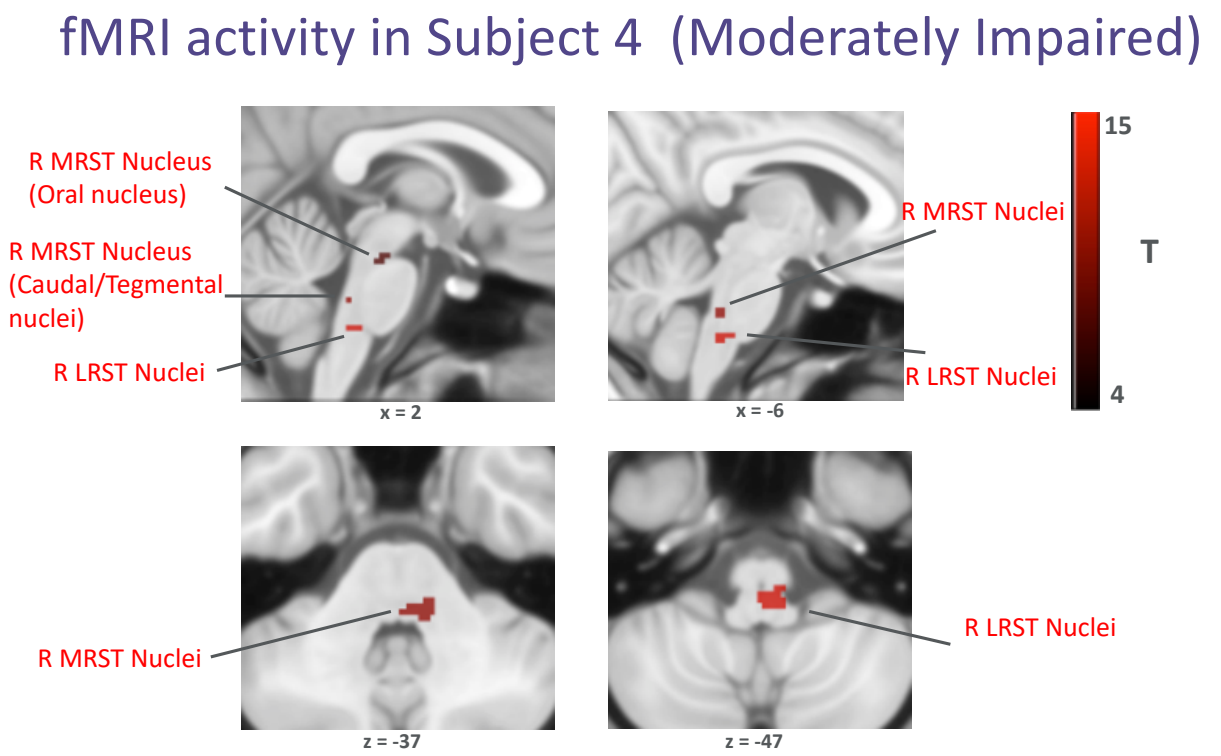

Figure 4.7. Brain activity in brainstem during the fMRI task in stroke subject 4. There is significant activity in nuclei of right medial reticulospinal tract and right lateral reticulospinal tract in this moderately impaired individual with stroke during the fMRI task.

Stroke Subject 5

As shown in **Figure 4.8**, stroke subject 5, who was also moderately impaired, had a significant activity only in right medial reticulospinal tract nuclei (caudal/tegmental pontine reticular nuclei) and pontine nuclei projecting to cerebellum.

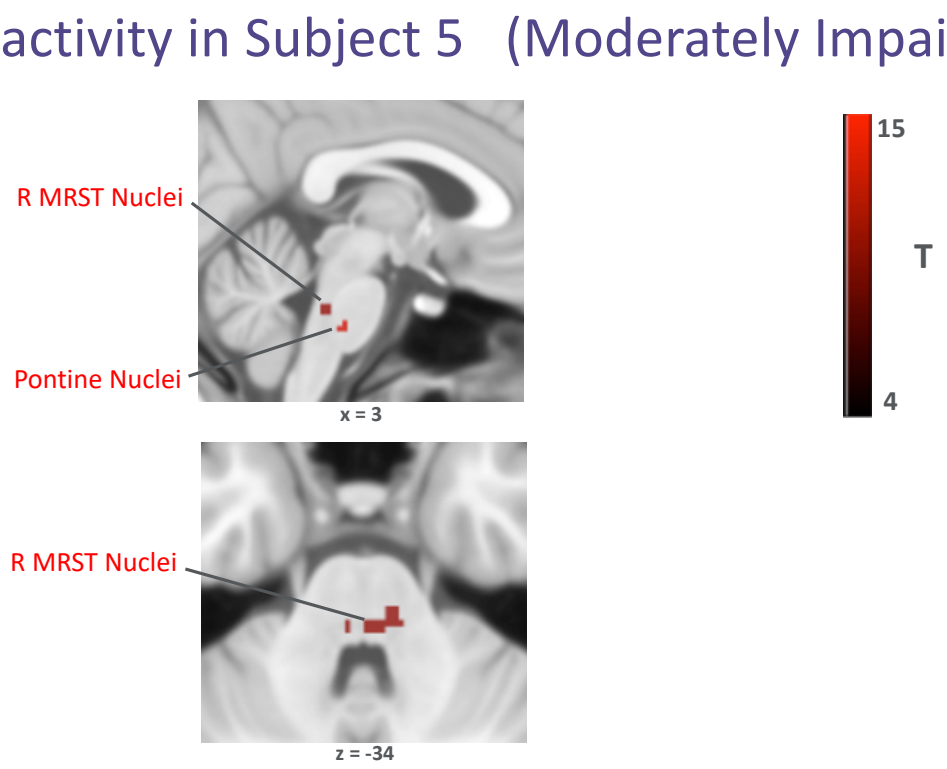

Figure 4.8. Brain activity in brainstem during the fMRI task in stroke subject 5. There is significant activity in nuclei of right medial reticulospinal tract and pontine nuclei which receive input from motor cortices and project to cerebellum.

Stroke Subject 6

The next moderately impaired subject also showed a significant activity in a large cluster which appears to belong to bilateral medial reticulospinal tract nuclei (caudal/tegmental pontine reticular nuclei) and pontine nuclei projecting to cerebellum. (**Figure 4.9**)

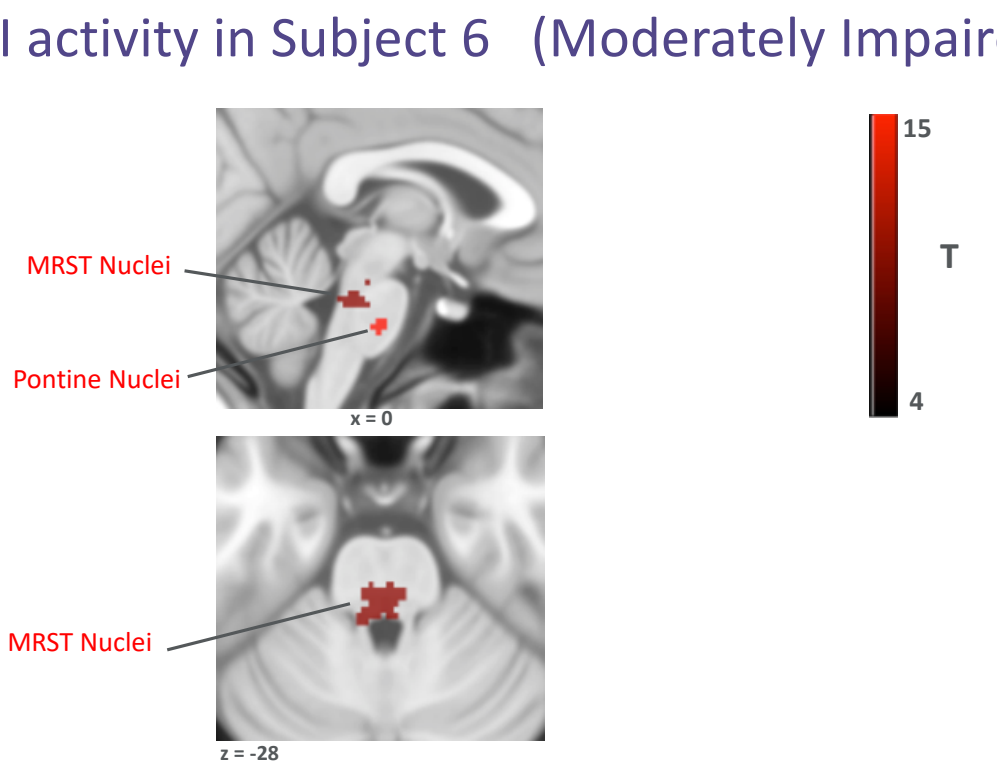

Figure 4.9. Brain activity in brainstem during the fMRI task in stroke subject 6. There is significant activity in nuclei of bilateral medial reticulospinal tract and pontine nuclei which receive input from motor cortices and project to the cerebellum.

Stroke Subject 7

Stroke subject 7, who was mildly impaired, showed significant activity only in left pontine nuclei which receive input from motor cortex and project to the cerebellum. In other words, this individual with stroke demonstrates higher reliance only on cortico-ponto-cerebellum pathway. (**Figure 4.10**)

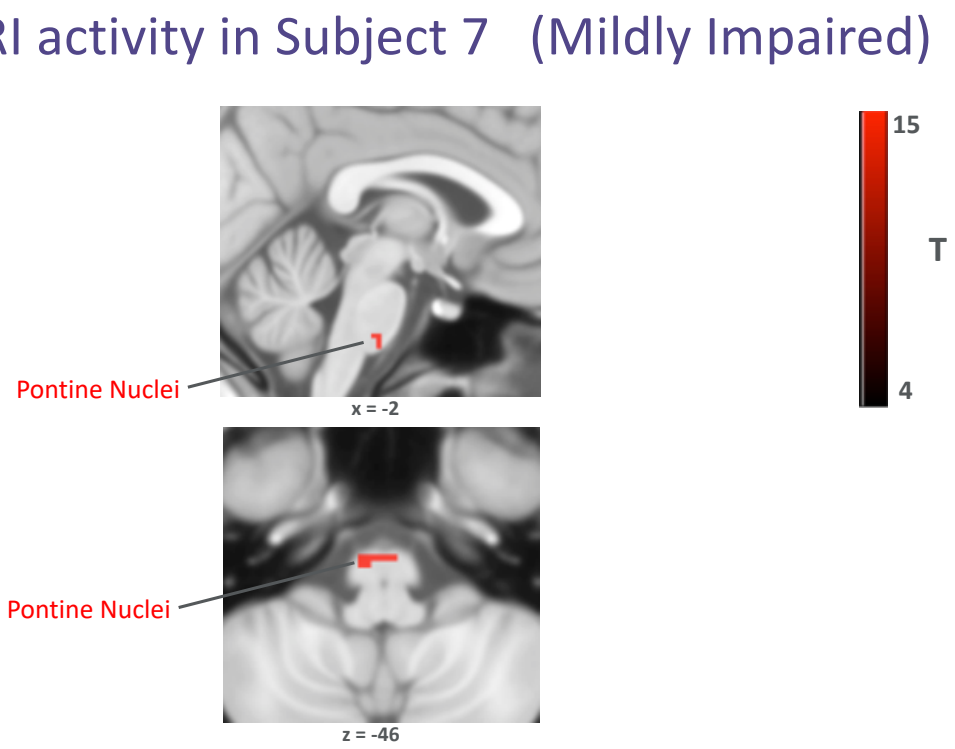

Figure 4.10. Brain activity in brainstem during the fMRI task in stroke subject 7. There is significant activity in pontine nuclei receiving input from motor cortex and projecting to the cerebellum.

Stroke Subjects 8

As shown in **Figure 4.11**, the mildly impaired stroke subjects 8 did not show any significant activity in brainstem nuclei during squeeze task.

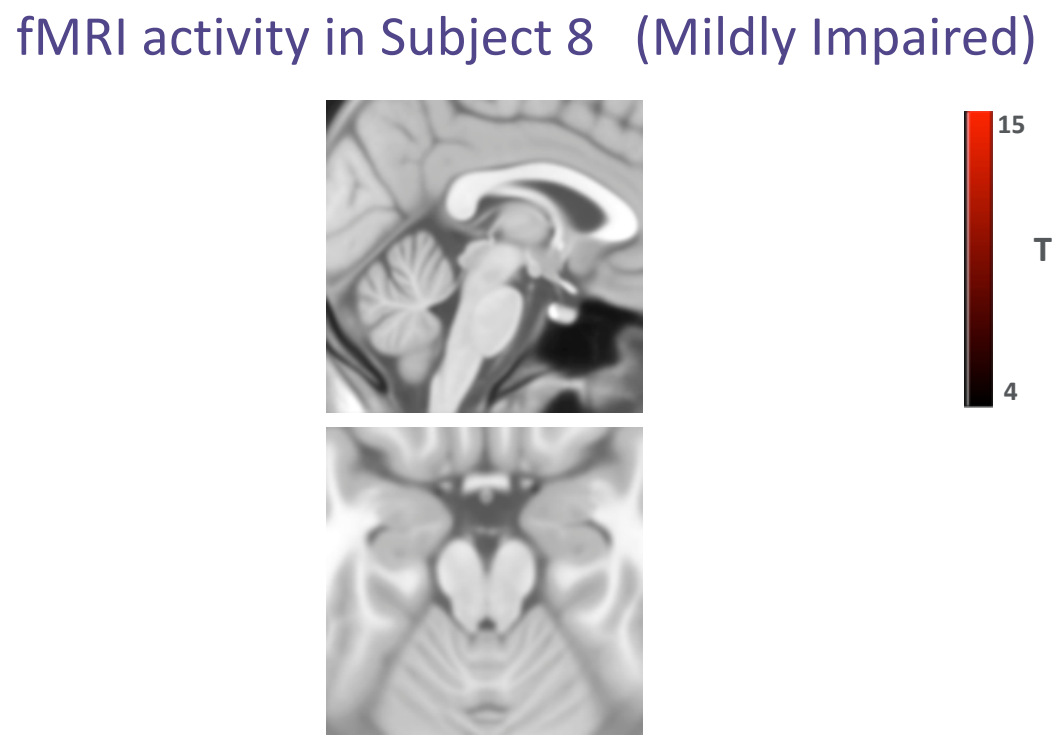

Figure 4.11. Brain activity in brainstem during the fMRI task in stroke subject 8. There is no significant activity in brainstem nuclei in this mildly impaired individual.

Stroke Subject 9

Similar to previous mildly impaired individual, the stroke subject 9, who was the most mildly impaired participant in this study, did not have any significant activity in brainstem nuclei during squeeze task (**Figure 4.12**). This can be due to less damage to corticospinal tract pathway in these mildly impaired individuals, which allows them to continue using the main motor pathways post stroke.

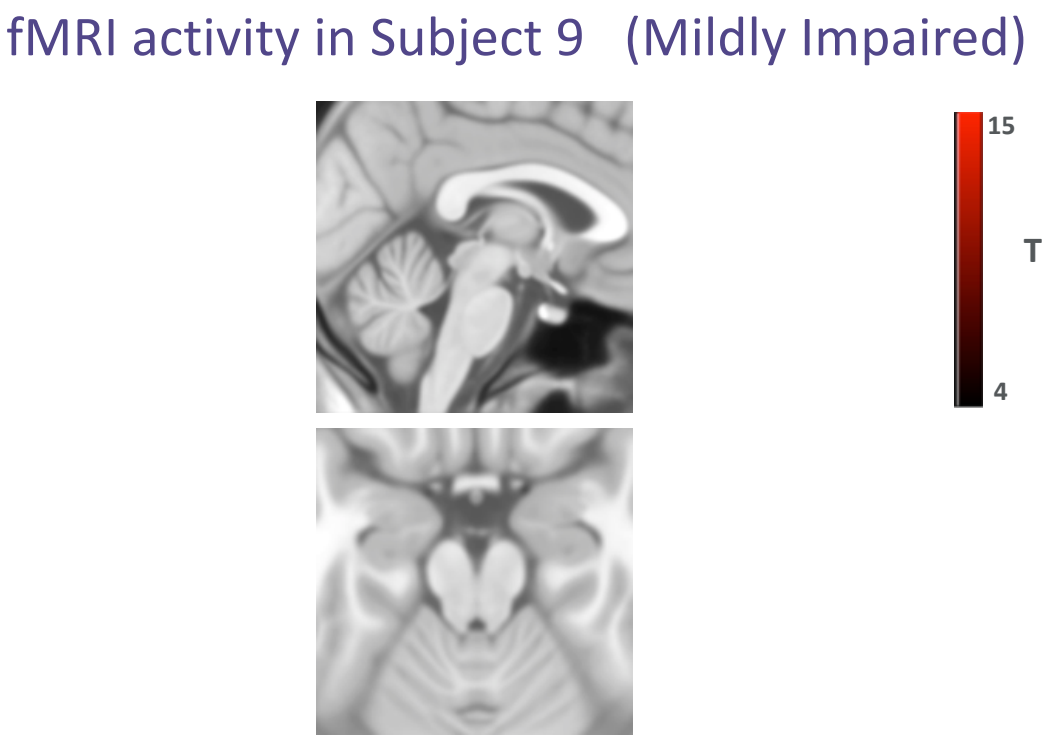

Figure 4.12. Brain activity in brainstem during the fMRI task in stroke subject 9. There is no significant activity in brainstem nuclei in this mildly impaired individual.

Brainstem Activity in Healthy Control Participants

There was no significant activity in brainstem nuclei in healthy control participants (**Figure 4.13**). This seems to indicate that healthy controls do not appear to use their brainstem motor pathways during the squeezing task.

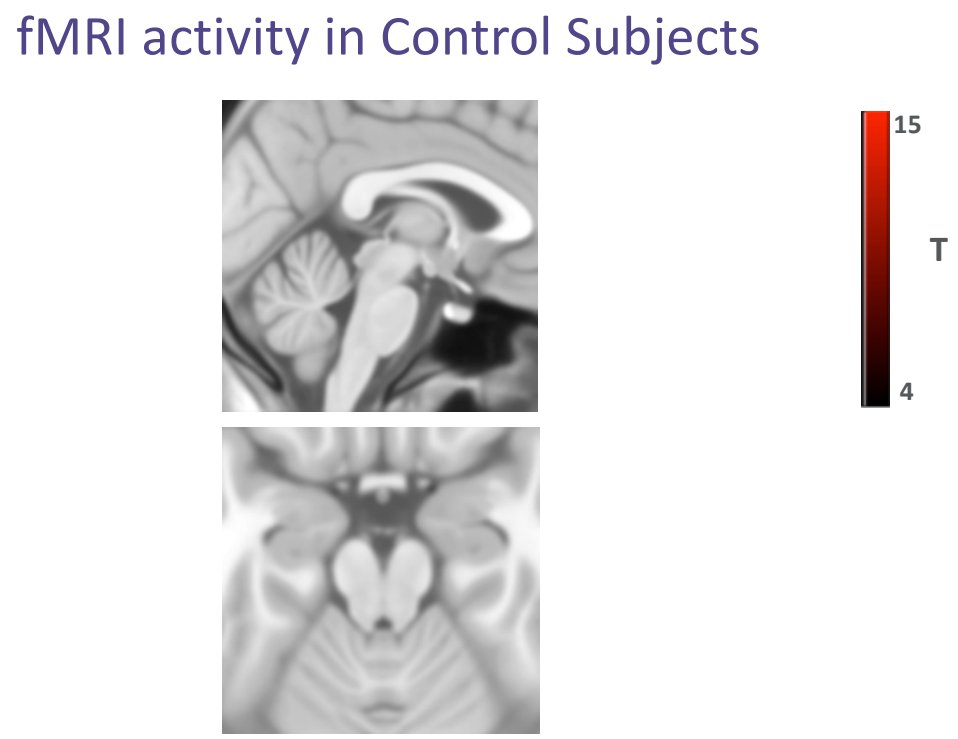

Figure 4.13. Brain activity in brainstem during the fMRI task in control participants. There is no significant activity in brainstem nuclei in healthy controls.

Discussion

Previous brain imaging studies in individuals with chronic hemiparetic stroke have frequently reported increased neural activity in motor cortices of both contralateral and ipsilateral hemispheres during the movement of affected hand (Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Cao, Olhaberriague et al. 1998, Carey, Kimberley et al. 2002, Johansen-Berg, Rushworth et al. 2002, Ward, Brown et al. 2003, Grefkes, Nowak et al. 2008, Rehme, Fink et al. 2011, Rehme, Eickhoff et al. 2012, McPherson, Chen et al. 2018). They have also reported that the more severe the impairment, the greater hyperactivity in the ipsilesional and contralesional hemispheres (Cramer, Nelles et al. 1997, Cao, Olhaberriague et al. 1998, Johansen-Berg, Rushworth et al. 2002, Rehme, Fink et al. 2011). However, it is still unclear what descending motor pathways allow the non-lesioned hemisphere to control the ipsilateral paretic arm.

Moreover, the results of my first aim on microstructural changes in descending and ascending brain pathways indicate an increased white matter integrity of medial reticulospinal tract from non-lesioned hemisphere post stroke(Karbasforoushan, Cohen-Adad et al. 2019). Considering there is a direct correlation between brain function and structural patterns, the goal of this aim was to test the functional activity in brainstem nuclei of descending motor pathways. Therefore, high resolution fMRI of brainstem and a task-dependent block design was used to investigate the activation in brainstem nuclei of 9 individuals with chronic hemiparetic stroke and 3 healthy controls, while they tried to squeeze a pressure ball with their paretic/right hand.

The between group and within group analyses in individuals with stroke did not show any significant activity in brainstem nuclei. This could be due to the small sample size used in this project, or because of differences in activity patterns for each individual with stroke. However,

checking the functional activation in each individual with stroke after choosing a conservative t value > 4 and also a cluster size corrected $p<0.5$, an interesting and meaningful pattern of activation was observed in each participant. Interestingly, all severely and moderately impaired individuals had some activity in medial reticulospinal tract nuclei during the fMRI task. This finding is consistent with my results from first aim of my PhD work which indicated an increase in microstructure of medial reticulospinal tract in individuals with stroke and also a significant correlation between the increased white matter integrity of this pathway and impairment severity.

Moreover, some stroke participants showed a less intense activity in lateral reticulospinal tract and medial vestibulospinal tract. Also, there were some activities observed in few individual's pontine nuclei in the area where cortical projections from sensorimotor cortices synapse to, which may suggest the contribution of cortico-ponto-cerebellum circuitry and possibly a greater use of the cerebellum after a stroke. Interestingly, mildly impaired stroke subjects, as well as, healthy controls did not show any activation in ipsilaterally projecting descending motor pathways' nuclei in brainstem, suggesting that they continue to use the main motor pathway, the corticospinal tract, during the squeezing task.

These findings for the first time demonstrate some activation in nuclei of descending motor pathways, including medial reticulospinal tract, lateral reticulospinal tract, medial vestibulospinal tract, as well as, pontine nuclei of motor cortex-ponto-cerebellum pathway in individuals with chronic stroke while closing their hand. Moreover, these results show the medial reticulospinal tract as the most commonly used pathway across more impaired individuals with chronic hemiparetic stroke.

Further investigation with a larger sample size may help demonstrate the activity pattern in brainstem nuclei in the whole group of participants as opposed to at the individual level. Furthermore, it allows us to determine to determine a possible link between amount of brainstem activity and impairment severity.

5. DISCUSSION AND FUTURE DIRECTIONS

Thesis Summary

The goal of this dissertation was to identify altered sensorimotor pathways and their role in motor impairments in individuals with chronic hemiparetic subcortical stroke. Damage to the corticospinal tract has been widely studied following a unilateral subcortical stroke. However, less was known about changes to other sensorimotor pathways. Moreover, previous neuroimaging studies in stroke over the last two decades had reported increased neural activity in motor cortices of both lesioned and non-lesioned hemisphere during hand/arm movement post stroke. However, it was still unclear what descending motor pathway allows the contralesional motor cortex to control the ipsilateral paretic arm. An important reason for this lack of knowledge was that previous studies had only investigated the morphological or functional activity in the brain, where the majority of descending and ascending brain pathways mostly overlap. Sensorimotor pathways, in fact, delineate from each other at the brainstem and continue travelling through separate regions in the spinal cord. In this dissertation, I therefore used advanced structural MRI of brainstem and cervical spinal cord, as well as, functional MRI of brainstem to identify all the sensorimotor tracts with morphological and functional changes in individuals with chronic hemiparetic stroke.

In Chapter 1, I provided an overview of unanswered questions with regard to descending motor pathways involved in arm movements post stroke and specified the aims of this dissertation. In Chapter 2, I discussed upper extremity motor impairments post stroke, previous neuroimaging studies on cortical activity post stroke, and provided anatomical information on main descending and ascending brain pathways which would help better understand the results of work presented in subsequent chapters. In Chapter 3, I presented the work that aimed to identify sensorimotor pathways with morphological changes post-stroke, using high resolution structural MRI of both

the brainstem and the cervical spinal cord. In Chapter 4, I presented the results from investigating the activity in brainstem nuclei during a hand closing task (squeezing a ball) in individuals with chronic hemiparetic stroke, using functional MRI of brainstem and a task-dependent fMRI design.

Morphological changes in sensorimotor pathways post-stroke

The results from my investigation on pathways with morphological changes post stroke at the level of brainstem (Aim 1a) indicated decreased white matter integrity in corticospinal tract, medial and lateral reticulospinal tracts and descending medial vestibulospinal tract at the side of lesioned hemisphere. It is worth mentioning that these corticospinal and cortico-bulbospinal pathways all travel through the internal capsule of lesioned hemisphere.

My findings investigating pathways with morphological changes in cervical spinal cord (Aim 1b) further revealed decreased white matter integrity in cuneate fasciculus, gracile fasciculus and tectospinal tract of paretic (contralesional) side, which are also linked with the lesioned hemisphere. Decreased white matter integrity of gracile and cuneate fasciculi clearly provides support to previous studies that indicate impairments in tactile and proprioceptive sensory modalities post unilateral stroke.(Carey 1995, Kim and ChoiKwon 1996, Tyson, Hanley et al. 2008, Dukelow, Herter et al. 2010)

Most interestingly, the results from both brainstem and cervical spinal cord analyses indicated increased white matter integrity of the medial reticulospinal tract, initiating from oral pontine reticular nucleus, which receives the cortico-bulbar projections from non-lesioned hemisphere motor cortices and projects ipsilaterally from reticular nuclei to spinal cord. (Haines 2004, Mai and Paxinos 2011, Vanderah and Gould 2015, Gray, Standring et al. 2016) This may provide an

explanation for a large number of previous studies over past two decades reporting an increase in activation of motor cortices on non-lesioned hemisphere during use of the paretic arm in individuals with stroke.(Chollet, DiPiero et al. 1991, Weiller, Chollet et al. 1992, Grefkes, Nowak et al. 2008)

The results of our investigation on any association between these morphological changes and motor impairments post stroke indicated that decrease in corticospinal tract integrity of the lesioned hemisphere and increase in medial reticulospinal tract integrity of the non-lesioned hemisphere in stroke individuals were significantly correlated with motor impairment severity. These results imply that motor impairment post unilateral stroke is associated with the damage to the corticospinal tract of lesioned hemisphere and also with increased reliance on the medial reticulospinal tract of the non-lesioned hemisphere. The positive correlation between increased white matter integrity of contra-lesional medial reticulospinal tract and impairment severity in these individuals is consistent with previous reports of correlations between impairment severity and greater shift of activity to contra-lesional hemisphere.(Cramer, Nelles et al. 1997, Cao, Olhaberriague et al. 1998, Cramer, Finklestein et al. 1999, Cramer, Moore et al. 2000, Marshall, Perera et al. 2000, Carey, Kimberley et al. 2002, McPherson, Chen et al. 2018)

It is noteworthy to mention that these findings demonstrate a correlation - not a causation - between morphological changes in these pathways and motor impairment severity. Further investigation into role of reticulospinal tract post stroke will indeed help us understand whether this pathway is helping or hurting with upper extremity movement post stroke. Given the flexor-biased role of reticulospinal tract (Sprague and Chambers 1954, Drew, Rossignol et al. 1990, Drew, Rossignol et al. 1990, Davidson, Buford et al. 2004, Davidson and Buford 2006), we can agree that the

excessive flexion in elbow, wrist and fingers, as well as, flexion synergy impairment observed in individuals with stroke is most likely a result of increased reliance on reticulospinal tract post stroke. However, it is still unclear how well the stroke survivors could recover and how much upper extremity movement they could gain without the help of alternative non-lesioned hemisphere and ipsilaterally projecting motor pathways. In other words, in severely impaired individuals with a significant damage to the corticospinal tract (i.e. insufficient remaining resources on lesioned hemisphere), an increased reliance on non-lesioned hemisphere and ipsilaterally projecting motor pathways might, in fact, be the only way to gaining some - although not a perfect - movement.

Functional activity changes in brainstem nuclei post stroke

The results of my investigation of functional activity in brainstem during squeezing a pressure ball (Aim 2) indicated significant activity in medial reticulospinal tract nuclei (oral pontine reticular nucleus, tegmental pontine reticular nucleus and caudal pontine reticular nucleus) in severely and moderately impaired individuals with stroke, but not the mildly impaired. This finding was consistent with my results from my first aim which indicated an increase in microstructure of medial reticulospinal tract in individuals with stroke and also a significant correlation between the increased white matter integrity of this pathway and impairment severity.

Furthermore, some individuals with stroke showed a less frequent activity in lateral reticulospinal tract, medial vestibulospinal tract, as well as, pontine nuclei which were part of motor cortex-ponto-cerebellum pathway. Interestingly, mildly impaired stroke subjects, as well as, healthy controls did not show any activation in ipsilaterally projecting descending motor pathways' nuclei

in brainstem, suggesting that they continue to use the main motor pathway, the lateral corticospinal tract, during the hand squeezing task.

These results, therefore, demonstrated the activation in nuclei of ipsilaterally projecting pathways and pontine nuclei of motor cortex-ponto-cerebellum pathway in individuals with chronic stroke, and suggest that this activation may be correlated with impairment severity. Moreover, these findings suggested the medial reticulospinal tract as the most commonly used pathway in individuals with chronic hemiparetic stroke during movement of upper extremity.

Future Directions

The findings from this dissertation, as well as, the limitations experienced during this research, open up a few potential future lines of research:

a) The cervical spinal cord imaging approach I used in my research and the results I obtained, demonstrated that the spinal cord MRI method to be a novel and promising approach for the study of morphology or function of human brain pathways at the level of cervical spine. This opens up new investigational avenues for the study of a variety of movement disorders using advanced spinal cord imaging methods. Moreover, with regard to the spinal cord MRI protocols, although our acquisition setup was comprised of the current state-of-the-art in the field of neuroimaging, there is still room for their improvement and further development, which will then allow their application in study of many other neurological questions.

b) During this research, I realized that there are some inconsistencies between resources in regard to the location of white matter tracts in spinal cord. Especially, the exact location and size of tracts in medial and ventral part of spinal cord in humans is not completely defined and clear. This gap in our knowledge opens up new doors for further investigations to refine the maps of spinal cord tracts using the advanced brain and spinal cord imaging methods which are available to us nowadays.

c) The results from between-group and within-group analyses in individuals with stroke during the hand closing task (Aim 2) did not show any significant activation in brainstem nuclei. This may be due to the small sample size used in this project, or because of some differences in activity patterns in each individual with stroke. Further investigation using a larger sample size is warranted to help us understand activity patterns in brainstem nuclei in the whole group of individuals with hemiparetic stroke. Furthermore, it can allow us to determine the correlation between brainstem activity and impairment severity level.

d) As I mentioned earlier, this research demonstrated a significant correlation - not causation - between greater use of reticulospinal tract of non-lesioned hemisphere and upper extremity motor impairment severity in individuals with chronic hemiparetic stroke. It therefore remains unclear whether the higher reliance on reticulospinal tract is helping or hurting the upper extremity motor control post stroke. Although the expression of the flexion synergy impairment observed in individuals with stroke is most likely the result of an increased reliance on reticulospinal tract post stroke (because of flexor-biased nature of this pathway), we still do not know whether individuals with stroke - especially, the very

severely impaired ones – any movement control would reappear without help of non-lesioned hemisphere and alternative ipsilaterally projecting motor pathways. One of the next potential lines of inquiry to answer this question can be a longitudinal and interventional study with brain stimulation treatments on both lesioned and non-lesioned hemispheres of individuals with acute stroke (especially severely impaired patients) to better identify the role of non-lesioned hemisphere and ipsilaterally projecting pathways in motor recovery after stroke.

e) Finally, this dissertation aimed to identify the altered sensorimotor pathways post stroke and also test their activation during closing the hand (i.e. squeezing a ball). Another potential line of inquiry is to test the activation in brain and brainstem during hand opening task. As mentioned earlier, individuals with stroke have more difficulty with hand opening than closing. Also, the more severely impaired individuals involuntarily close the hand when trying to open. It is, therefore, worth investigating the activity in brainstem nuclei during hand opening task as well. It will also help us understand if the involuntary close of the hand when attempting to open is indeed a result of higher activation in nuclei of brainstem projecting pathways.

Conclusion

The work here, for the first time, identifies all morphologically and functionally altered sensorimotor pathways and their correlation with upper extremity motor impairment post hemiparetic subcortical stroke. Moreover, it demonstrates the higher reliance on ipsilaterally projecting motor pathways - including medial reticulospinal tract, lateral reticulospinal tract, and medial vestibulospinal tract - of non-lesioned hemisphere post stoke and suggests the medial

reticulospinal tract to be the most commonly used pathway in individuals with chronic hemiparetic stroke.

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