CHARACTERIZING THE IMPACT OF TYPE-2 DIABETES ON CORTICAL SENSORIMOTOR PATHWAYS IN CHRONIC STROKE:
A MULTIMODAL NEUROIMAGING STUDY

by

Jennifer Ferris

B.A., The University of British Columbia, 2013

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Neuroscience)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

April 2016

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Abstract

Individuals with type-2 diabetes have an increased incidence of ischemic stroke, and experience higher rates of disability after stroke than non-diabetics. Recent research suggests that type-2 diabetes has adverse effects on neuronal integrity and function, however, to date very little work has examined the interactions of diabetes with chronic stroke recovery. The goal of the present thesis is to address this gap in the literature by employing multimodal magnetic resonance imaging (MRI) techniques to examine the impact of type-2 diabetes on the integrity of surviving sensorimotor neural tissue in individuals with chronic hemiparesis as a result of ischemic stroke. We employ volumetric MRI, diffusion tractography, and magnetic resonance spectroscopy (MRS) to explore the structure of motor and sensory cortex grey matter and white matter projections. We found individuals with chronic stroke and diabetes had lower regional cortical thickness in primary somatosensory cortex, and primary and secondary motor cortices. Contralesional primary and secondary motor cortex thicknesses were negatively related to motor outcomes of the paretic upper-limb in the diabetes group. MRS revealed stroke survivors with diabetes had bilaterally reduced creatine levels in sensorimotor cortex. Diabetes status did not impact gross cortical volumes, white matter volumes, or white matter microstructure in projections from the primary motor and sensory cortex. These results suggest that type-2 diabetes alters cerebral metabolic function, which may result in thinning to sensorimotor grey matter. This work provides preliminary evidence for differential profiles of cerebral recovery from stroke in individuals with diabetes. Given the worldwide increase in the prevalence of diabetes it is critical that we examine the mechanisms of increased post-stroke disability in type-2 diabetes to inform targeted therapies for this population.
Preface

This thesis contains three experiments that were completed by the candidate Jennifer K. Ferris under the supervision of Dr. Lara A. Boyd.

All research described in this thesis was approved by the University of British Columbia’s Clinical Research Ethics Board, certificate # H09-00368. This work was supported by the Canadian Institutes of Health Research (MOP-106651) to L.A.B.

This thesis will be prepared for publication as a multi-authored manuscript in a peer reviewed journal. Experimental conception and design, data analysis, and documentation were principally the work of Jennifer Ferris. Kaitlyn Brown, Sue Peters, Courtney Pollock and Drs. Cameron Mang and Michael Borich collected portions of the data used in this thesis. Sue Peters and Kaitlyn Brown contributed to the development of the tractography procedures used in Experiment 2 and helped with editing the manuscript. Dr. Jason Neva provided assistance with data analyses and helped with editing the manuscript. Dr. Angela Auriat assisted with editing the manuscript.
Table of Contents

Abstract ................................................................................................................................. ii
Preface ................................................................................................................................. iii
Table of Contents .................................................................................................................... iv
List of Tables ........................................................................................................................... vii
List of Figures .......................................................................................................................... viii
List of Abbreviations .............................................................................................................. ix
Acknowledgements ................................................................................................................ xi

Chapter 1: Introduction ......................................................................................................... 1

1.1 Stroke and Diabetes Epidemiology .............................................................................. 1
1.2 Neural Basis of Stroke Recovery .................................................................................. 2
1.3 Neurological Impact of Type-2 Diabetes ...................................................................... 4
1.4 Volumetric Magnetic Resonance Imaging (MRI) ....................................................... 6
   1.4.1 Volumetric MRI in Stroke Research .................................................................... 7
   1.4.2 Volumetric MRI in Diabetes Research ............................................................... 8
1.5 Diffusion Imaging ......................................................................................................... 9
   1.5.1 Tractography in Stroke Research ........................................................................ 11
   1.5.2 Tractography in Diabetes Research ..................................................................... 13
1.6 Magnetic Resonance Spectroscopy (MRS) .............................................................. 15
   1.6.1 MRS in Stroke Research .................................................................................... 17
   1.6.2 MRS in Diabetes Research ................................................................................ 18

Chapter 2: Rationale and Specific Aims ............................................................................. 20
Chapter 3: Methods ........................................................................................................ 22

3.1 Participants ........................................................................................................... 22
3.2 Functional Assessments ....................................................................................... 24
3.3 MRI Acquisition .................................................................................................... 25
3.4 Experiment 1: Cortical Volumetrics ..................................................................... 25
3.5 Experiment 2- Constrained Spherical Deconvolution (CSD) Tractography ........... 26
3.6 Experiment 3: Magnetic Resonance Spectroscopy ............................................ 29
3.7 Statistical Analysis .............................................................................................. 30
  3.7.1 Volumetrics ..................................................................................................... 30
    3.7.1.1 Gross Cerebral Volumes ......................................................................... 30
    3.7.1.2 Regional Cortical Thickness .................................................................. 31
  3.7.2 CSD ................................................................................................................ 31
  3.7.3 MRS ............................................................................................................... 31
  3.7.4 Relationships to Motor and Sensory Function ............................................. 32

Chapter 4: Results ......................................................................................................... 33

4.1 Volumetrics .......................................................................................................... 34
  4.1.1 Gross Cerebral Volumes .............................................................................. 34
  4.1.2 Regional Cortical Thickness ....................................................................... 34
  4.2 CSD .................................................................................................................... 36
  4.3 MRS .................................................................................................................... 37
  4.4 Correlations with Motor Function ..................................................................... 38

Chapter 5: Discussion .................................................................................................... 40

5.1 Changes to Cortical Grey Matter in Chronic Stroke and Diabetes ....................... 40
5.2 White Matter Volumes and Microstructure in Chronic Stroke and Diabetes ............... 42
5.3 Alterations to Cerebral Metabolites in Chronic Stroke and Diabetes ..................... 43
5.4 Limitations ............................................................................................................. 47
5.5 General Conclusions ............................................................................................. 48

Bibliography .................................................................................................................. 50

Appendix A Fugl-Meyer Upper Extremity Assessment .................................................. 64
Appendix B Wolf Motor Function Task .......................................................................... 70
List of Tables

Table 1-1: Summary of MRS metabolites assessed at a field strength of 3.0T .......................... 16
Table 3-1: Participant characteristics....................................................................................... 23
Table 4-1: Demographic variables between groups..................................................................... 33
List of Figures

Figure 1-1: Example Freesurfer segmentation of an individual with chronic stroke ....................... 7
Figure 1-2: A. Visual representation of the eigenvectors of a tensor. B. Different FA estimates from a tensor model. .......................................................................................................................................................... 10
Figure 1-3: Thalamocortical projections to primary motor and sensory cortices ......................... 13
Figure 1-4: Example MRS spectra.................................................................................................................. 16
Figure 3-1: Example ROI drawing and output for thalamocortical tracts ............................................. 28
Figure 3-2: Example MRS voxel placement and LC model output on a participant with cortical involvement in the lesion ....................................................................................................................................................................... 30
Figure 4-1: Group differences in global cortical grey and white matter volumes ....................... 35
Figure 4-2: Group differences in regional cortical thickness................................................................. 35
Figure 4-3: Group differences in CSD FA................................................................................................. 36
Figure 4-4: Group differences in cerebral metabolite profiles.............................................................. 37
Figure 4-5: Negative correlation between motor function in the paretic upper-limb and mean thickness of contralesional primary motor cortex (M1) ................................................................. 39
Figure 4-6: Negative correlation between motor function (A) and motor impairment (B) in the paretic upper-limb and mean thickness of contralesional Brodmann’s Area 6 (BA) ............... 39
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA-</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>BA6-</td>
<td>Brodmann’s Area 6</td>
</tr>
<tr>
<td>CRLB-</td>
<td>Cramér-Rao lower bound</td>
</tr>
<tr>
<td>CSD-</td>
<td>Constrained Spherical Deconvolution</td>
</tr>
<tr>
<td>CST-</td>
<td>Corticospinal Tract</td>
</tr>
<tr>
<td>DCS-</td>
<td>Individual with Diabetes and Chronic Stroke</td>
</tr>
<tr>
<td>DM-</td>
<td>Type-2 Diabetes Mellitus</td>
</tr>
<tr>
<td>DTI-</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>FA-</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>FM-</td>
<td>Fugl-Meyer Upper Extremity Motor Assessment</td>
</tr>
<tr>
<td>fMRI-</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>HA1C-</td>
<td>Glycated Hemoglobin</td>
</tr>
<tr>
<td>MCA-</td>
<td>Middle Cerebral Artery</td>
</tr>
<tr>
<td>ml-</td>
<td>myo-inositol</td>
</tr>
<tr>
<td>mM-</td>
<td>millimolar</td>
</tr>
<tr>
<td>MRI-</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MRS-</td>
<td>Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>M1-</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>NAA-</td>
<td>N-Acetylaspartate</td>
</tr>
<tr>
<td>NDCS-</td>
<td>Individual with no Diabetes and Chronic Stroke</td>
</tr>
<tr>
<td>PLIC-</td>
<td>Posterior Limb of the Internal Capsule</td>
</tr>
<tr>
<td>ppm-</td>
<td>Parts Per Million</td>
</tr>
</tbody>
</table>
PSD- Post-Stroke Duration
ROI- Region of Interest
SD- Standard Deviation
SEM- Standard Error of the Mean
S1- Primary Somatosensory Cortex
T- Tesla
Thal-M1- Thalamus to Primary Motor Cortex Tract
Thal-S1- Thalamus to Primary Somatosensory Cortex Tract
VAN- Ventral Anterior Nucleus of the Thalamus
VLN- Ventral Lateral Nucleus of the Thalamus
VPN- Ventral Posterior Nucleus of the Thalamus
WMFT- Wolf Motor Function Task
Acknowledgements

I would like to thank Dr. Lara Boyd for her supervision and mentorship through my MSc work. Thank you Lara for creating such a stimulating, supportive and enriching environment to train in. I am so looking forward to continue learning from you in my PhD. Thank you to the members of my supervisory committee: Drs. Teresa Liu-Ambrose, Craig Brown, and Kenneth Madden. Your direction and advice were invaluable in the completion of this research.

Thanks to all the members of the Brain Behaviour Lab for your collaboration and friendship. You all make coming to work a joy every day, and I am always amazed by the generosity and talent surrounding me. Special thanks to Kate Brown, Sue Peters, Katie Wadden and Dr. Jason Neva for their contribution and guidance in completion of this project, and to Katherine Touringy for her help with data processing.

It’s impossible to express the extent of my gratitude to my parents for always encouraging me to pursue my passions. You two are constant sources of inspiration.

Finally, thank you to Scott Veale taking every step of this journey with me. I couldn’t have done it without you.
Chapter 1: Introduction

1.1 Stroke and Diabetes Epidemiology

Stroke is a leading cause of adult disability in Canada and worldwide. More than 400,000 Canadians are living with chronic disability as a result of stroke, and stroke incidence is projected to rise\(^1\). The etiology of stroke is complex with multiple factors interacting to influence the probability of first-time stroke. Many of these risk factors are modifiable and dependent on lifestyle. One such factor is type-2 diabetes, an acquired chronic metabolic disorder. Type-2 diabetes is the most prevalent form of diabetes, encompassing 90% of total diabetes cases\(^2\). Type-2 diabetes (hereafter referred to as “diabetes”) is one of the most significant risk factors for ischemic stroke, increasing the risk of stroke by 2-3 fold\(^3\), with some studies estimating a 5 fold greater risk in individuals over 65 years old\(^4\). A high proportion of stroke survivors are also managing diabetes; it is currently estimated that 30% of stroke survivors have diabetes\(^5\).

Not only is diabetes an important risk factor for stroke, research suggests that diabetes negatively impacts stroke outcomes. Individuals with diabetes experience poorer motor\(^6\)-\(^8\) and cognitive\(^9,10\) outcomes after acute stroke, resulting in increased rates of disability\(^11\) and lower self-reported physical health\(^12,13\). Diabetes also increases the risk of deterioration of activities of daily living between 3 and 12 months post stroke\(^11\). The research on diabetic mortality after stroke is mixed. Some studies of acute stroke outcomes showed that diabetes does not increase acute stroke mortality\(^6,14\), yet more recent longitudinal studies have shown diabetes reveal a long term penalty that results in increased rates of mortality in the chronic recovery period\(^15\). Therefore, it appears diabetes may confer greater disability in the acute window and greater decline of function in the chronic window after stroke.
In the past decade research on diabetes has uncovered deleterious effects of this condition on neuronal health in preclinical populations. The mechanisms by which diabetes impacts neuronal function are still far from understood, but there is sufficient evidence to suggest diabetes and stroke may interact over the course of recovery to influence functional outcomes. To date, however, there is scarce research examining how diabetes impacts the brain in stroke recovery, particularly in clinical neuroimaging studies. The present thesis seeks to address this knowledge gap by employing multimodal neuroimaging to explore the impact of diabetes on the brain in individuals with chronic stroke.

Diabetes rates have risen by 70% in Canada since 1999, currently affecting 2.5 million Canadians. Given the aging of our population and increases in obesity and sedentary lifestyles, rates of comorbid stroke and diabetes are projected to continue to rise. It is critical to examine how diabetes impacts the brain after stroke if we hope to mitigate the increased burden of disability in this population.

1.2 Neural Basis of Stroke Recovery

Around two thirds of stroke survivors experience lasting deficits in upper limb motor function, a major contributor to post-stroke disability. After stroke there is a 3-month window in which spontaneous recovery occurs, this window is typically where rehabilitative efforts are focused. Past this point functional recovery slows, but it remains possible for individuals with chronic stroke to learn new movement patterns and make improvements in their rehabilitation. Recent years have seen advances in stroke therapies and management, yet there remains a great deal of unexplained variability in the prognosis of motor outcomes for stroke survivors, particularly for individuals with more severe initial impairment. Clinical
measures alone fail to predict which individuals will make a full recovery from stroke and which will not\textsuperscript{32,33}. Examining the gross characteristics of the stroke lesion, such as lesion size, also does not provide an accurate predictive measure of motor recovery\textsuperscript{34,35}. Therefore, research is increasingly focused on using advanced neuroimaging techniques to discover typical neurological patterns of motor recovery in stroke survivors.

Stroke recovery is heavily dependent on lesion location\textsuperscript{36,37}, with a greater extent of damage to key motor areas such as the corticospinal tract being associated with poorer recovery of motor function\textsuperscript{37}. Furthermore, a stroke injury does not only impact the direct lesion site, networks that are connected to the injury can be impacted through diaschisis\textsuperscript{38–41} meaning that a stroke lesion can have wide ranging effects in connected networks throughout the brain. If primary motor areas are damaged by a stroke, functions must be remapped onto surviving regions capable of subsuming the role of lost tissue\textsuperscript{42,43}. The integrity or health of remaining motor networks in the brain after stroke may be a key predictor of recovery, as these regions will provide the neural substrate for remapping lost functions by changing the structure and function of the surviving brain\textsuperscript{44}. Factors that alter the brain’s ability to reroute lost functions onto healthy neural tissue could theoretically influence the degree of behavioural recovery. Advances in neuroimaging have allowed for the study of the integrity of surviving tissue and have yielded some insights into the process of functional recovery. These known networks implicated in stroke recovery can be used to inform a hypothesis-driven investigation of how comorbid conditions impact motor recovery after stroke.
1.3 Neurological Impact of Type-2 Diabetes

Type-2 diabetes mellitus is characterized by hyperglycemia as a result of deficiencies in insulin signaling or secretion. The precise dietary composition that leads to manifestation of diabetes remains controversial, however, it is well established that diabetes often accompanies obesity and a sedentary lifestyle. The impact of diabetes on the peripheral nervous system has long been recognized, with peripheral neuropathy constituting a major health complication in diabetes. Research has only recently begun to examine the impact of diabetes on the central nervous system. There are several potential mechanisms by which type-2 diabetes could negatively impact the brain’s ability to recover function after a stroke insult.

One possibility is that diabetes increases the total amount of vascular damage in the brain. Diabetes increases cerebral small vessel disease, though this increase depends on the microlesion subtype. Strong evidence supports an increase in lacunar infarcts in individuals with diabetes. Evidence for increased white matter hyperintensities or cerebral microbleeds has been mixed, but a general consensus exists that diabetes increases the total amount of small vessel vascular damage in the brain. Diabetes increases the risk of recurrent stroke, but it is currently unclear whether diabetes also increases infarct volume. Hyperglycemia at the time of stroke admission is associated with a larger ischemic lesion and greater lesion expansion into the penumbra. However, this may be the result of stress hyperglycemia provoked by the ischemic event, rather than a consequence of baseline blood glucose status. Rodent models of diabetes and stroke have not observed an increase in primary lesion size from diabetes alone, without a large bolus of glucose delivered beyond levels which are typically observed in clinical settings. Additionally hyperglycemia’s impact on lesion outcomes in clinical studies are independent of diabetes status. It is also telling that...
while hyperglycemia on admission is associated with higher mortality, stroke survivors with diabetes do not have increased mortality in the acute window, therefore the observed relationship between hyperglycemia and lesion size is likely an independent effect from diabetes status. Diabetes is therefore more liable to increase neuronal dysfunction from microvascular damage rather than increasing the volume of the ischemic lesion. Given the documented decline of function in diabetes in the chronic window after stroke, a more likely explanation for increases in post-stroke disability is that diabetes somehow predisposes the brain to poorer recovery over the long term.

Another possibility is that diabetes alters neuronal function such that the ability to remap lost sensorimotor functions is reduced. Diabetes reduces neuroplasticity in hippocampal tissue in animal models. Reduced cortical plasticity would result in less use-dependent driving of cortical reorganization to regain function after stroke. Confirming this hypothesis for diabetes and sensorimotor function, Sweetnam (2012) reported reduced cortical plasticity in sensorimotor cortex after an ischemic insult in a rat model of type-1 diabetes. An interesting pattern emerging from the literature is alterations to central somatosensory signaling in diabetes. Otherwise healthy individuals with diabetes show reduced functional connectivity between primary somatosensory cortex and the rest of the brain, independent of an effect of peripheral neuropathy. Similarly diabetic rodents show reduced central somatosensory signaling, which is also independent of lower conduction velocity from peripheral neuropathy. Reductions of stimulus-evoked amplitudes were specific to the primary somatosensory cortex in this study and were not observed in the hippocampus. Diabetes likely reduces cortical plasticity, which may result in poorer somatosensory cortex function, but the precise nature of this relationship and its relevance to stroke recovery is far from understood.
The connection between diabetes and cerebral health was first observed in relation to the increased risk of Alzheimer’s disease in diabetic populations\textsuperscript{75,76}. As such, the majority of previous research has focused on the relationship of diabetes to cognitive decline and hippocampal dysfunction in elderly populations\textsuperscript{77–81}. The study of the impact of diabetes on sensorimotor function and on stroke recovery is very much in its infancy. However, based on available evidence from the cognitive literature there is appropriate justification to extend exploratory imaging examinations to motor and sensory circuits in chronic stroke populations. We will now review previous research on stroke and diabetes for three imaging modalities to be employed in this thesis investigation to inform a hypothesis driven investigation of changes to sensorimotor circuits in diabetes after stroke.

1.4 Volumetric Magnetic Resonance Imaging (MRI)

Volumetric analyses of T1-weighted Magnetic Resonance Imaging (MRI) scans involves delineating regions of interest and quantifying their volume and thickness. This may be accomplished manually or by using automated software such as the Freesurfer package (http://surfer.nmr.mgh.harvard.edu). This enables quantification of volumes of normal appearing brain tissue, which may then be related to behavioural outcomes. Freesurfer uses cortical folds as landmarks by which to segment the cortex with a high degree of reliability\textsuperscript{82,83}. Freesurfer determines the outermost (or pial) surface of the brain and the boundary between cortical grey and white matter by modeling and inflating these surfaces; the thickness of the cortex is then estimated by measuring the distance between these two reconstructed surfaces\textsuperscript{84,85}. Cortical thickness is calculated as the average distance between the pial and white matter surfaces across the entire region of interest (in mm), while cortical volume is the overall volume (in mm\textsuperscript{3}) of the
region of interest\textsuperscript{85} (Figure 1-1). Freesurfer can also quantify total grey and white matter volumes in the brain and total intracranial volume\textsuperscript{86}, for a gross measure of cerebral volume.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{example_freesurfer_segmentation.png}
\caption{Example Freesurfer segmentation of an individual with chronic stroke. Cortical thickness is measured as the average difference between the pial (red) and white matter (blue) boundaries across an entire region of interest parcellated by a surface-based atlas (Destrieux, 2009)}
\end{figure}

1.4.1 \textbf{Volumetric MRI in Stroke Research}

Freesurfer has been utilized to estimate cortical volumes and thickness after stroke, providing a metric to examine surviving sensorimotor cortices and relate volumes to motor outcomes. A recent comparison of three commonly employed automated volumetric programs demonstrated that Freesurfer has the best accuracy and sensitivity for use in stroke\textsuperscript{87}. However, as Freesurfer relies primarily on an intact cortical surface in order to perform segmentation analyses, care must be taken for individuals with cortical lesions, which may disrupt accurate
segmentation of the cortical surface. Manual inspection of Freesurfer segmentation is required to confirm the accuracy of estimated cortical volumes.

Sensorimotor cortices undergo structural changes after stroke, likely representing compensatory mechanisms of functional recovery. Longitudinal analyses from the acute to subacute period reveal ipsilesional primary motor cortex (M1) and supplementary motor areas become thinner over time, perhaps caused by perhaps caused by neuronal death, or loss of dendritic density as a result of diaschisis or disuse. Contralesional M1 and primary sensory cortex (S1) become thicker in both subacute and chronic stroke. This likely reflects structural plasticity as a result of activity in homologous regions in the contralesional sensorimotor cortex increasing to compensate for the injury. Supporting the notion of a relationship between cortical thickness and functional activity, sensory areas with higher cortical thickness also show greater functional activation measured by functional MRI. As a general principle it appears that greater thickness in ipsilesional motor areas relates to better motor outcomes. Cortical thickness can also predict response to therapeutic interventions, with individuals with bilaterally thinner M1 showing less response to constraint-induced therapy. Cortical volumetrics are therefore a useful index of structural plasticity occurring in stroke recovery. Asymmetry in the thickness between ipsilesional and contralesional sensorimotor cortices might reflect diaschisis of tissues affected by the stroke infarct as well as compensatory mechanisms in the contralesional hemisphere coming online to facilitate recovery.

1.4.2 **Volumetric MRI in Diabetes Research**

The most consistent finding from imaging studies of adults with diabetes is global cortical grey matter atrophy. Reductions to cerebral volumes may be specific to cortical
grey matter as some volumetric analyses have revealed no reduction in total white matter volumes\textsuperscript{54,98}. Cortical atrophy is associated with cognitive decline in older adults with diabetes in several reports\textsuperscript{100,101}. However, patterns of cortical thinning are heterogeneous across the cortical mantle, as revealed by more recent region-specific volumetric analyses. Reductions to grey matter volumes in diabetes are most pronounced in the medial temporal lobe\textsuperscript{102–104}, dorsolateral prefrontal cortex\textsuperscript{105}, and diffusely in regions associated with the default mode network\textsuperscript{104}. These changes likely mediate disruptions in cognitive functions in diabetes, though this has yet to be directly assessed. Importantly the impact of diabetes on cortical thickness does not seem to be due to advancing age, adolescents with diabetes also show reduced grey matter thickness in the frontal lobes relating to markers of insulin resistance\textsuperscript{106}. Only one study has reported changes to sensorimotor grey matter volumes in diabetes, Chen (2012) reported lower grey matter volumes in the right M1 in individuals with diabetes, relative to healthy controls\textsuperscript{107}. This study was notable since they carefully excluded participants with any microvascular complications, and therefore this result can be attributed to an effect of diabetes itself rather the result of increased insults from microlesions\textsuperscript{107}. Overall it appears that diabetes reduces grey matter volumes heterogeneously across the cortical mantle and this risk is conferred across the lifespan. To date no volumetric analyses have been performed in individuals with diabetes after stroke.

1.5 Diffusion Imaging

Diffusion tensor imaging (DTI) and other tractography techniques allow for the examination of white matter pathways in the brain, and are sensitive to microstructural alterations in white matter tracts. Fractional anisotropy (FA) is the most commonly reported DTI measure. FA indexes the degree of anisotropic water diffusion within the region of interest\textsuperscript{108}.
FA is calculated from the eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) of the diffusion tensor as a ratio of the differences in diffusivity between the eigenvalues over the concordance in diffusivity in the eigenvalues\textsuperscript{108}. FA is scalar value ranging from 0 to 1 where 0 indicates complete isotropic diffusion and 1 indicates complete anisotropic diffusion (Figure 1-2). Several properties of the underlying tissue have been shown to influence FA, including fiber density, fiber diameter, and degree of myelination\textsuperscript{109}. In well defined white matter tracts, such as the corticospinal tract, reduced FA is typically interpreted as a loss of integrity to the white matter tract, though the exact physiological nature of the change to tissue integrity cannot be determined from FA alone\textsuperscript{109,110}.

**Figure 1-2:** A. Visual representation of the eigenvectors of a tensor. B. Different FA estimates from a tensor model.
1.5.1 Tractography in Stroke Research

FA has been extensively employed to examine microstructural changes to the corticospinal tract (CST) as they relate to motor outcomes after stroke. A consistent finding in the stroke literature is a reduction of FA in the ipsilesional CST in both acute\textsuperscript{111,112} and chronic\textsuperscript{25,113,114} stroke patients. Ipsilesional FA is related to multiple motor outcomes including manual dexterity\textsuperscript{114,115}, motor learning\textsuperscript{25}, and response to motor training interventions\textsuperscript{113}. Asymmetry between contralesional and ipsilesional CST FA has emerged as a useful predictor of motor outcomes after stroke\textsuperscript{30,116–118}, and predicts more variance in motor outcomes than lesion volume\textsuperscript{119}. Though DTI measures of CST have been purported to index post-stroke disability, they do not explain all the variance in stroke recovery\textsuperscript{35,120}, necessitating the examination of other relevant pathways in the brain.

Thalamocortical tracts have received significantly less research attention than the CST in the stroke literature, however thalamocortical tracts may also be related to motor recovery as they have a demonstrated importance in motor signaling. The thalamus is a critical relay center between the cerebral cortex and subcortical structures. The ventral anterior nucleus of the thalamus relays signals from cerebellar and basal ganglia afferents and the ventral lateral nucleus relays signals from basal ganglia afferents to premotor and primary motor cortex. The ventral posterior nucleus receives incoming somatosensory information from spinal and cranial nerve afferents and relays them to the primary somatosensory cortex (Figure 1-3). Disruptions along thalamocortical pathways would theoretically impact the performance of the motor and somatosensory systems. Investigations of thalamocortical pathways as they relate to stroke recovery are quite rare, but there is some empirical support for thalamocortical involvement in motor recovery. Volumes of the mediodorsal thalamus (which has connectivity with the
dorsolateral prefrontal cortex) expand over the course of stroke recovery, and the magnitude of this expansion relates to degree of motor recovery\textsuperscript{96}. Similarly, covariance between thalamic and cortical sensorimotor grey matter volumes is predictive of hand function\textsuperscript{121}, indicating the structural integrity of this network is important for stroke recovery. Functional imaging also reveals the importance of thalamic pathways in motor performance. Individuals with good recovery after stroke show increased metabolic coupling (a measure of functional connectivity) between the thalamus and cerebellum\textsuperscript{122}. Additionally, young healthy individuals with stronger functional connectivity between the thalamus and cortical motor areas show faster motor learning, assessed by resting state fMRI\textsuperscript{123}. Therefore evidence from both structural and functional neuroimaging suggests a role of thalamocortical networks in motor recovery from stroke, yet to date no study has used DTI to explore the microstructural integrity of the white matter pathways mediating previously observed connectivity. These pathways can be identified through diffusion tensor imaging\textsuperscript{124}, and this examination may yield insight into motor and somatosensory integration and remodeling after injury.
1.5.2 Tractography in Diabetes Research

Numerous alterations to white matter microstructure have been identified in otherwise healthy individuals with type-2 diabetes. The strongest available evidence for white matter disruptions in diabetes suggests decreased FA in circuits relating to the temporal\textsuperscript{105,125,126} and frontal lobes\textsuperscript{125–128}. While much attention has been paid to the impact of diabetes on the hippocampus, the uncinate fasciculus is the most commonly reported white matter tract with reduced FA in diabetes\textsuperscript{52,127–129}. These alterations to white matter microstructure relate to cognitive performance in several reports\textsuperscript{52,125,128,129}. Though the relationship of white matter microstructure to motor function has not been directly addressed, several pathways the relate to
motor performance have been reported to be reduced in diabetes including the anterior corpus callosum\textsuperscript{127,129}, corona radiata\textsuperscript{129}, cerebellum\textsuperscript{126} and prefrontal cortex\textsuperscript{105,125,127,130}. Hsu (2012) reported that FA of the frontal lobes and cerebellum was negatively correlated with diabetes disease duration\textsuperscript{126}, suggesting a negative cumulative impact of diabetes on motor circuits.

Thalamocortical pathways are also likely impacted by diabetes. FA is reduced in thalamic radiations in older adults with diabetes\textsuperscript{129,131}. FA is also reduced in the anterior limb of internal capsule, and these FA levels correlate negatively with glycated hemoglobin (HA1c)\textsuperscript{131}. Specific to sensorimotor circuits, resting state fMRI has revealed lowered connectivity between the thalamus and S1\textsuperscript{73} and M1\textsuperscript{132} in individuals with diabetes. Piriz (2009) reports reductions to S1 responsivity to thalamic, but not callosal, inputs in a rodent model of diabetic neuropathy\textsuperscript{74}. Therefore it is likely that the structural connectivity between the thalamus and primary motor and sensory circuits is disrupted by diabetes, but no DTI study to date has assessed the microstructural status of these pathways.

There exists some data on the impact of diabetes on white matter status after stroke. The animal literature on this topic provides histological evidence for white matter alterations in diabetic rodents after stroke, with mice showing greater axonal damage in the ischemic boundary zone, independent of greater lesion damage\textsuperscript{133}. A recent study by Ding (2015) followed diabetic rats longitudinally after ischemic stroke using DTI imaging and post-mortem histological assessments. Diabetes significantly lowered corpus callosum FA extending to the ischemic lesion, and histology revealed lower axonal density in the regions of interest with reduced FA\textsuperscript{134}. Taken together this research suggests that diabetes may increase white matter damage before a stroke event, and increase the vulnerability of white matter pathways to stroke-induced damage.
1.6 Magnetic Resonance Spectroscopy (MRS)

Magnetic Resonance Spectroscopy (MRS) is an imaging technique that allows for the quantification of biologically relevant metabolites in vivo in a defined region of tissue. Proton magnetic resonance spectroscopy (H\textsuperscript{1} MRS) uses signals from hydrogen nuclei to determine the unique resonance signatures of different metabolites. Protons in different molecular environments will resonate at unique frequencies in a static magnetic field. The resonance frequencies are measured in parts per million (ppm), and are represented along the x-axis in MRS output. The intensity of the resonance signal changes depending on the concentration of a molecule with a given resonance signature, and is reported in molarity units (millimolar (mM)) along the y-axis (Figure 1-4). At a field strength of 3-Tesla it is possible to resolve the peaks of 5 cerebral metabolites: N-Acetylaspartate (NAA), which is primarily found in intact neurons; myo-inositol (mI), a cerebral osmolyte that is found in glial cells; glutamate, the principal excitatory neurotransmitter of the central nervous system; choline, a marker of cellular membrane turnover or integrity; and creatine, a marker of energy metabolism/storage in the brain (see Table 1-1 for summary of metabolite functions). MRS provides a valuable compliment to structural MRI techniques as it gives information of the biochemical characteristics occurring in target tissues.
**Figure 1-4:** Example MRS spectra. Resonance peaks corresponding to different cerebral metabolites (measures in ppm). Concentration of the metabolite is measures in mM along the y-axis.

<table>
<thead>
<tr>
<th>Cerebral Metabolite</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Acetylaspartate (NAA+NAAG)</td>
<td>Principally found in intact neurons</td>
</tr>
<tr>
<td></td>
<td>Synthesized in neuronal mitochondria</td>
</tr>
<tr>
<td></td>
<td>Function unknown</td>
</tr>
<tr>
<td>Myo-inositol</td>
<td>Principally found in astrocytes</td>
</tr>
<tr>
<td></td>
<td>Cerebral osmolyte</td>
</tr>
<tr>
<td>Glutamate (glutamate + glutamine)</td>
<td>Main excitatory neurotransmitter of central nervous system</td>
</tr>
<tr>
<td>Choline</td>
<td>Phospholipid membrane synthesis</td>
</tr>
<tr>
<td>Creatine (creatine + phosphocreatine)</td>
<td>Cellular oxidative metabolism-ATP synthesis and high energy phosphate storage</td>
</tr>
</tbody>
</table>

**Table 1-1:** Summary of MRS metabolites assessed at a field strength of 3.0T
1.6.1 MRS in Stroke Research

Of the available metabolites for quantification, NAA has most consistently been related to motor outcomes after stroke. The precise physiological role of NAA in neurons remains unclear; low NAA levels could either indicate neural death or reduced neuronal function\textsuperscript{138}. In chronic subcortical stroke NAA is reduced in spared ipsilesional motor cortex\textsuperscript{139,140}, and ipsilesional premotor areas\textsuperscript{140,141}, relative to healthy controls. This is consistent with neuronal loss or dysfunction by diaschisis. Ipsilesional NAA levels in primary and non-primary motor cortex positively correlate with motor function in several reports\textsuperscript{139–141}. NAA correlates negatively with the extent of M1 activity in response to a handgrip task, perhaps indicating greater cortical recruitment is necessary to offset dysfunctional neurons\textsuperscript{142}. Myo-inositol has also been reported as altered in subcortical stroke, though the functional implications of these findings are less clear. Myo-inositol is elevated in ipsilesional M1\textsuperscript{139,140}, and premotor cortex\textsuperscript{141} relative to healthy controls. Elevated myo-inositol levels could either reflect an adaptive characteristic through increased glial-mediated plasticity\textsuperscript{143,144}, or may reflect gliosis occurring as a result of neural death\textsuperscript{145}. To our knowledge, hemispheric alterations to glutamate have not been reported in chronic stroke but one study has reported a positive relationship between ipsilesional glutamate levels and motor impairment\textsuperscript{139}. Choline and creatine have not been reported as altered in chronic stroke, because they are commonly used as ratios to normalize other cerebral metabolites of interest\textsuperscript{146–148}. However, choline and creatine levels change after acute cerebral infarct\textsuperscript{149,150}, and therefore uncorrected (raw) levels of these metabolites should be examined in the chronic stroke window.
1.6.2 MRS in Diabetes Research

As with the other imaging modalities discussed thus far, the majority of MRS work in diabetes has mostly been performed in the context of cognitive impairment in otherwise healthy individuals. No study to date has examined changes to metabolite levels in primary motor or sensory cortex in diabetes. From studies that report raw metabolite levels, elevated myo-inositol has been reported in the dorsolateral prefrontal cortex$^{151}$ and in the hippocampus$^{152,153}$. Increased creatine levels have been reported in subcortical grey matter structures such as the hippocampus in rats$^{152}$ and humans$^{153}$ with overt diabetes, and in the thalamus of individuals with a high risk of diabetes$^{154}$. Increased myo-inositol and creatine levels are suggestive of increased glial metabolism or proliferation and changes to cellular energy pathways in diabetes$^{145}$.

The majority of previous MRS studies in diabetes have used metabolites ratios, frequently normalizing metabolites to creatine. In the diabetes literature there have been multiple reports of decreased levels of NAA/creatine in the prefrontal cortex$^{155–157}$, and in the hippocampus$^{156,158}$. Individuals with vascular risk factors, including diabetes have decreased NAA/creatine in prefrontal cortex grey matter$^{155}$. Low NAA/creatine ration in the prefrontal cortex relate negatively to HAIc levels$^{157}$, and increase in response to insulin infusion in insulin-sensitive participants only$^{156}$, providing evidence than insulin resistance decreases NAA/creatine levels in the prefrontal cortex. These findings are typically interpreted as reduced NAA levels indicating lower neuronal density or neural health conferred by diabetes. This complements findings from structural MR imaging showing cerebral atrophy in diabetes$^{54,80,97–99}$. Previous studies also report changes to glutamate/creatine levels in diabetes. Glutamate/creatine is higher in cortical frontal$^{156}$ and temporal tissue$^{155,156}$, and occipitoparietal tissue$^{159}$, and lower in the hippocampus$^{158}$. Hippocampal glutamate/creatine levels in the hippocampus correlate negatively
with vascular risk factors for stroke (including diabetes)\textsuperscript{158}. This finding is typically interpreted as excess cerebral glucose causing an osmotic imbalance resulting in dysregulated neurotransmitter levels\textsuperscript{158}. However, using creatine to normalize metabolite concentrations limits the interpretation of the data. Given the evidence for alterations to creatine levels in diabetes\textsuperscript{152--154} we cannot be sure whether changes are due to alterations to NAA or glutamate, or to creatine, or both.

Only one previous study has employed MRS to examine diabetes in individuals with acute stroke\textsuperscript{160}. The authors report significantly lower NAA/creatine ratios in the infarcted area and in contralesional basal ganglia in diabetic stroke survivors relative to non-diabetic controls\textsuperscript{160}. This study only reported NAA/creatine, choline/creatine and lactate/creatine ratios so there were no data speaking to whether glutamate or myo-inositol were disrupted after stroke. No study to date has examined changes to raw cerebral metabolites in diabetes after stroke.
Chapter 2: Rationale and Specific Aims

Evidence from the diabetes literature suggests that diabetes impacts sensorimotor integrity and neuronal metabolic function. It is likely that these changes interact with neurological processes of recovery from stroke to result in worse recovery outcomes observed in patients with comorbid diabetes and stroke. However, to date very little research has examined the impact of diabetes on neural health after stroke. The objective of this thesis is to examine known neurological networks that are important for sensorimotor recovery after stroke and compare their integrity between individuals with and without a diagnosis of type-2 diabetes in a cohort of chronic stroke survivors. This study employs multimodal neuroimaging for a broad and exploratory examination of altered sensorimotor structure in individuals with diabetes after stroke.

Aim 1: To examine whether individuals with type-2 diabetes show reduced cerebral volume and reduced cortical grey matter thickness in surviving motor and somatosensory cortices.

Hypotheses: Individuals with chronic stroke and diabetes will show reduced gross grey matter volumes and bilaterally reduced regional cortical thickness in primary sensory cortex, and primary and secondary motor cortices.

Aim 2: To evaluate if type-2 diabetes alters the microstructural properties of white matter tracts in the corticospinal tract and in motor and sensory integration pathways between the thalamus and primary motor and sensory cortices, respectively.

Hypothesis: Individuals with diabetes will show bilaterally reduced FA in thalamocortical pathways.
**Aim 3:** To examine alterations to cerebral metabolites profiles in primary sensorimotor cortex in individuals with type-2 diabetes

Hypothesis: Individuals with diabetes will show reduced NAA and higher creatine and myo-inositol in primary sensorimotor cortex

**Aim 4:** To evaluate whether any observed differences in imaging measures conferred by type-2 diabetes status relate to motor and sensory functioning in the hemiparetic limb across the sample of stroke survivors and within the group of individuals with diabetes.

Hypothesis: Any observed changes to structural integrity of motor or sensory networks in diabetes will relate to decreased motor or sensory function in patients with diabetes.

The advantages to studying a chronic stroke cohort in the present analysis are two-fold: First given that the research on hyperglycemia and ischemic conversion in the acute period is still unclear, studying chronic stroke will allow for the investigation of the integrity or surviving regions after the infarct has stabilized. Secondly, given data that suggests that diabetes increases a decline of functional outcomes in the chronic period, this may be a clinically sensitive time period in which diabetes impacts neural recovery. This multimodal neuroimaging approach provides preliminary evidence to inform future research on sensorimotor recovery in diabetes.
Chapter 3: Methods

3.1 Participants

Participants were recruited from the local community. Participants were excluded if they had a history of seizure, head trauma, neurodegenerative disease, hypothyroidism, type-1 diabetes, or if they reported any contraindications to MRI. The University of British Columbia Research Ethics Board approved all aspects of the study design (H09-00368). Informed consent was obtained from each participant in accordance with the declaration of Helsinki.

Twenty-five individuals in the chronic phase of their first clinically diagnosed stroke were recruited to participate in this study (means ± SD: age: 67 ± 8.8; post stroke duration (months): 65 ± 61.4; Fugl-Meyer score: 41 ± 22.6; 7 females). Eleven individuals had a diagnosis of type-2 diabetes (diabetes + chronic stroke: DCS; 2 females); fourteen individuals did not (no diabetes + chronic stroke: NDCS; 5 females). We recruited a heterogeneous stroke group in lesion size, location, and degree of motor impairment (assessed by Fugl-Meyer Upper Extremity Motor Assessment\textsuperscript{16}) (Table 3-1).
<table>
<thead>
<tr>
<th>Participant</th>
<th>DM</th>
<th>Sex</th>
<th>Age (y)</th>
<th>PSD (mo)</th>
<th>FM (/66)</th>
<th>Freesurfer</th>
<th>DTI</th>
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</tbody>
</table>

**Table 3-1:** Participant characteristics. DM: Type-2 diabetes mellitus; PSD: post stroke duration; FM: Fugl-Meyer score; MCA: middle cerebral artery; R: right; L: left; M: male; F: female; N: no; Y: yes
3.2 Functional Assessments

Licensed physiotherapists completed the functional assessments (SP; MB; CP). To index motor impairment in the hemiparetic arm we employed the upper extremity portion of the Fugl-Meyer assessment (FM)\(^{161}\). The FM scale is widely used in clinical and research settings to characterize motor impairment after stroke\(^{162}\). The FM assessment is scored from 0-66 with higher scores indicating less motor impairment. To index motor function we employed the Wolf Motor Function Task (WMFT)\(^{163}\), which consists of 15 movement items in which performance is indexed by time to complete the task. The mean value is then used to calculate a projected mean rate per minute of task completion as follows: Task rate = 60 (s) / Performance time (s). If an individual was unable to complete a task within 120s then a score of 0 was assigned for that task. The average rate of performance was then calculated across all tasks for a mean total score. WMFT assessments were conducted for both the paretic and non-paretic arm. Mean WMFT rate score is a valid and sensitive measure of motor function after stroke\(^{164}\).

Somatosensory function was assessed by pressure perception thresholds using graded monofilaments. Perceptual thresholds were tested on three sites of each hand (dorsum, thenar and hypothenar regions). Participants were asked to indicate when they felt pressure from a monofilament while their vision was occluded. Somatosensory testing was conducted on both hands by applying monofilament pressure to each testing site in a random order. The lowest monofilament thickness required to elicit an indication of sensation from the participant was recorded. Sensory perception threshold was calculated separately for each hand by summing the perceptual threshold level on each testing site for a total score out of a possible 19.95, with lower values indicating more sensitive sensory perception and less somatosensory impairment. Monofilament testing is a reliable measure of somatosensory function in the paretic limb\(^{165,166}\).
3.3 MRI Acquisition

MR acquisition was conducted at the University of British Columbia MRI research center on a Philips Achieva 3.0T whole body MRI scanner (Philips Healthcare, Best, The Netherlands), using an eight-channel sensitivity encoding head coil (SENSE factor = 2.4) and parallel imaging. All participants received a high-resolution three-dimensional T\(_1\)-weighted anatomical scan (T\(_R\) = 7.47 ms, T\(_E\) = 3.65 ms, flip angle \(\theta = 6^\circ\), FOV = 256 X 256 mm, 160 slices, 1 mm\(^3\) isotropic voxel). A high angular resolution diffusion imaging (HARDI) scan was performed using a single shot echo-planar imaging (EPI) sequence (T\(_R\) = 7096 ms, T\(_E\) = 60 ms, FOV = 224 X 224 mm, 70 slices, voxel dimensions = 2.2 x 2.2 x 2.2 mm\(^3\)). Diffusion weighting was applied across 60 independent non-collinear orientations \((b = 700 \text{s/mm}^2)\) along with five unweighted images \((b = 0 \text{s/mm}^2)\).

3.4 Experiment 1: Cortical Volumetrics

T1 scans were processed using Freesurfer Software v5.3.0 (http://surfer.nmr.mgh.harvard.edu). Freesurfer analysis was restricted to individuals with subcortical lesions, as Freesurfer segmentation is done through identification of cortical landmarks, and therefore accurate parcellation of cortical regions is not possible in the presence of large cortical lesions or significant loss of cortex due to atrophy. Seventeen participants in the current sample were processed by the Freesurfer pipeline (8 DCS, 9 NDCS; means ± SD: age: 67 ± 8.8; time since stroke (months): 62 ± 69.5; Fugl-Meyer score: 49 ± 19.2).

Cortical reconstruction and volumetric segmentation were performed using standard processing pipelines\(^{84,167}\). Briefly, the process includes motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of subcortical white and grey matter
structures\textsuperscript{168}, intensity normalization, tessellation of the cortical grey and white matter boundaries, and automated topology correction and surface deformation following intensity gradients. Scans are then registered to an atlas which utilizes cortical folding patterns to segment cortical geometry across subjects\textsuperscript{82}, and data on cortical regions of interest are extracted. All scans were visually inspected by a single rater (JKF) and, where necessary, lesions were manually masked and Freesurfer segmentation was re-run to ensure accuracy of cortical segmentation based on intensity normalization. Eight scans included in the final analysis required manual masking of lesions. Final data was deemed acceptable if parcellation of healthy appearing brain tissue was accurate based on visual inspection, and stroke lesions were not encroaching on regions of interest (ROIs). Whole brain cortical grey and white matter volumes were calculated by normalizing total cortical grey and total white matter volumes to total estimated intracranial volumes separately for each hemisphere. Estimated intracranial volumes in Freesurfer have good reliability between adult subjects, but Freesurfer does systematically overestimate intracranial volume\textsuperscript{169,170}. However, this overestimation is consistent across subjects and any estimation bias introduced by estimated intracranial volumes is less than what would be introduced by variations in head size in non-normalized scans\textsuperscript{171}. ROIs were selected \textit{a priori} based on demonstrated relevance to sensorimotor function after stroke; bilateral cortical thickness of M1, S1 and Brodmann’s Area 6 (BA6; premotor and supplementary motor cortices) were used in analyses.

3.5 \textbf{Experiment 2- Constrained Spherical Deconvolution (CSD) Tractography}

Diffusion-weighted images were processed using the Matlab-based software package ExploreDTI (www.exploredti.com). Raw image quality was inspected for motion artifacts or
instrumental noise using quality assurance tools in ExploreDTI. Diffusion images were then corrected for motion and eddy-current induced distortions; during motion correction, signal intensity was modulated and b-matrix was rotated\textsuperscript{172}. Scans were left in native space for analysis due to variability in lesion size and location across subjects. Constrained spherical deconvolution (CSD)-based whole-brain fiber tractography was initiated at each voxel using a seedpoint resolution of $2\text{mm}^3$, $0.2\text{mm}$ step size, angle threshold of $>40^\circ$, and fiber length range of $50$–$500\text{mm}$\textsuperscript{173}. CSD-based tractography was selected due to previously published work from our group showing superior fiber detection with CSD rather than tensor-based tractography for use in chronic stroke with tracts that are known to be uniform in orientation\textsuperscript{173}. CSD tractography has high reliability in chronic stroke\textsuperscript{174}.

ROIs were drawn on the whole-brain diffusion map to isolate data from tracts of interest. ROIs were delineated manually by a single experienced rater (KT) for each participant in native space. ROIs were drawn bilaterally in the axial plane. For the CST; first a SEED ROI was placed on the posterior limb of the internal capsule (PLIC) at the level of the anterior commissure, subsequently an AND ROI was drawn in the ipsilateral middle pons, in accordance with previously published methods from our group\textsuperscript{173}. For thalamocortical tracts: first a “SEED” region was drawn on the whole thalamus at the level of the anterior commissure; subsequently an “AND” region was drawn on the ipsilateral M1 (thal-M1) or S1 (thal-S1) at the level of the hand knob. M1 was outlined between the border of the central sulcus and the precentral sulcus\textsuperscript{175}, S1 was delineated by tracing the gyrus immediately posterior to M1. The SEED and AND ROIs ensure that only tracts passing through both ROIs are counted towards analysis. For thal-M1 tracts a “NOT” region was additionally included to the ipsilateral middle pons to prevent tracts from the CST to be counted towards analysis (see Figure 3-1 for representative thalamocortical...
ROI drawings and output). For all tracts, fiber tract reconstruction was performed for CSD with a deterministic streamline algorithm\textsuperscript{173,174}. Mean values for FA were calculated along the entire length of reconstructed fiber projections initiated from ROIs.

**Figure 3-1:** Example ROI drawing and output for thalamocortical tracts. A: “SEED” ROI drawn over entire thalamus; B: “AND” ROI drawn over primary somatosensory cortex at the level of hand knob in primary motor cortex; C: CSD tractography for thalamus-S1 tract.
3.6 Experiment 3: Magnetic Resonance Spectroscopy

A single-voxel $^1$H-MRS PRESS spectra was acquired ($T_R = 2000\text{ms}$, $T_E = 35\text{ms}$, sampling frequency = 2000Hz, data points = 1024, signal averages = 128 voxel dimensions = 30mm x 22mm x 15mm), with the voxel placed bilaterally centered over the hand representation in primary motor cortex$^{176}$ (Figure 3-2). Automatic second-order projection-based shimming was performed. Voxels were placed manually, ensuring that they captured grey matter of the motor cortex without exciting the surrounding cerebrospinal fluid. Individuals with lesions encroaching in ipsilesional sensorimotor cortex were excluded from the current analysis.

Eighteen individuals in the current sample met criteria for inclusion in the MRS dataset (9 DCS, 9 NDCS; means ± SD: age: $67 ± 9.3$; post stroke duration (months): $78 ± 62.7$; Fugl-Meyer score: $45 ± 21.6$; 4 females).

Raw MRS files were processed using the automated software LCModel$^{177}$. Spectral fits were visually inspected (JKF) to ensure quality of MRS data. To index data fitting quality metabolite concentrations were rejected based on the Cramér-Rao lower bound (CRLB) estimations from LCModel; metabolites were rejected when the CRLB was greater than 25% of the median value of the metabolite concentrations$^{178}$. No metabolites in the current study required rejection on this basis. Absolute concentrations of MRS metabolites (NAA, mI, glutamate, choline, creatine) were determined and used towards analysis.
Figure 3-2: Example MRS voxel placement and LC model output on a participant with cortical involvement of the lesion. Voxels were manually placed bilaterally over the “hand knob” region of primary motor cortex

3.7 Statistical Analysis

All statistical analyses were conducted using SPSS software (SPSS V23). For all variables, assumptions of normality were examined by visual inspection of the data and objectively confirmed by the Shapiro-Wilk test. Post hoc testing was performed using Tukey’s HSD where appropriate. We did not correct for multiple comparisons on the principle that the restrictiveness of Bonferroni correction would hinder the identification of potentially important relationships in an initial exploratory study with low numbers of participants\textsuperscript{179,180}.
3.7.1 Volumetrics

3.7.1.1 Gross Cerebral Volumes

A mixed-model 3-way Analysis of Variance (ANOVA) was performed to assess differences in normalized cortical grey matter and global white matter volumes with within-subjects factors Tissue Type (two levels: Grey, White), and Hemisphere (two levels: Ipsilesional, Contralesional), and between-subjects factor Group (two levels: DCS, NDCS).

3.7.1.2 Regional Cortical Thickness

A mixed-model 3-way ANOVA was performed to assess differences in mean cortical thickness at sensorimotor regions of interest, with within-subjects factors Region (three levels: M1, S1, BA6), and Hemisphere (two levels: Ipsilesional, Contralesional), and between-subjects factor Group (two levels: DCS, NDCS).

3.7.2 CSD

A mixed-model 3-way ANOVA was performed to assess differences in FA in all CSD tracts with within-subjects factors Region (three levels: CST, thal-M1, and thal-S1), and Hemisphere (two levels: Ipsilesional, Contralesional) and between-subjects factor Group (two levels: DCS, NDCS).

3.7.3 MRS

Mixed-model 2-way ANOVAs were performed to assess differences in MRS measures with within-subjects factor Hemisphere (two levels: Ipsilesional, Contralesional) and between-
subjects factor Group (two levels: DCS, NDCS) for each of the 5 MRS metabolites (NAA, mI, glutamate, choline, creatine).

3.7.4 Relationships to Motor and Sensory Function

Exploratory correlation analyses were performed to evaluate whether the imaging measures identified as significantly different between Group (DCS/NDCS) related to sensory or motor function in the paretic limb. Correlations were performed first across the entire sample to investigate relationships across the full sample of stroke survivors, and subsequently performed for only the DCS group to examine whether imaging variables were uniquely related to motor or sensory function in stroke survivors with diabetes. Spearman’s correlations were used to explore relationships between FM score, WMFT rate, and sensory threshold score in the paretic limb and imaging measures that differed significantly between DCS and NDCS group.
Chapter 4: Results

DCS and NDCS participants did not differ significantly on age, time since stroke, FM score or measures of peripheral somatosensory function for the Freesurfer, CSD and MRS subsets (Table 4-1; all p > 0.07).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DCS</th>
<th>NDCS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 7.7</td>
<td>65 ± 9.2</td>
<td>0.143</td>
</tr>
<tr>
<td>Time since stroke (months)</td>
<td>88 ± 77.3</td>
<td>49 ± 41.9</td>
<td>0.104</td>
</tr>
<tr>
<td>Fugl-Meyer score (/66)</td>
<td>42 ± 23.0</td>
<td>41 ± 23.2</td>
<td>0.868</td>
</tr>
<tr>
<td>Peripheral sensation- affected hand</td>
<td>13 ± 3.6</td>
<td>12 ± 3.3</td>
<td>0.401</td>
</tr>
<tr>
<td>Peripheral sensation- unaffected hand</td>
<td>10.3 ± 1.3</td>
<td>10.4 ± 1.4</td>
<td>0.878</td>
</tr>
</tbody>
</table>

Table 4-1: Demographic variables between Groups. Data presented are mean ± standard deviation. DCS: Diabetes with chronic stroke; NDCS: No Diabetes with chronic stroke. Significance set to p < 0.05.
4.1 Volumetrics

4.1.1 Gross Cerebral Volumes

Figure 4-1 displays results for all white and grey matter volume measures. 3-way ANOVA revealed no significant main effect of Group (DCS/NDCS) on total grey and white matter volumes. The ipsilesional hemisphere displayed significantly lower grey and white matter volumes than the contralesional hemisphere, regardless of Group ($F(1, 15) = 12.208, p = 0.003, \eta^2_p = 0.449$). There was a main effect of Tissue Type, with cortical grey matter volumes being significantly lower than white matter volumes ($F(1, 15) = 66.930, p <0.001, \eta^2_p = 0.817$). There were no significant interactions between any measures, though there was a trend towards a significant Group x Tissue Type interaction ($F(1, 15) = 4.123, p = 0.060, \eta^2_p = 0.216$).

4.1.2 Regional Cortical Thickness

Figure 4-2 displays results for all region cortical thickness analyses. 3-way ANOVA revealed a significant main effect of Group on regional cortical thickness, with thinner sensorimotor cortical grey matter in the DCS group than the NDCS group ($F(1, 15) = 7.282, p = 0.017, \eta^2_p = 0.327$). The ipsilesional hemisphere had significantly lower mean cortical thickness than the contralesional hemisphere across the entire sample ($F(1, 15) = 5.174, p = 0.038, \eta^2_p = 0.256$). There was a main effect of Region ($F(2, 14) = 365.185, p <0.001, \eta^2_p = 0.961$), post hoc analyses revealed that S1 had lower mean cortical thickness than M1 or BA6 (M1: $p < 0.001$; BA6: $p < 0.001$), while M1 and BA6 were not significantly different in mean thickness. There were no significant interactions between any regional cortical thickness measures.
Figure 4-1: Global cortical grey and white matter volumes in individuals with chronic stroke with and without type-2 diabetes mellitus. There was no significant main effect of diabetes on grey or white matter volumes. There was a significant main effect of hemisphere with lower grey and white matter volumes in the ipsilesional hemisphere. Grey and white matter volumes are normalized values expressed as total hemispheric volume/total intracranial volume. Ipsi: ipsilesional hemisphere; contra: contralesional hemisphere; GM: grey matter; WM: white matter; DCS: diabetes with chronic stroke; NDCS: no diabetes with chronic stroke. Significance set to p< 0.05; Error bars are SEM

Figure 4-2: Regional cortical thickness in sensorimotor regions in individuals with chronic stroke with and without type-2 diabetes mellitus. There was significantly lower grey matter thickness in individuals with diabetes, and significantly lower grey matter thickness in the ipsilesional cortex across the sample. Ipsi: ipsilesional hemisphere; contra: contralesional hemisphere; M1: primary motor cortex; S1: primary somatosensory cortex; BA6: Brodmann’s area 6 (secondary motor cortex); DCS: diabetes with chronic stroke; NDCS: no diabetes with chronic stroke. Significance set to p< 0.05; Error bars are SEM.
4.2 CSD

Figure 4-3 displays results for all FA analyses. 3-way ANOVA revealed no significant main effect of Group on FA of sensorimotor tracts. There was a main effect of Hemisphere on FA, with the ipsilesional hemisphere having significantly lower FA than the contralesional hemisphere \((F_{(1,17)} = 5.177, p = 0.036, \eta^2_p = 0.233)\). There was a main effect of Region \((F_{(2,16)} = 60.357, p < 0.001, \eta^2_p = 0.883)\), and a significant Group * Region interaction \((F_{(2,16)} = 4.227, p = 0.034, \eta^2_p = 0.346)\). Post hoc analyses revealed for both Groups FA of the CST was higher than FA of either thal-S1 (DCS: \(p < 0.001\); NDCS: \(p < 0.001\)) or thal-m1 (DCS CST/thal-M1: \(p < 0.001\); NDCS CST/thal-M1: \(p < 0.001\)).

![CSD FA in sensorimotor projections](image)

**Figure 4-3:** CSD FA in sensorimotor projections in individuals with chronic stroke with and without type-2 diabetes mellitus. There were no significant differences between groups. Ipsilesional FA was lower than contralesional FA across the entire sample. Ipsi: ipsilesional hemisphere; contra: contralesional hemisphere; FA: Fractional Anisotropy; CST: corticospinal tract; thal-M1: thalamocortical tracts to primary motor cortex; thal-S1: thalamocortical tracts to primary sensory cortex; DCS: diabetes with chronic stroke; NDCS: no diabetes with chronic stroke. Significance set to \(p < 0.05\); Error bars are SEM
4.3 MRS

Figure 4-4 displays results for all MRS ANOVAs. Separate 2-way ANOVAs revealed individuals with diabetes had significantly reduced creatine bilaterally in sensorimotor cortex ($F_{(1,16)} = 4.682, p = 0.046; \eta^2_p = 0.226$). There was a trend towards reduced NAA in the DCS group ($F_{(1,16)} = 4.047, p = 0.061, \eta^2_p = 0.202$). The ipsilesional hemisphere had significantly lower levels of NAA, glutamate and choline than the contralesional hemisphere, regardless of Group (NAA: $F_{(1,16)} = 6.608, p = 0.021, \eta^2_p = 0.292$; glutamate: $F_{(1,16)} = 10.27, p = 0.006, \eta^2_p = 0.391$; choline: $F_{(1,16)} = 5.49, p = 0.032, \eta^2_p = 0.255$). There were no significant interactions in cerebral metabolite levels.

Figure 4-4: Cerebral metabolite profiles in chronic stroke and type-2 diabetes in primary sensorimotor cortex. Creatine was significantly lower bilaterally in individuals with diabetes. NAA, glutamate, and choline were significantly lower in the ipsilesional hemisphere relative to the contralesional hemisphere. NAA: N-Acetylaspartate; DCS: diabetes with chronic stroke; NDCS: no diabetes with chronic stroke; ppm: parts per million. Significance set to $p < 0.05$; Error bars are SEM.
4.4 Correlations with Motor Function

Based on Shapiro-Wilk Test all measurements of motor and somatosensory performance in the hemiparetic arm were non-normal (p< 0.020; FM, WMFT, sensory threshold), thus Spearman’s correlations were performed for functional measures. Bilateral Cortical thickness of M1, S1 and BA6, and creatine concentrations were correlated to motor and sensory measures in the paretic arm. Across the entire sample (DCS + NDCS) none of these variables showed significant correlations with motor or sensory function. When Spearman’s correlations were restricted to DCS participants, contralesional M1 thickness correlated with WMFT rate (r = -0.714, p = 0.047; Figure 4-5), and contralesional BA6 correlated significantly with both FM and WMFT rate score (FM: r = -0.816, p = 0.015; WMFT: r = -0.881, p = 0.004; Figure 4-6).
**Figure 4-5:** Negative correlation between motor function of the paretic upper-limb and mean thickness of contralesional primary motor cortex (M1) in individuals with chronic stroke and type-2 diabetes ($r = -0.714, p = 0.047$). WMFT rate: Wolf Motor Function Task rate score.

**Figure 4-6:** Negative correlations between motor function (A) and motor impairment (B) of the paretic upper-limb and mean thickness of contralesional Brodmann’s Area 6 (BA) in individuals with chronic stroke and type-2 diabetes (A: $r = -0.881, p = 0.004$; B: $r = -0.816, p = 0.015$). WMFT rate: Wolf Motor Function Task rate score; FM: Fugl-Meyer Upper Extremity
Chapter 5: Discussion

Individuals with diabetes and chronic stroke, compared to individuals with chronic stroke only, have bilaterally reduced cortical grey matter in primary and secondary motor cortices and primary somatosensory cortex, and bilaterally reduced creatine levels in sensorimotor cortex. We found contralesional primary and secondary motor cortex thickness was negatively correlated with motor outcomes in individuals with diabetes and chronic stroke only. Diabetes did not impact white matter volumes or white matter microstructure in motor and somatosensory pathways. These data suggest that diabetes negatively impacts cortical grey matter and cerebral metabolism, which may influence sensorimotor recovery after stroke. Additionally these data expand on previous stroke literature to characterize structural changes in sensorimotor circuits distal from the cerebral infarct.

5.1 Changes to Cortical Grey Matter in Chronic Stroke and Diabetes

Individuals with chronic stroke and diabetes showed reductions to regional cortical thickness compared to chronic stroke survivors without diabetes. Chronic stroke survivors with type-2 diabetes had significantly lower grey matter thickness bilaterally in 3 regions that are linked with sensorimotor recovery after stroke: primary motor cortex, primary somatosensory cortex, and secondary motor cortex. Changes to the cortical mantle caused by diabetes are supported by previous research on cortical atrophy in diabetes\textsuperscript{54,80,97–99}. Prolonged hyperglycemia\textsuperscript{181}, increased inflammatory factors\textsuperscript{182} or increased microlesion load\textsuperscript{51,75} could all contribute to thinning of cortical grey matter in diabetes. It is also possible that reduced activation of cerebral insulin receptors due to insulin resistance causes reduced dendritic spine density by blunting long-term potentiation in the cortex\textsuperscript{66,133}. Previous findings indicate that
surviving grey matter in motor cortices is important to maintain chronic motor function and mediate functional gains in stroke rehabilitation\textsuperscript{94–96,183}. Our data suggest that individuals with type-2 diabetes may be at a disadvantage in stroke recovery as they demonstrate reductions to these key neural substrates for remapping sensorimotor function. However, given that changes to cortical grey matter where seen between groups that had equivalent levels of upper-limb impairment, individuals with diabetes may have distinct cortical mechanisms to facilitate regain of function compared to non-diabetic individuals. Contralesional M1 thickness increases in the subacute period of stroke recovery\textsuperscript{90,91}, and may support functional gains in response to constraint-induced movement therapy\textsuperscript{94}. Interestingly, contralesional primary and secondary cortical thickness was negatively related to motor outcomes after stroke for individuals with diabetes in the current sample. This may indicate that individuals with diabetes show a unique pattern of cortical recruitment or plasticity compared to non-diabetic individuals.

In contrast to previous reports showing global cerebral atrophy in otherwise healthy individuals with type-2 diabetes\textsuperscript{54,80,97,98}, we did not detect significantly reduced total cortical grey matter or white matter volumes in individuals with diabetes after stroke. Given this previous research we expected individuals with diabetes to show greater reductions to cortical volumes after a neurological insult. Perhaps diabetes does not increase the amount of retrograde neuronal loss after an ischemic event. Or it may be necessary to match participants on total lesion volume in order to differentiate between the effects of grey matter loss caused by diaschisis from grey matter changes caused by diabetes comorbidity.

Across our full sample of stroke survivors, both regional sensorimotor cortical thickness and global cortical grey matter volumes were significantly lower in the ipsilesional hemisphere. Reduced ipsilesional sensorimotor thickness corroborates previous findings in chronic
subcortical stroke of reduced ipsilesional M1 and supplementary motor area thickness. A recent study by Cheng et al (2015) reported that cortical thickness atrophy is specific to regions with connectivity to the subcortical lesion; lending support to the hypothesis that loss of cortical thickness after stroke is a result of retrograde degeneration of areas connected to the stroke injury. The thickness of motor areas also relates to degree of motor impairment, with thinner ipsilesional M1, supplementary motor area, and premotor cortex correlating with greater motor impairment after stroke. Reduced primary motor cortex thickness also predict response to training interventions, with individuals with thinner ipsilesional M1 making less improvements on motor training tasks. In the present study motor cortical thickness did not relate to upper-limb impairment or function across the sample. This may be because only 3 individuals in the Freesurfer sample had a severe level of motor impairment (with a Fugl Meyer score <28). Our full Freesurfer subgroup may therefore have lacked an adequate range of motor impairment to characterize the relationships between cortical thickness and motor function.

5.2 White Matter Volumes and Microstructure in Chronic Stroke and Diabetes

There were no changes to total white matter volume in stroke survivors with diabetes. This finding is consistent with previous reports on otherwise healthy adults with diabetes showing reductions to cortical grey matter, but not white matter volumes. Contrary to our hypothesis, diabetes did not impact white matter microstructure in the corticospinal tract or thalamocortical tracts to primary motor and primary sensory cortices. Multiple previous tractography studies have reported differences to tracts relating to cognitive function, and one study to the corona radiata, in individuals with diabetes who have not experienced
stroke. In addition, data from functional neuroimaging studies suggests reduced connectivity between the thalamus and cortical targets in otherwise healthy individuals with diabetes\textsuperscript{129,131,187}, including reduced functional connectivity between the thalamus and M1\textsuperscript{132} and S1\textsuperscript{73}. To our knowledge, this is the first study that has attempted diffusion imaging from the thalamus to primary sensorimotor cortices in diabetes or in stroke. Considering previously reported results examining white matter microstructure and thalamic connectivity in diabetes, it is possible that our sample size was too small to detect a difference between groups, but is equally possible that that diabetes does not negatively impact the microstructural status of these tracts. This will have to be examined in preclinical populations in order to best characterize the impact of diabetes on these networks of interest for stroke recovery.

Across the sample of stroke survivors there was significantly lower FA in ipsilesional tracts relative to contralesional tracts. Reduced FA of ipsilesional CST is a well-documented event in chronic stroke\textsuperscript{113,119,188}. A reduction to thalamocortical FA in the ipsilesional hemisphere indicates these pathways are also affected in chronic stroke. The thalamus is a critical relay center in the brain and thalamocortical circuits have demonstrated importance for sensorimotor integration\textsuperscript{189} and motor learning\textsuperscript{123,190}. Diffusion imaging of thalamocortical tracts may provide a useful index of sensorimotor impairment and recovery after stroke, and should be investigated further as predictors of motor skill acquisition in hemiparesis.

5.3 Alterations to Cerebral Metabolites in Chronic Stroke and Diabetes

A central finding of the MRS analysis was bilaterally reduced creatine in the primary sensorimotor cortex of individuals with type-2 diabetes and chronic stroke. Creatine and phosphocreatine are widely recognized for their ubiquitous role in oxidative metabolism through
high-energy phosphate transfer is ATP synthesis in metabolically active tissues\textsuperscript{191}. Low levels of creatine indicates reduced oxidative metabolism in neural cells in diabetes\textsuperscript{191}. This is supported by previous findings of a negative impact of type-2 diabetes on mitochondria, with a well-documented decrease in skeletal muscle mitochondrial metabolism in insulin-resistant diabetes\textsuperscript{192}.

Changes to creatine alone are difficult to interpret in terms of their biological relevance, as changes to creatine levels could reflect alterations to neuronal or glial metabolism or both\textsuperscript{145,193}. However, as we observed a trend towards a decrease in NAA levels and no changes to myo-inositol levels in individuals with diabetes, low creatine levels in the present analysis are suggestive of altered neuronal rather than glial metabolism in individuals with diabetes. NAA is synthesized in the mitochondria of neurons\textsuperscript{194,195}, and remains primarily localized in the mitochondria\textsuperscript{196}. Though the function of NAA remains unknown, the majority of available evidence supports a role of NAA in regulating neuronal energy metabolism through actions in the mitochondria\textsuperscript{138}. Therefore a decrease in creatine and NAA levels is suggestive of reduced neuronal mitochondrial function. This is supported by recent evidence demonstrating a reduction to cerebral mitochondrial function in diabetic rodents in cortical\textsuperscript{197} and peripheral\textsuperscript{198} neurons. Reductions to neuronal oxidative metabolism are proposed to underlie cerebral and peripheral neurodegeneration in diabetes\textsuperscript{198,199}. Our data suggests that a drop in cerebral oxidative metabolism further exists after stroke in individuals with diabetes. Previously reported reductions to NAA/creatine ratios in diabetes\textsuperscript{155–157,160} may be driven primarily by changes to cellular metabolism and the creatine/phosphocreatine system, rather than reflecting a loss of neurons indexed by NAA.
Our finding of reduced creatine in diabetes was contrary to our hypothesis that diabetes would increase levels of creatine in the brain, based on previously published literature in otherwise healthy individuals with diabetes\textsuperscript{152,153}. There are a few reasons why this discrepancy with previous literature may have occurred. The first may be due to a different choice of regions of interest for quantifying metabolite levels, as previous studies have reported elevated creatine in subcortical structures, not cortical tissue. Wang (2015) observed elevated creatine in the hippocampus, and Heikkilä (2008) in the thalamus, but creatine was not increased in the frontal cortex in the same studies\textsuperscript{153,154}, perhaps indicating differential effects of diabetes on subcortical and cortical metabolism. The second reason may be differences in the participant population. Heikkilä (2008) studied individuals with prediabetes, and found thalamic creatine levels increased with increasing plasma and central glucose levels\textsuperscript{154}. This may indicate that creatine levels change as you move from hyperglycemia to overt insulin resistance in diagnosed instances of the disorder. Therefore given that our sample was comprised of individuals with a diagnosis of diabetes it is likely that these individuals are experiencing reduced cerebral glucose transport across the blood brain barrier\textsuperscript{200,201}. If creatine relates to cerebral glucose levels we would expect to see a decrease of creatine in line with cerebral hypometabolism observe in diabetes. Consistent with this hypothesis, a previous MRS study has shown an inverse relationship between body weight and creatine in occipital grey matter\textsuperscript{202}. A final possibility is that creatine changes in the present study are interacting with conditions from the stroke-affected brain. Creatine levels decrease in peri-infarct tissue from acute to subacute stroke\textsuperscript{148,149}, but creatine is not decreased in cortical primary motor cortex in chronic stroke survivors relative to healthy controls\textsuperscript{141}. As we did not observe hemispheric differences in creatine levels it is likely that the
reduction in creatine is occurring due to diabetes globally reduced cerebral metabolism, rather than a loss of cellular metabolism in regions connected to the cerebral infarct.

Contrary to our hypothesis, we did not observe increased myo-inositol in the diabetes group. Previous research has shown increased myo-inositol in frontal white matter and the hippocampus in otherwise healthy individuals with diabetes, though this finding is inconsistent with other reports showing no change between diabetes and non-diabetes groups on myo-inositol levels in frontoparietal white matter and frontal grey matter. Myo-inositol decreases in the peri-lesional area after stroke, but may change longitudinally as elevated myo-inositol has been reported in spared motor cortex in chronic stroke. Elevated myo-inositol has been interpreted as a sign of gliosis in diabetes and in stroke, but increases to myo-inositol levels could also reflect increased glial-mediated plasticity. Despite the fact that either of these proposed functions for myo-inositol should relate to behavioural outcomes, myo-inositol has never been reported as correlated with motor outcomes after stroke. Current evidence for the role of myo-inositol in diabetes and stroke recovery is inconclusive and requires further examination.

Across our sample of stroke survivors NAA, glutamate, and choline were significantly lower in ipsilesional sensorimotor cortex, relative to contralesional cortex. Reduced NAA in the ipsilesional sensorimotor cortex is in accordance with previous work. This could perhaps indicate a loss of viable neurons or neuronal dysfunction in response to distal infarct. To our knowledge this is the first MRS report of reduced glutamate levels in the ipsilesional hemisphere in chronic stroke. This finding may result from an imbalance of cortical excitation in the ipsilesional hemisphere, or it could be the result of overall loss of excitatory cortical neurons. Choline was significantly lower in the ipsilesional motor cortex. Elevated choline is
considered a marker of demyelination\textsuperscript{145}, yet decreases in choline in peri-lesional areas have also been reported in subacute stroke\textsuperscript{149,207,208}. To our knowledge this is the first report of reduced choline in spared ipsilesional grey matter in chronic stroke. Low choline levels may be indicative of cellular membrane breakdown or reduced membrane turnover. Choline should be examined longitudinally in grey matter post-stroke to see how levels of this compound evolve over the course of recovery.

5.4 Limitations

As we had a mixed sample of individuals with cortical and subcortical lesions, we could not perform Freesurfer across the entire sample. Therefore our analysis on sensorimotor thickness in relationship to motor outcomes was confined to individuals with subcortical lesions, unlike the CSD and MRS analyses. This may limit the generalizability of these findings. However, this choice did increase the accuracy of our Freesurfer data, which served our primary aim of examining alterations to surviving motor networks in diabetes.

Segmentation of the MRS voxel was not performed, therefore observed changes in cerebral metabolite concentrations may be the result of changing composition to grey and white matter in the MRS voxel as a result of reduced cortical volumes. Creatine is higher in cortical grey matter than in white matter\textsuperscript{209}, however given that the difference between diabetics and non diabetic in cortical thickness was 0.2mm on average, and the voxel had dimensions of 30mm x 22mm x 15mm, the overall changes to the composition to the grey matter layer were minute in comparison to the total size of the sampled voxel. We therefore do not expect cortical grey matter reductions to impart a significant amount of change to the creatine data between groups.
We did not collect information on these individuals with regards to other cardiovascular risk factors that frequently cluster with diabetes, such as hypertension, obesity, and hypercholesterolemia. Some previous research has demonstrated an additive effect of multiple cardiovascular risk factors on markers of cerebral health such as silent infarcts and cortical atrophy. This may be an additional explanatory variable in our findings that is not presently accounted for, and should be examined in future research.

A more significant limitation to the present analysis is that as we did not collect information on blood glucose levels, it is possible that some individuals in our non-diabetes group may have undiagnosed type-2 diabetes. This likely reduces the power of the present analysis. However, the observed reductions in cortical grey matter and creatine in this sample suggests that these are robust effects. As diabetes represents a continuum of impaired metabolism rather than a strict binary condition, future research should investigate the relationships of these effects with glycated hemoglobin and fasting glucose levels.

5.5 General Conclusions

Taken together, these results suggest that diabetes results in reductions to cortical grey matter thickness and reduced creatine in sensorimotor regions. The reduced creatine observed in sensorimotor cortex in type-2 diabetes may reflect a downregulation of cerebral oxidative metabolism in type-2 diabetes. Reduced mitochondrial function increases ischemic cell death and reduces neuronal plasticity, and low creatine levels in peri-infarct tissue have previously been linked to greater ipsilesional cerebral atrophy. Reduced mitochondrial function is therefore a potential mechanism linking both reduced cortical thickness in the present sample and the poorer outcomes observed after stroke in with the pathophysiology of type-2 diabetes.
However, given that these changes to cortical grey matter were seen between groups that had equivalent levels of upper-limb impairment, this also may mean that individuals with diabetes have other cortical mechanisms that facilitate regain of function. It is interesting that we saw changes to cortical grey matter thickness and metabolism but not white matter volumes or microstructure. This suggests that diabetes primarily influences the function and plasticity of the cortical layer rather than increasing structural damage in sensorimotor networks. This would be consistent with animal literature showing reduced cortical plasticity in diabetic models. The diabetes group showed a significant relationship of contralesional motor cortex thickness to motor outcomes, perhaps indicating a specific neurological profile of stroke recovery influenced by differential rates of neuroplasticity in this population. Plasticity of sensorimotor regions in stroke and diabetes should be examined longitudinally to evaluate whether diabetes results in altered patterns of structural plasticity in the subacute to chronic periods of stroke recovery.

Here we provided an exploratory analysis of changes to grey matter, white matter, and cerebral metabolites conferred by diabetes after stroke. We propose that reduced oxidative metabolism may result in degradation of cortical grey matter in type-2 diabetes. Given that surviving cortical motor and sensory regions are hypothesized to critical sites for remapping of lost sensorimotor functions, the additional burden of diabetes on the cortical grey matter may increase the risk of poorer functional outcomes in diabetic stroke survivors. These results provide preliminary evidence for differences in neural structure in surviving sensorimotor circuits in individuals with chronic stroke and diabetes. We expect these findings to inform future research examining patterns of neural recovery in individuals with diabetes after stroke.
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Appendix A  Fugl-Meyer Upper Extremity Assessment

ARM MOTOR FUGL-MEYER ASSESSMENT

Patient #: ________
Examiner Name: ________________________________

Date: __________ / ______ / ______
Month Day Year

Time: ______ ______

Assessment Period:

☐ Baseline (Initial Testing)
☐ 3 months
☐ 6 months
☐ 9 months
☐ 12 months

Instructions:
Use the number scoring system provided to score patients’ affected upper extremity abilities in each category. The patient is allowed three tries for each category. Place a mark in the appropriate boxes to indicate patients’ scores. Total the score for each category as it is completed. Upon completion, total the score for all categories.

Do not facilitate any movements during the testing, however, verbal encouragement is permissible.

What side of the patient is the affected side that is being assessed?  ☐ Right  ☐ Left

Motor – Upper Extremity (Sitting)

I. Reflexes
Biceps or finger flexor
☐ 0 – No reflex activity can be elicited
☐ 2 – Reflex activity can be elicited

Elbow/triceps
☐ 0 – No reflex activity can be elicited
☐ 2 – Reflex activity can be elicited

II. Flexor Synergy: Instruct seated patient to voluntarily supinate his forearm fully, fully flex the elbow, and bring the forearm to the ear of the affected side. The shoulder should be abducted at least 90°, externally rotated, retracted, and elevated.

Shoulder elevation
☐ 0 – Cannot be performed at all
☐ 1 – Performed partly
☐ 2 – Performed faultlessly

Shoulder retraction
☐ 0 – Cannot be performed at all
☐ 1 – Performed partly
☐ 2 – Performed faultlessly
Arm Motor Fugl-Meyer Assessment (page 2 of 6)

Shoulder abduction
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

Shoulder external rotation
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

Elbow flexion
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

Forearm supination
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

III. Extensor Synergy: Starting with the full flexor synergy position (passively placed if necessary), instruct the seated patient to abduct/externally rotate the shoulder and extend his arm toward the opposite knee with the forearm pronated. The elbow may be supported to avoid passive movement due to gravity.

Shoulder abduction/Internal rotation
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

Elbow extension
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

Forearm pronation
- 0 – Cannot be performed at all
- 1 – Performed partly
- 2 – Performed faultlessly

IV. Movement Combining Synergies

Actively position hand on the lumbar spine
- 0 – No specific action performed
- 1 – Hand must pass anterior superior iliac spine
- 2 – Action is performed faultlessly

Pure shoulder flexion from 0 to 90°, elbow fully extended at 0°, forearm midposition between supination and pronation
- 0 – Arm is immediately abducted or elbow flexes at start of rotation, or shoulder flexion cannot be performed at all
- 1 – Abduction or elbow flexion occurs after start of motion, or shoulder flexion can only be partly performed
Arm Motor Fugl-Meyer Assessment (page 3 of 6)

☐ 2 – Faultless motion

Pronation/supination of forearm with elbow actively flexed at approximately 90° and shoulder at 0°
☐ 0 – Correct position of shoulder and elbow cannot be attained, and/or pronation or supination cannot be performed at all
☐ 1 – Action pronation or supination can be performed even within a limited ROM and at the same time the shoulder and elbow are correctly positioned
☐ 2 – Complete pronation and supination with correct positions at elbow and shoulder

V. Movement out of Synergy (patient seated)
Shoulder abduction to 90°, elbow fully extended at 0°, and forearm pronated
☐ 0 – Initial elbow flexion or supination occurs or any deviation from pronated forearm occurs
☐ 1 – Motion can be performed partly, or if during motion, elbow is flexed or forearm supination during motion
☐ 2 – Faultless motion

Pure shoulder flexion to 90°-180°, elbow at 0° throughout, and forearm in midposition between pronation and supination
☐ 0 – Initial flexion of elbow or should abduction occurs, or cannot be performed at all
☐ 1 – Elbow flexion or shoulder abduction occurs during shoulder flexion, or can only be partly performed
☐ 2 – Faultless motion

Pronation/supination of forearm, elbow fully extended at 0°, and shoulder between 30-90° of flexion
☐ 0 – Supination and pronation cannot be performed at all or elbow and shoulder position cannot be attained
☐ 1 – Elbow and shoulder properly positioned and pronation and supination performed in a limited range
☐ 2 – Faultless motion

VI. Normal Reflex Activity
Biceps and finger flexion and triceps (Assess patient only if the patient has a score of 6 in stage V.)
☐ 0 – Stage V score <6 or at least 2 of the 3 phasic reflexes are markedly hyperactive
☐ 1 – One reflex markedly hyperactive or at least 2 reflexes are lively
☐ 2 – No more than 1 reflex is lively and 0 are hyperactive

Final rev. 01 3/3/03
VII. Wrist: Test the wrist functions independent of that of the arm.

Stability, elbow at 90°, shoulder at 0°, forearm pronated (can assist patient to achieve this position)

- □ 0 – Patient cannot dorsiflex wrist to required 15°
- □ 1 – Dorsiflexion accomplished, but not with resistance
- □ 2 – Position can be maintained with some (slight) resistance

Flexion/tension, elbow at 90°, shoulder at 0°, fingers somewhat flexed (may support elbow if necessary)

- □ 0 – Volitional movement does not occur
- □ 1 – Active ROM is less than passive ROM
- □ 2 – Faultless, smooth movement

Stability, elbow fully extended at 0°, shoulder at 30°, forearm pronated (may support arm)

- □ 0 – Patient cannot dorsiflex wrist to required 15°
- □ 1 – Dorsiflexion accomplished, but not with resistance
- □ 2 – Position can be maintained with some (slight) resistance

Flexion/tension, elbow at fully extended at 0°, shoulder at 30°, fingers somewhat flexed (may support elbow if necessary)

- □ 0 – Volitional movement does not occur
- □ 1 – Active ROM is less than passive ROM
- □ 2 – Faultless, smooth movement

Circumduction

- □ 0 – Cannot be performed
- □ 1 – Jerky motion or incomplete circumduction
- □ 2 – Complete motion with smoothness

VIII. Hand: Test the hand functions independent of that of the arm, with elbow at 90° of flexion.

If necessary, the elbow may be supported.

Finger mass flexion – (flex all fingers)

- □ 0 – No flexion occurs
- □ 1 – Some flexion, but not full active flexion
- □ 2 – Complete active flexion (compared with unaffected hand)

Finger mass extension – extend all fingers, starting from position of active (passive if necessary) full flexion

- □ 0 – No extension occurs
- □ 1 – Partial extension occurs or patient can release an active mass flexion grasp
- □ 2 – Full active extension
Arm Motor Fugl-Meyer Assessment (page 5 of 6)

Grasp #1 - MCP joints II-V extended and PIPs and DIPs are flexed, grasp is tested against resistance
   ☐ 0 – Required position cannot be acquired
   ☐ 1 – Grasp is weak
   ☐ 2 – Grasp can be maintained against relatively great resistance

Grasp #2 - Patient is instructed to adduct thumb, 1st carpometacarpophalangeal and interphalangeal joint at 0° (keep fingers extended; use thick paper)
   ☐ 0 – Function cannot be performed
   ☐ 1 – Scrap of paper interposed between thumb and index finger can be kept in place, but not against a light tug
   ☐ 2 – Paper is held firmly against a tug

Grasp #3 - Patient opposes thumb pad against pad of index finger. A pencil is interposed.
   ☐ 0 – Function cannot be performed
   ☐ 1 – Pencil interposed between thumb and index finger can be kept in place, but not against a slight tug
   ☐ 2 – Pencil is held firmly against a tug

Grasp #4 - Patient should grasp a cylinder-shaped object, the volar surface of the 1st and 2nd finger against each other
   ☐ 0 – Function cannot be performed
   ☐ 1 – Cylinder-shaped object is gripped within the thumb and fingers and can be kept in place, but not against a slight tug
   ☐ 2 – Cylinder-shaped object is held firmly against a tug

Grasp #5 - A spherical grasp. The patient grasps a tennis ball.
   ☐ 0 – Function cannot be performed
   ☐ 1 – Tennis ball is gripped with tips of fingers and thumb and can be kept in place, but not against a slight tug
   ☐ 2 – Tennis ball is held firmly against a tug

IX. Coordination/Speed - While blindfolded, patient places finger to nose, 5 repetitions in rapid succession; use stopwatch to time this activity

Tremor
   ☐ 0 – Marked tremor
   ☐ 1 – Slight tremor
   ☐ 2 – No tremor

Dysmetria
   ☐ 0 – Pronounced or unsystematic dysmetria
   ☐ 1 – Slight or systematic dysmetria
   ☐ 2 – No dysmetria

Speed
   ☐ 0 – Activity is more than 6 seconds longer than unaffected hand
   ☐ 1 – Activity is 2 to 6 seconds longer than unaffected hand
   ☐ 2 – Activity is less then 2 seconds difference

Final rev. 01 3/3/03
Total Score = ______ points out of 66 possible
Appendix B  Wolf Motor Function Task

Compensatory Brain Activation After Stroke

WOLF MOTOR FUNCTION TEST

Patient ID#: __________________

Date: _____ / _____ / _____  Time: ______

Examiner: ______________________

Testing Instructions and Scoring

The WMFT consists of 17 tasks performed without the subject’s awareness of how the components are defined or scored. All tasks will use both arms, starting with the unaffected arm first. Each task is timed and rated by Functional Ability (0 – 5 Ordinal Scale). Subjects are given a maximum time limit of 120 seconds to complete the assigned task.

Score – Functional Ability

0  Does not attempt with upper extremity (UE) being tested
1  UE being tested does not participate functionally; however, attempt is made to use the UE
2  Does, but requires assistance of the UE not being tested for minor readjustments or changes of position, or requires more than two attempts to complete, or accomplishes very slowly
3  Does, but movement is influenced to some degree by synergy or is performed slowly or with effort
4  Does, movement is close to normal*, but slightly slower; may lack precision, fine coordination or fluidity
5  Does, movement appears to be normal

*Normal – the less involved UE can be utilized as an available index comparison, with pre-morbid UE dominance taken into consideration
Read the follow statement aloud to the patient:
Today we are going to take a look at how you are able to use your arm. Let me tell you how we are going to do this. First, I will give you instructions on how to do the task, and then I will show you how to do it. I will describe and demonstrate each task 2 times. Do not practice the task while I’m describing and demonstrating it. However, I will be happy to clarify any confusing points. Then I will say, “Ready, set, go,” and you will do the task. It is important that you do not start until I say “go”, otherwise, we will need to repeat the entire task. Each of the activities you will be asked to do should be carried out as rapidly as possible. You can work on each task for up to two minutes. We ask that you attempt each part of the test even if you do not think you can do it. If you are unable to carry out a task, then we will go on to the next one. Again, try to do each task as rapidly as possible. Do you have any questions?

<table>
<thead>
<tr>
<th>Task</th>
<th>Time</th>
<th>Functional Ability</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Forearm to table (side)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. Forearm to box (side)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. Extend elbow (side)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>4. Extend elbow (weight)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>5. Hand to table (front)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>6. Hand to box (front)</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>7. Weight to box</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>8. Reach and retrieve</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>9. Lift can</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>10. Lift pencil</td>
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<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>11. Lift paper clips</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>12. Stack checkers</td>
<td></td>
<td>0 1 2 3 4 5</td>
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<tr>
<td>13. Flip cards</td>
<td></td>
<td>0 1 2 3 4 5</td>
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<tr>
<td>14. Grip strength</td>
<td></td>
<td>0 1 2 3 4 5</td>
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<tr>
<td>15. Turn key in lock</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
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<tr>
<td>16. Fold towel</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
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<td>17. Lift basket</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
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<tr>
<td>AFFECTED HAND</td>
<td>Task</td>
<td>Time</td>
<td>Functional Ability</td>
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Clinician Signature

Date: ____/____/____

Month Day Year

Final rev. 02 3/23/03