AN INVESTIGATION OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

ACTIVATION IN WHITE MATTER AT 4 TESLA

by

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Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that allows for visualization of active brain regions. Although white matter (WM) constitutes approximately 50% of brain tissue, fMRI activation in WM has conventionally been dismissed. There are two main reasons WM fMRI remains controversial: 1) the blood oxygen level dependent (BOLD) fMRI signal depends on cerebral blood flow and volume, which are lower in WM than gray matter and 2) fMRI signal has been associated with post-synaptic potentials as opposed to action potentials. Despite these observations, there is no direct evidence against measuring fMRI activation in WM.

This thesis is comprised of four manuscripts that investigate fMRI activation in WM at 4T. The first study evaluated whether it was possible to detect WM activation using an interhemispheric transfer task and examined whether certain MRI contrast mechanisms were more sensitive to activation in WM. Activation was detected in the anterior corpus callosum at the individual and group level and we discovered that T2 weighted imaging may provide increased sensitivity to activation in WM. The second study used two established interhemispheric transfer tasks to examine whether callosal activation could be experimentally manipulated using a within subjects design. The results replicated previous findings and demonstrated an ability to map functional activation in the corpus callosum that was task dependent. The third study examined WM fMRI activation in a different structure and focused on the posterior limb of the internal capsule using a motor task; activation was elicited at both individual and group levels. The fourth study linked advances in the ability to detect WM fMRI activation to current clinical approaches to the assessment of WM dysfunction. An adapted Symbol Digit Modalities Test was used to evaluate WM activation in healthy controls. The results revealed individual level activation in both the corpus callosum and internal capsule.

Taken together this stream of research represents a major advance in the methods used to non-invasively study brain function. Future applications may include improved assessment methods for patients with WM dysfunction.

LIST OF ABBREVIATIONS AND SYMBOLS USED

ω   Larmor frequency

γ   magnetogyric ratio

3D   three dimensional

ASE   asymmetric spin echo

B_0 static magnetic field

BET   brain extraction tool

BOLD   blood oxygen level dependent contrast

CC   corpus callosum

CNR   contrast to noise ratio

CSF   cerebrospinal fluid

DOF   degrees of freedom

DTI   diffusion tensor imaging

FA   fractional anisotropy

FEAT   FMRI expert analysis tool

FILM   FMRIB's improved linear model

FLIRT   FMRIB's linear image registration tool

fMRI   functional magnetic resonance imaging

FMRIB   Functional MRI of the Brain

FOV   field of view

FSL   FMRIB software library

FWHM	full width at half maximum
GM	gray matter
H	hydrogen
HRF	hemodynamic response function
ICBM	International Consortium for Brain Mapping
JHU	Johns Hopkins University
K+	potassium ion
MCFLIRT	motion correction FLIRT
MPFLASH	magnetization prepared fast low angle shot
MRI	magnetic resonance imaging
MS	multiple sclerosis
Na+	sodium ion
NMR	nuclear magnetic resonance
PLIC	posterior limb of the internal capsule
RF	radiofrequency
ROI	region of interest
SD	standard deviation
SDMT	symbol digit modalities test
SNR	signal to noise ratio
T	tesla
T1	longitudinal relaxation time
T2	transverse relaxation time
T2*	transverse relaxation time

TR	repetition time
TE	echo time
TE*	effective echo time
TEM	transverse electromagnetic

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CHAPTER 1 INTRODUCTION

1.1 OVERVIEW

Functional magnetic resonance imaging (fMRI) is used to visualize the neuroanatomical regions responsible for processing information. Since the conception of fMRI in the early 1990's (Ogawa et al., 1992), significant advances in research have broadened our understanding of how the brain functions under both healthy and diseased conditions (e.g, Dolan, 2008; Haller and Bartsch, 2009; Rosen et al., 1998). Although fMRI continues to grow in popularity in both research and clinical settings, the full potential of this technique remains untapped because fMRI activity is not considered to be detectable in white matter (WM) tissue (Logothetis and Wandell, 2004). WM comprises approximately 50% of brain volume (Black, 2007) and is compromised in diseases such as multiple sclerosis (MS). However, the notion of using fMRI to examine WM regions remains relatively unexamined and highly debated (as explained below). The current thesis represents some of the first hypothesis driven investigations of WM fMRI activation.

The following manuscript-based thesis begins with an overview of the principles underlying MRI and fMRI. Subsequently, the corpus callosum and internal capsule are reviewed with a focus on neuroimaging findings within these structures. Next, a background on the clinical assessment of WM disease is provided. Finally, a brief introduction is given to each of the four manuscripts that comprise this thesis.

1.2 MAGNETIC RESONANCE IMAGING (MRI)

MRI has become an essential technique in diagnostic radiology as well as the scientific study of the brain. This is largely because MRI techniques can non-invasively

reveal anatomic detail (as well as indicate the regions involved in a specific task) with high spatial resolution (sub mm). The underlying principles of MRI are based in nuclear magnetic resonance (NMR; Brown and Semelka, 2010). NMR relies on an inherent property of atomic nuclei called spin. In nuclei with an odd number of protons/neutrons (e.g., ^{1}H), the overall spin results in a magnetic moment and angular momentum. In the presence of an external magnetic field (B_0), nuclei with spin will begin to precess about and align parallel or anti-parallel to the direction of an applied magnetic field. In a typical sample composed of many nuclei, slightly more nuclei align parallel to the direction of the magnetic field, which results in the development of bulk magnetization. The strength of the external magnetic field dictates the frequency at which the nuclei precess. This is known as the Larmour Frequency (ω), where, $\omega = \gamma Bo$, and γ represents the magnetogyric ratio for a particular nucleus (each type of nuclei has a characteristic value for γ).

In MRI, hydrogen nuclei (which consist of one unpaired proton) are most commonly focused on because they are abundant in body tissues composed of water and fat (Jezzard and Clare, 2001). In a homogeneous magnetic field, all hydrogen nuclei in the brain would have the same precession frequency. In order to create an image of the brain, the different regions must be distinguishable. This is accomplished by the application of three linear magnetic field gradients that are superimposed in orthogonal directions; the slice selecting gradient, the frequency encoding gradient, and the phase encoding gradient. The slice selecting gradient is used to introduce different magnetic field strengths in different locations, thereby leading the hydrogen nuclei in different areas to have different precession frequencies that can be targeted. In order to determine

the origin of a signal within a slice, frequency and phase encoding gradients are used. For frequency encoding, a gradient is applied that causes the precession frequency of nuclei to change along the axis in which the gradient is applied, thereby causing the nuclei in different areas to emit signals of different frequencies. For phase encoding, a gradient is applied for a fixed period of time that creates changes in phase along a slice.

In order to measure a signal from the bulk magnetization of the precessing nuclei, an oscillating electromagnetic field known as a radio frequency (RF) pulse is applied (Brown and Semelka, 2010). Specifically, the application of an RF pulse (where the frequency matches the precession of the spins) can lead the bulk magnetization vector to rotate from the longitudinal plane into the transverse plane. The strength and/or duration of the pulse can be used to determine the rotation. A pulse that causes a rotation of 90° is common, and is called an excitation pulse. Some pulse sequences also involve the subsequent application of a 180° pulse that causes the spins to regain phase coherence and recovers a measurable signal (referred to as a spin echo; Jezzard and Clare, 2001). Following the application of an RF excitation pulse, a receiving coil can measure the voltage created by the oscillating magnetic field of the sample as it returns to the previous state.

There are two types of relaxation that occur during the acquisition of MRI signal: longitudinal relaxation and transverse relaxation (Brown and Semelka, 2010; Jezzard and Clare, 2001). Longitudinal relaxation is also known as spin-lattice relaxation because energy is transferred to the surrounding molecular environment; the time constant of this process is known as T1. T1 varies depending on how efficiently energy is exchanged between hydrogen nuclei and their environment. Transverse relaxation is also known as

spin-spin relaxation because energy is transferred to nearby nuclei. The time constant for this process is called T2. T2 results from relaxation due a loss of phase coherence between neighboring nuclei. A related measure, T2* refers to measured phase decay that results from the additional presence of local inhomogeneities in the magnetic field.

Given that different tissue types have distinct relaxation rates, it is possible to derive images with different contrasts. For example, if the MRI signal is acquired when tissue differences in the longitudinal plane are maximized, the resulting image is considered T1 weighted. In this case, CSF appears dark (because it has a long T1 value), WM appears bright (because it has a short T1 value) and GM appears gray (because it has an intermediate T1 value). Conversely, if the MRI signal is measured when tissue differences in the transverse plane are maximized, the resulting image is considered T2 weighted. In this case, CSF appears bright (because it has a long T2 value) and white and GM matter appears dark (because they have short T2 values; Brown and Semelka, 2010).

1.3   FUNCTIONAL MRI

Functional MRI has made it possible to examine active brain regions. Typically, fMRI relies on blood oxygen level dependent (BOLD) contrast. The source of BOLD contrast is derived from the difference between deoxygenated blood, which is paramagnetic (attracted to an external magnetic field) and oxygenated blood, which is diamagnetic (repelled from an applied magnetic field; Kim and Ugurbil, 2003).

Deoxygenated blood causes local magnetic field inhomogeneities, which lead to shorter T2* (faster transverse relaxation). For this reason, fMRI traditionally uses a T2* weighted pulse sequence in which oxygenated blood leads to increased signal intensity

and deoxygenated blood leads to decreased signal intensity. Conventionally, it is thought that when a brain region becomes engaged in a task there is an associated increase in metabolic demands that must be supported. Consequently, regional increases in cerebral blood flow and volume occur to deliver oxygenated blood to active neurons. As required, deoxygenated blood is produced, although a surplus of oxygenated blood remains, resulting in a small measurable increase in signal intensity (Matthews, 2001).

1.4 FUNCTIONAL MRI IN WHITE MATTER

Until recently, MRI was only used to study functional activation in GM. There are two main reasons that WM fMRI is controversial; 1) BOLD signal relies on cerebral blood volume and flow, which are 3-6 times lower in WM (Helenius et al., 2003; Preibisch and Haase, 2001; Rostrup et al., 2000; van der Zande et al., 2005; Wise et al., 2004), and 2) the primary source of fMRI signal is thought to arise from post-synaptic potentials (which occur mainly in GM) as opposed to action potentials (Logothetis et al., 2001). These assertions have led WM fMRI activation to be contested; one review states that "a reasonable investigator may doubt the presence of a [blood oxygen level dependent] signal in white matter altogether" (Logothetis and Wandell, 2004, p. 755). As a result, some investigators that detect WM activation are reluctant to interpret the results. For example, Weis et al. (Weis et al., 2011), examined memory encoding in patients with Alzheimers and healthy controls and noted that "there appear to be some activation clusters extending into WM regions, both in healthy subjects and in [Alzheimer's disease] patients. To date, the notion of fMRI activation in white matter regions remains contentious. For these reasons, we are reluctant to interpret activations in white matter and will focus on discussing GM activations only."

Notably, even though the notion of fMRI activation in white matter remains controversial, there is no direct evidence against the idea (Tettamanti et al., 2002). Indeed, white matter tissue has metabolic demands that must be met (e.g. axonal conduction depends upon ion pumps to restore ionic gradients at the nodes of Ranvier; Weber et al., 2002). As a result, fMRI activation in WM is increasingly becoming an open avenue of investigation with growing support. Haller and Bartsch (2009) note that "fMRI is mainly focused on GM. However, WM fMRI is feasible and may reveal relevant activations within, for example, the corpus callosum". Burlucchi (2012) also acknowledged WM fMRI in his review of frontal callosal disconnection syndromes, stating that, "perhaps this method will prove to be appropriate for a most direct approach to the construction of functional maps of the corpus callosum." In fact, some of the initial evidence for WM fMRI activation comes from studies of interhemispheric transfer that primarily focused on GM, but also showed activation in the corpus callosum.

1.5   THE CORPUS CALLOSUM

1.5.1   CORPUS CALLOSUM: BACKGROUND

The corpus callosum is the largest WM bundle in the brain, consisting of approximately 180 million axons (Blume, 1984) that serve to connect the left and right cerebral hemispheres for the purpose of (inhibiting or enhancing) communication.

The corpus callosum was first studied behaviorally by Poffenberger (1912), who used a reaction time paradigm to estimate interhemispheric transfer time. Specifically, visual stimuli were presented to one hemifield at a time in order to provide information to the contralateral occipital cortex and then participants responded with either the hand opposite to (creating a 'crossed' condition that requires transfer across the corpus

callosum) or the same as (creating a 'no cross' condition) the visual stimulation. By subtracting the crossed from the uncrossed condition, he was able to estimate the transfer time across the corpus callosum to be 5-6 ms.

Beginning in the 1960s, Gazzaniga, Bogen and Sperry studied patients who had undergone corpus callosotomies for treatment of medically intractable epilepsy, in what are now known as the 'split brain' experiments (Gazzaniga et al., 1965). The main goal of these experiments was to study the laterality of the cerebral hemispheres; they found that the left hemisphere was dominant for language and the right hemisphere was specialized for visuospatial processing. There was also evidence that the right hemisphere is specialized in processing unfamiliar faces (Gazzaniga and Smylie, 1983). In addition to providing insight into hemispheric specialization, studies on patients with complete callosal resection has revealed information regarding the role of the corpus callosum in interhemispheric transfer. For example, when tested with the Poffenberger paradigm, split brain patients demonstrated reaction times that were 4-14 times longer than healthy controls (Marzi, 1999).

1.5.2 *OVERVIEW OF STRUCTURAL AND FUNCTIONAL MRI FINDINGS*

A technique that has increasingly been used to study WM organization and integrity is diffusion tensor imaging (DTI). Importantly, DTI has been used to examine the connections of the corpus callosum. Zarei et al. (2006) reported that the genu connects pre-frontal regions, the body connects pre-motor cortex, the splenium connects primary motor, sensory motor, and posterior parietal regions and the posterior-most part of the corpus callosum connects temporal and occipital cortex.

Although techniques such as DTI can provide valuable information regarding the structure of the corpus callosum and the structure-function relationship, in many cases, structural measures of WM integrity do not correlate to functional deficits (i.e., the clinico-radiological paradox; e.g., Pelletier et al., 2009). In these cases, fMRI may provide a more direct assessment of function. Furthermore, there are an increasing number of studies that lend support to the notion that it is possible to measure activation in WM. A chronological review of studies that have reported fMRI activation in the corpus callosum follows.

The first study to report WM fMRI activation in the corpus callosum was conducted by Mosier and Bereznaya (2001). They investigated activation related to swallowing in eight healthy subjects (at 1.5T) and recognized the involvement of the corpus callosum, among other cortical and subcortical GM regions.

Subsequently, Tettamanti et al. (2002) employed the Poffenberger paradigm to "test the hypothesis that the interhemispheric transfer of visuomotor information requires the corpus callosum." They tested eight healthy participants (at 1.5T) and found activation in the genu of the corpus callosum (as well as activation in frontal, parietal and temporal regions) during the Poffenberger crossed condition. Tettamanti et al. (2002) interpreted their findings as evidence that the Poffenberger task relies on interhemispheric transfer, which likely occurred at the premotor level, given the location of callosal activation.

In a similar approach, Omura et al. (2004) used the Poffenberger paradigm with a focus on GM activation resulting from condition comparisons. Twenty-one healthy

participants were tested at 1.5T. The results revealed activation in the genu of the corpus callosum and the thalamus (bilaterally) for the crossed-uncrossed contrast, and activation in the fronto-occipital network, left precentral gyrus, bilateral precuneus and cerebellum for the uncrossed-crossed contrast. Activation in the genu of the corpus callosum was consistent with the findings of Tettamanti et al. (2002).

In 2005, Weber et al. (2005) aimed to determine the role of attentional effects on interhemispheric transfer. Using an 'oddball' Poffenberger paradigm to test 10 participants (at 3T), they found crossed-uncrossed activation in the right genu of the corpus callosum, as well as in the right cuneus and frontal lobe. The uncrossed-crossed analysis did not result in callosal activation. Similar to Tettamanti et al. (2002), the authors interpreted the activation in the genu of the corpus callosum as being related to the transfer of information between hemispheres at the premotor level.

D'Arcy et al. (2006) used more complex stimuli (faces and words) to study interhemispheric transfer. Based on the original split brain studies by Sperry's group (Gazzaniga et al., 1965), faces were presented to the right visual field (left hemisphere) and words were presented to the left visual field (right hemisphere) to create a 'crossed' condition, and visual field presentation was reversed to create an 'uncrossed' condition. Six healthy participants were tested at 1.5T. An exploratory analysis revealed increased activation in the crossed condition, including activation near the splenium of the corpus callosum. Further examination of the activation results clearly showed clusters in WM.

Given the accumulating evidence in support of functional activation in WM, Mazerolle et al. (2008) followed up with a prospective study of WM fMRI at 4T.

9

Mazerolle et al. (2008) used a Sperry (face/word) task designed to elicit interhemispheric transfer across the corpus callosum (improved from D'Arcy et al., 2006). The results from twenty-four participants revealed activation in the isthmus of the corpus callosum in 20% of the subjects and at the group level.

In related work, Mazerolle et al. (2010), used fMRI activation elicited during the Sperry task as a DTI tractography seed with the aim of determining whether corpus callosum activation is structurally connected to the functional network in GM. The results indicated that the tracts originating from seeds in GM were co-localized with corpus callosum fMRI activation in each subject (N=8), thereby confirming structural connections between task activated regions in WM and GM (Mazerolle et al., 2010). These results impart confidence to the interpretation of WM activation as functionally significant.

Yarkoni et al. (2009) reported WM fMRI activation when reaction time was used as a predictor variable in an analysis across five data sets. Importantly, they reported "reaction time variability reliably modulated the BOLD signal not only in GM but also in diffuse regions of white matter." Specifically, WM activation was detected in the genu of the corpus callosum and in the posterior corona radiata (bilaterally) and was associated with a late onset HRF with reduced amplitude. The authors suggest that modeling trial-by-trial reaction time in fMRI analyses can be a useful tool to investigate WM fMRI.

Newman et at. (2010) reported fMRI activation in WM in a study of the underlying neuroanatomical basis of different aspects of language processing.

Specifically, they reported corpus callosum activation in the genu that was "indicative of greater information flow between the two hemispheres".

Recently, Fabri et al. (2011) cited our group and acknowledged that "a rising number of researchers have been reporting fMRI activation in white matter, particularly the corpus callosum." Consequently, Fabri et al. (2011) sought to create a topographical map of the corpus callosum. Specifically, they analyzed data from healthy participants (at 1.5T) who completed tactile, gustatory, visual and motor tasks. The results indicated that the corpus callosum was activated anteriorly by taste, centrally by motor tasks, centrally and posteriorly by tactile tasks and posteriorly by visual stimuli. The central motor related activation and posterior visual activation is consistent with our previous findings.

Taken together, experiments such as these provide strong support for WM fMRI activation and have paved the way for future research in this area. However, as these studies have noted, the majority of evidence for WM fMRI activation has come from studies involving the corpus callosum. In order to thoroughly establish these controversial findings, it is essential to investigate WM activation in other regions.

1.6 THE INTERNAL CAPSULE

1.6.1 INTERNAL CAPSULE: BACKGROUND

The corticospinal tract is a prominent WM tract, and the primary motor pathway in the human brain. The tract originates in the motor cortex with axons extending down to the spinal cord (hence the name: 'corticospinal' tract). As the axons travel ventrally, they form the internal capsule. Conceptually, the internal capsule can be divided into the genu, the anterior limb and the posterior limb. Whereas the genu and anterior limb contain

corticobulbar and frontopontine/thalamocortical fibers respectively, the posterior limb contains corticospinal fibers and is directly connected to the primary motor cortex (Jang, 2009).

1.6.2   *OVERVIEW OF STRUCTURAL AND FUNCTIONAL MRI FINDINGS*

Relative to the corpus callosum, there are few neuroimaging studies that focus on the internal capsule. Kim et al. (2008) used functionally guided tractography to study the corticospinal tract in ten healthy controls who performed a hand squeezing task (at 1.5 T). Regions of interest included the motor cortex and pons. Using a probabilistic tractography approach, they "demonstrated that the corticospinal tract for the hand descended through the posterior portion of the posterior limb at the mid-thalamic level." Although this study did not report WM activation, the results imply that a simple motor task could potentially elicit activation in the posterior limb of the internal capsule.

Interestingly, Maldjian et al. (1999) employed a motor task to study WM activation in the internal capsule. They tested 14 healthy controls with both a ball-squeezing task as well as a thumb-wiggling task at 1.5T and 4T. The group level results indicated that the ball-squeezing task elicited significant activation in the posterior limb of the internal capsule at 4T. The authors concluded that "lower levels of blood flow change related to the WM may require the recruitment of a larger functional topographic region (all the fingers plus a sensory component in this study) in order to achieve statistically detectable changes" and that the increased sensitivity to BOLD signal that 4T offers may be "critical in detecting white matter blood flow changes." This work provided promising evidence that white matter fMRI is not restricted to the corpus

callosum, however, the study was only presented in abstract form (at the International Society for Magnetic Resonance in Medicine) and further follow up was required.

1.7 *EVALUATION OF WHITE MATTER DYSFUNCTION*

Given that fMRI activation has been detected in WM regions, there are clear implications for the evaluation of WM disease/damage. In order to prepare WM fMRI for clinical use, research on WM fMRI must be linked to well known clinical tests. In the clinic, neurological patients are routinely assessed with standardized neuropsychological measures of function. Such testing has shown that patients with WM disease (e.g. MS) show various impairments on measures of attention, memory, and executive function (Chiaravalloti and DeLuca, 2008; Hoffmann et al., 2007; Rogers and Panegyres, 2007; Wishart et al., 2001). However, the most common and profound cognitive deficits associated with WM disorder are evident on measures of information processing speed (Chiaravalloti and DeLuca, 2008; Hoffmann et al., 2007; Rogers and Panegyres, 2007). Accordingly, one of the most common tests for assessing WM disorders is the Symbol Digit Modalities Test (SDMT; Hoffmann et al., 2007). The SDMT is considered a sensitive measure that is able to identify cognitive impairment across WM disorders (Chiaravalloti and DeLuca, 2008; Felmingham et al., 2004; Hoffmann et al., 2007; Rogers and Panegyres, 2007).

Briefly, the SDMT is a standardized clinical measure that is used to assess a wide range of neuropsychological disorders (including brain injury and MS). It consists of a legend depicting nine symbols with the numbers 1-9 written beneath. Below the legend there is a series of symbols paired with blank boxes. During written administration, the

patient is asked to use the legend to fill in as many missing numbers as possible within 90 seconds (Smith, 1982).

Recently, the SDMT was modified for use with fMRI (e.g., Forn et al., 2009). Functional MRI can potentially provide information about which WM areas are active during test administration and thus better localize areas affected by disease/damage. GM activation has been reported in occipital, inferior parietal, superior temporal and frontal regions (including bilateral middle, inferior and precentral gyri), as well as in the anterior cingulate and cerebellum (Forn et al., 2009; Genova et al., 2009).

Interestingly, in addition to the GM activation reported during the SDMT, some studies have published figures depicting WM activation (but have not reported it). A study, by Genova et al. (2009) used the SDMT to compare seventeen healthy individuals with sixteen patients with MS. They reported that controls had greater activation than patients in bilateral parietal and frontal regions. Their figures also suggest, (but they did not report) more activation in the anterior corpus callosum and internal capsule in healthy controls during the SDMT (Genova et al., 2009). It is likely that changes in both GM and WM lead to different processing between healthy and diseased conditions, however WM activation results have been ignored and are likely unreported in these studies because of the controversial nature of such findings. Further studies are required to thoroughly characterize WM fMRI activation that occurs during clinical tasks that are sensitive to WM disease.

1.8 OVERVIEW OF CURRENT STUDIES

This manuscript-based thesis is composed of the following four studies:

1.8.1 OPTIMIZING THE DETECTION OF WM FMRI USING ASYMMETRIC SPIN ECHO SPIRAL

In this study, we evaluated 1) whether it is possible to detect WM fMRI activation

and 2) whether certain MRI contrast mechanisms are more sensitive to WM activation.

To accomplish this, data were acquired using an asymmetric spin echo spiral sequence

(ASE spiral) that collected three images with equal T2* weighting and increasing T2

weighting. An interhemispheric transfer task based on the Poffenberger paradigm was

used to elicit activation in the corpus callosum. WM fMRI activation was examined at the

group and individual levels for the averaged ASE spiral data and for each image

separately.

1.8.2 FUNCTIONAL MAPPING IN THE CORPUS CALLOSUM: A 4T FMRI STUDY OF WHITE MATTER

Evidence of fMRI activation in WM reported by our group used a Sperry task and

found activation in the posterior corpus callosum (D'Arcy et al., 2006; Mazerolle et al.,

2008). The subsequent study (the first work presented in this thesis) used a simple

Poffenberger paradigm to elicit interhemispheric transfer and detected fMRI activation in

the anterior corpus callosum. In this study, we investigated whether location of callosal

activation could be experimentally manipulated using a within-subjects design.

1.8.3 INVESTIGATION OF FMRI ACTIVATION IN THE INTERNAL CAPSULE

Given that nearly all of the evidence for fMRI activation in WM involved the

corpus callosum, the objective of this study was to determine whether WM activation

could be detected in another white matter region. Given preliminary evidence in favor of the ability to measure activation in the internal capsule (in the form of an abstract), we focused on this structure. A motor task was selected to elicit activation in the posterior limb of the internal capsule. WM fMRI activation was examined at the individual and group levels.

1.8.4   *FUNCTIONAL MRI SUPPORTS WHITE MATTER INVOLVEMENT IN THE SYMBOL DIGIT MODALITIES TEST*

The objective of this study was to bridge the gap between advances in the ability to detect WM activation and the approaches used to clinically assess WM disorder. We investigated whether a neuropsychological test that is sensitive to WM damage/dysfunction could elicit WM activation. Specifically, we used an adapted SDMT to examine WM fMRI activation in healthy controls.

CHAPTER 2 OPTIMIZING THE DETECTION OF WHITE MATTER FMRI USING ASYMMETRIC SPIN ECHO SPIRAL

This chapter includes work published in **Gawryluk, J.R.,** Brewer, K.D., Beyea, S.D., and

D'Arcy, R.C. (2009) Optimizing the detection of fMRI activation in WM using

asymmetric spin echo spiral. NeuroImage; 45(1): 83-88.

Student contributions to the manuscript include: helping to design the experiment, recruit

participants, collect data, analyze the data, intepret the results, and write the manuscript.

2.1 ABSTRACT

The majority of fMRI studies restrict their focus to GM regions because this

tissue is highly perfused relative to WM. However, an increasing number of studies are

reporting fMRI activation in WM. The current study had two objectives: 1) to evaluate

whether it is possible to detect WM fMRI activation and 2) to determine whether certain

MRI contrast mechanisms are more sensitive to WM activation (i.e., T2* versus T2

weighting). Data were acquired from a 4 T MRI using an asymmetric spin echo spiral

sequence (ASE spiral). This technique collected three images with equal T2* weighting

and increasing T2 weighting. An interhemispheric transfer task was used to elicit

activation in the corpus callosum. WM fMRI activation was examined for the averaged

ASE spiral data and for each image separately. Callosal activation was present in all

subjects as well as in the group analysis. Analyses revealed that increasing T2 contrast

improved sensitivity as measured by percent signal change. It is possible to detect WM

activation in fMRI. As T2 weighting increased, ASE spiral showed increasing sensitivity to this activation. The findings provide further support for the investigation of WM fMRI.

2.2   *INTRODUCTION*

The majority of BOLD fMRI studies focus on highly perfused GM. To date, the notion of fMRI activation in WM remains contentious. There are two main reasons for this controversy. Firstly, the BOLD contrast signal is highly dependent on cerebral blood flow and volume, which are thought to be much lower in WM than in GM. While estimates vary, the white to GM ratios are typically in the range of 1:3 for cerebral blood volume (Helenius et al., 2003; Preibisch and Haase, 2001; Rostrup et al., 2000) and 1:6 for cerebral blood flow (Helenius et al., 2003; van der Zande et al., 2005; Wise et al., 2004). Secondly, the source of the fMRI signal is thought to arise primarily from post-synaptic potentials rather than action potentials. There is evidence that local field potentials (which reflect post-synaptic potentials) are more closely linked to changes in BOLD-fMRI than multi-unit activity (which reflect action potentials; Logothetis et al., 2001). Despite this, an increasing number of fMRI studies have shown WM activation (Baudewig et al., 2008; D'Arcy et al., 2006; Maldjian et al., 1999; Mazerolle et al., 2008; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Zeffiro et al., 2007).

The majority of these studies use an interhemispheric transfer task that was first implemented nearly a century ago (Poffenberger, 1912). The task takes advantage of the crossed nature of the visual and motor systems. It involves visual field presentation of light flashes or checkerboards combined with left and right hand responses. When the response hand is on the same side as the visual stimulus, it is assumed that information does not need to cross between the hemispheres ("uncrossed"). However, when the

18

opposite response hand is used, it is assumed that information must be sent between the hemispheres in order to respond ("crossed"). While there is on-going debate about the crossed-uncrossed differences in behavioural studies (Marzi, 1999; Marzi et al., 1991), this task has been widely used to investigate interhemispheric transfer.

As a result, a number of studies have used this simple visuo-motor task in fMRI (Baudewig et al., 2008; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Zeffiro et al., 2007). A review of the literature revealed that of the seven studies conducted to date (Baudewig et al., 2008; Iacoboni and Zaidel, 2004; Martuzzi et al., 2006; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Zeffiro et al., 2007), five show supra-threshold activation in the corpus callosum (Baudewig et al., 2008; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Zeffiro et al., 2007). Importantly, the activation reported in these studies tends to converge on the anterior regions of the corpus callosum. The region identified is thought to involve tracts transferring information between pre-frontal and pre-motor regions (Bonzano et al., 2008; Meyer et al., 1995; Stančák Jr et al., 2000; Zarei et al., 2006).

In addition to using basic stimuli to study interhemispheric transfer, it is also possible to employ more complex stimuli, such as words and faces (D'Arcy et al., 2006; Mazerolle et al., 2008). We have previously shown that visual field presentation of words and faces activates regions near the splenium of the corpus callosum at 1.5 T (D'Arcy et al., 2006). To build on this, we recently employed the same type of task at 4 T and isolated corpus callosum activation in the isthmus in 5 out of 24 subjects (Mazerolle et al., 2008). Two important observations emerged from this work: 1) the WM fMRI activation occurred in a different region of the corpus callosum – one that was again consistent with the nature

of the task; and 2) WM fMRI activation was difficult to detect – largely because assumptions derived out of GM studies must be revisited.

One basic assumption relates to the relative contributions of different relaxation parameters. Traditionally, BOLD contrast derived from T2*-weighting has been used to study fMRI activation in GM; the origin of this signal is mostly associated with susceptibility induced gradients from larger blood vessels (e.g. veins). In contrast, T_2-weighted spin echo images are known to be sensitive to diffusion within the sharp susceptibility-induced gradients from smaller vessels (e.g. capillaries, venules; Boxerman et al., 1995; Kim and Uğurbil, 1997), which exist in WM. Furthermore, the combination of a spin echo sequence and high field MRI can enhance the measurement of extra-vascular BOLD effects from small vessels (Duong et al., 2003; Kim and Uğurbil, 1997). Given that T2 weighting is more sensitive to smaller vessels and/or extravascular signals, it may provide a more sensitive means of detecting BOLD contrast signal in WM.

Recognizing that the idea of WM fMRI remains controversial, we sought to directly answer the question: Can WM fMRI activation be reliably detected using a basic interhemispheric transfer paradigm at 4T? We also used a specific imaging approach in order to answer a second question: Are certain imaging parameters, such as T_2, more sensitive to activation in WM? Specifically, we wanted to investigate whether images with different T2 weighting would differ in their sensitivity to activation in WM. To evaluate whether differences in MRI contrast mechanisms exist, we used a method of image acquisition called asymmetric spin echo (ASE) spiral (Brewer et al., 2009) in combination with 4T MRI to collect three images with equivalent T2* weighting and increasing T2 weighting.

Accordingly, it was hypothesized that 1) It would be possible to detect WM fMRI activation at both the group and individual level, and 2) the three images collected with ASE spiral would differ in their sensitivity to WM activation, with the third (with the most T2 contrast) producing the strongest activation.

2.3   MATERIALS AND METHODS

2.3.1   PARTICIPANTS

Ten healthy, right handed subjects (five females) participated in the study. The mean age of the participants was 23.50 (SD = 3.95). Each participant received an explanation of the study and gave their informed consent. The study was approved by the National Research Council and Capital District Health Authority ethics boards.

2.3.2   MRI ACQUISITION

Data were acquired from a 4 T Varian INOVA whole body MRI system. Gradients were provided by a body coil (Tesla Engineering Ltd.) operating at a maximum of 35.5 mT/m at 120 T/m/s, and driven by 950 V amplifiers (PCI). The RF coil used was a TEM head coil (Bioengineering Inc.).

Functional MRI was conducted using the ASE spiral sequence (Brewer et al., 2009). The ASE spiral sequence collects three images (each with differing contrast) per slice per volume. An overview of ASE spiral is provided in Figure 1. The first image collected by ASE is equivalent to the 'in' of a conventional spiral in-out sequence (Glover and Law, 2001). All three images (spiral in, spiral out, and spiral in) are collected with an equivalent effective echo time (TE*), and therefore have an equivalent BOLD contrast weighting and increasing T2 weighting. Due to the parameters needed to collect

three images per slice per volume, the number of slices was limited to eight (5 mm axial slices, 0.5 mm gap). Slices were prescribed to cover the corpus callosum using a 64 x 64 matrix (240 x 240 mm), with 2 interleaved shots in a volume repetition time of 2 s (actual TR = 1 s, 154 volumes). The sequence had an acquisition echo time (TE) of 25 ms, and a spin-echo centre (TE) of 70 ms.
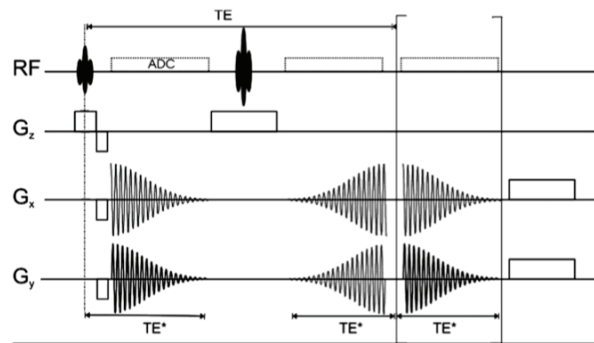
Figure 2.1 ASE pulse sequence diagram.

For structural registration, a high-resolution spiral out image was also collected, with 22 axial slices (128 x 128 matrix, 240 x 240 mm) and 4 interleaved shots. Structural imaging was performed using a 3D MP FLASH anatomical with TR = 10 ms, TI = 500 ms, TE = 5 ms, 256 x 256 matrix, 3 mm slice thickness and 192 mm phase encode.

2.3.3 EXPERIMENTAL DESIGN

A 2x2 hemifield by response hand design was used to investigate interhemispheric transfer. Stimuli consisted of checkerboards (1°x1°) presented to the

visual hemifields at 2.6° of visual eccentricity (100 ms duration with 1400 ms of separation). All stimuli were back-projected to a screen mounted inside the bore (and viewed through a mirror mounted on the head coil). The presentation time and degree of horizontal displacement were chosen to prevent visual saccades (Burde and Feldon, 1992; Hardyck et al., 1985; Rayner, 1998). The visual stimuli were presented randomly, in 10 blocks (8 stimuli/block) which were 12 seconds in length (rest blocks were 18 seconds in length). Participants focused on a central fixation point during both the blocks and the rest phases. Responses were made using either the left or the right hand in all cases. A cue was provided before each block indicating whether the responses were to be made on the same (uncrossed condition) or opposite (crossed condition) side as the visual stimulus. There were an equal number of uncrossed and crossed blocks, which were presented in pseudo-random order (with no more than three consecutive repeats of the same condition). E-prime (Psychology Software Tools, Inc.) was used to present the task and collect behavioral data (accuracy and reaction time). Prior to the task, each subject was instructed to respond as quickly as possible using an MR-compatible response pad. Each subject performed a short practice to ensure compliance.

2.3.4   *FUNCTIONAL MRI ANALYSES*

Statistical analyses were performed using a model-based approach (General Linear Model) in FMRIB Software Library (FSL) using fMRI expert analysis tool (FEAT) version 5.3 (FMRIB's Software Library). Pre-statistics processing steps included motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 6 mm, mean-based intensity normalisation of all volumes by the same factor, and highpass temporal

filtering. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Z statistic images were reported using a threshold for clusters determined by $Z > 2.5$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley et al., 1992). Images were initially registered to the high resolution spiral image (3 DOF) and then to the high resolution T1-weighted anatomical image (7 DOF) before being normalized to standard space (12 DOF) using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

The three images collected with ASE were examined separately and in combination (straight average). Data were first analyzed at the individual level and were then analyzed with a higher-level analysis at the group level. At the individual level, the corpus callosum was masked within Featquery (FMRIB's Software Library) to determine the presence of activation as well as to acquire time series data for the maximum Z voxel in each image. At the group level, the images were analyzed for activation versus rest as well as conditional differences (crossed, uncrossed, crossed>uncrossed, uncrossed>crossed).

Additional statistical analyses were done using a paired sample T-test (implemented in the Statistical Package for the Social Sciences, SPSS, version 11.0). These analyses compared the three ASE images in terms of percent signal change. SPSS was also used to compare the crossed and uncrossed conditions in terms of accuracy and reaction time results.

2.4   RESULTS

2.4.1   FUNCTIONAL MRI RESULTS

**ASE Spiral
Group Data**

Z=0 ▬▬▬▬ Z=6
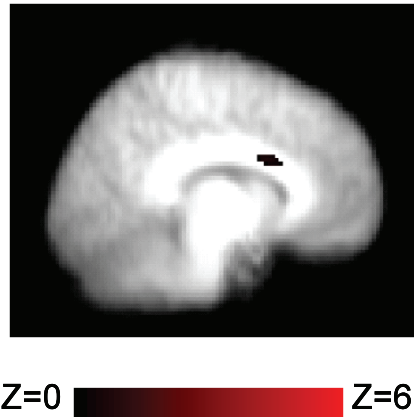
Figure 2.2 Group data showing activation in the anterior corpus callosum for ASE spiral.

Group data were first analyzed for differences between task and rest (Figure 2). The ASE spiral data with all images combined revealed activation in the anterior portion of the corpus callosum. Also, similar corpus callosum clusters were found for condition versus rest (both crossed and uncrossed; Figure 3), but there was no activation in the conditional contrasts (crossed vs. uncrossed or uncrossed vs. crossed).
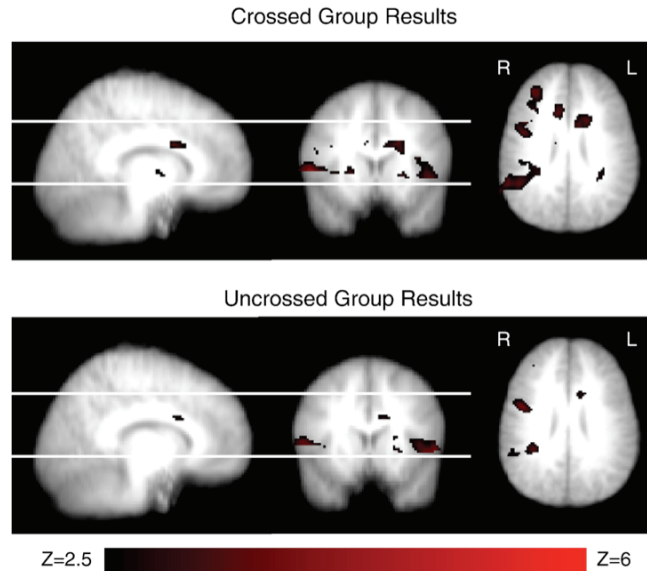
Figure 2.3 Group data displaying uncrossed and crossed activation in the anterior corpus callosum. The location of the imaging slab is indicated by the white lines.

When the three ASE spiral images were examined separately (task versus rest), a similar activation was observed in all three images (Figure 4). However, this cluster was only present in images 2 and 3 when the Z threshold was raised from 2.5 to 3.0.

At the individual level (task versus rest), there was significant activation in the corpus callosum for 90% of participants when the ASE spiral images were combined. When the three ASE images were examined separately, 100% of participants showed activation in the corpus callosum for at least one of the three images. Specifically, the first image revealed corpus callosum activation in 6 participants, and images 2 and 3 each revealed callosal activation in 9 participants. The average percent signal change for the maximum Z voxels in the first, second, and third images was 1.29% (SD = 0.95%), 2.77% (SD = 1.34%), 4.74% (SD = 1.89%). When these values were compared, the second image had significantly more percent signal change than the first (t (9) = 3.653, p (2-tailed) = 0.005)

and the third image had significantly more percent signal change than both the first (t (9)

= 5.172, p (2-tailed) = 0.001) and second images (t (9) = 4.210, p (2-tailed) = 0.002;

figure 5).
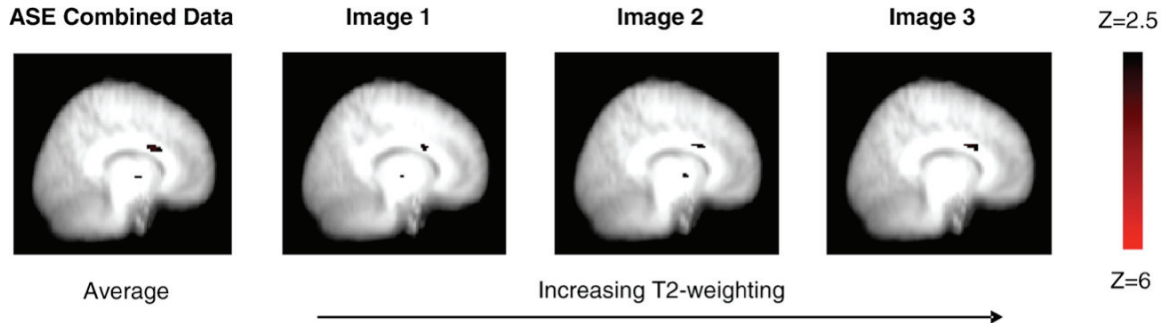
Figure 2.4 ASE spiral group data combined and for images 1, 2, and 3 separately.

2.4.2   *BEHAVIORAL VALIDATION*

Analyses of behavioral data demonstrated that participants performed the task

with a mean accuracy of 98.13% (SD = 1.80%). The mean reaction time in the crossed

condition (396.78 ms, SD = 112.90) was longer than the mean reaction time in the

uncrossed condition (322.95 ms, SD = 85.24). The mean crossed-uncrossed difference

was 73.83 ms, but this difference was not significant (p = 0.07). Note that the behavioral

data from one subject were lost due to technical failure of the response box.
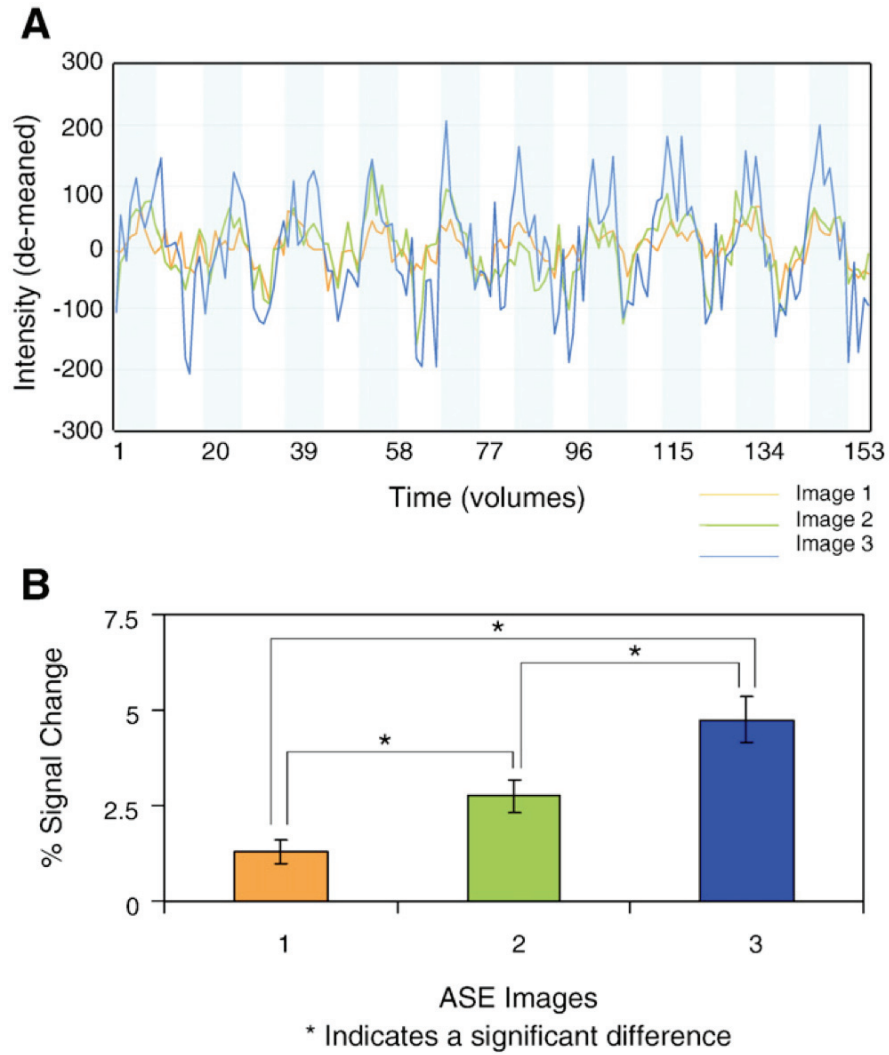
Figure 2.5 (A) Average time series of maximum Z voxel in the corpus callosum for ASE spiral images 1, 2 and 3 (shaded bars indicate blocks). (B) Average percent signal change in the maximum Z voxel in the corpus callosum for ASE spiral images 1, 2, and 3.

Table 2.1 Maximum Z score for each ASE spiral image across 10 participants.

Participant	Image 1	Image 2	Image 3
1	0.00	3.20	3.80
2	0.00	0.00	3.58
3	3.65	3.77	5.43
4	5.30	4.02	4.19
5	4.48	4.44	5.12
6	0.00	3.28	3.72
7	4.00	3.65	4.84
8	0.00	3.97	0.00
9	3.36	3.32	3.40
10	4.96	7.19	6.88

2.5 DISCUSSION

The current study used high field fMRI and an ASE spiral imaging sequence to study interhemispheric transfer across the corpus callosum. As predicted, it was possible to reliably detect WM activation at both the group and individual level (Hypothesis 1). In addition, the ASE spiral image with the most T2 weighting showed the highest percent signal change (Hypothesis 2).

The ASE spiral data showed a clear anterior corpus callosum cluster (Figures 2, 3, and 4). Although small sample size may be a caveat of this study, the group data were also confirmed at the individual level, with activation detected in all subjects for one or more of the ASE images. These results corresponded closely with those from other studies using the same visuo-motor interhemispheric transfer task (Baudewig et al., 2008; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Zeffiro et al., 2007). Given that the anterior corpus callosum is known to connect to pre- frontal areas

(involved in planning task responses) and motor cortical areas (involved in the manual response) (Iacoboni and Zaidel, 2004; Meyer et al., 1995; Stančák Jr et al., 2000; Zarei et al., 2006), the findings suggest that the WM activation is functionally consistent with the task.

The third image, which had the highest T2 weighting, was found to have significantly higher average percent signal change in the maximum Z voxel than both the first and second images (Figure 5). While the specific interpretation for increasing sensitivity with increasing T2 weighting remains to be determined, at least two potential explanations have been identified. First, the high magnetic field strength (such as 4T) in combination with the spin echo technique may have provided enhanced sensitivity to WM activation because it is thought that these techniques are able to detect extra vascular signal fluctuations around small vessels (i.e., parenchyma; Boxerman et al., 1995; Kim and Uğurbil, 1997). However, a second, and equally plausible explanation is that the third image is more sensitive to both white and GM activation due to a non specific increase in contrast-to-noise. While the focus of the current study was restricted to the corpus callosum, future work should address the challenges inherent in deriving an appropriate comparison between WM and GM.

Corpus callosum activation occurred in both crossed and uncrossed conditions (when contrasted with rest). While the activation intensity and extent were greater in the crossed condition, these differences were not significant when the two conditions were contrasted (i.e., crossed>uncrossed analysis). These results suggest that interhemispheric transfer occurred in both conditions; congruently there was bilateral GM activation in both conditions as well. While this may seem counterintuitive, it is not unreasonable to expect.

Behavioural studies have shown that the difference in crossed–uncrossed reaction times tends to be highly variable (Saron et al., 2003). Indeed, despite a 73 ms difference in the current study, the difference was not significant due to the variance (p = 0.07). Without evidence to the contrary, it is sensible to expect that fMRI activation differences are also variable. In addition, recent electrophysiological evidence from our group has shown that interhemispheric transfer occurs in *both* the crossed and uncrossed conditions (D'Arcy et al., 2008), suggesting that differences between the two conditions cannot be assumed. In this respect, a more appropriate manipulation of interhemispheric transfer in fMRI should involve testing different regions of transfer (between different types of tasks) rather than degree of transfer within the same location (and the same task).

2.5.1 CONCLUSIONS

WM fMRI has applications in both basic science (e.g. the study of connectivity), as well as clinical practice (e.g. the assessment of MS), yet has been relatively disregarded in the literature. The current study demonstrates that it is possible to detect WM activation in the anterior corpus callosum using 4 T fMRI. Additionally, this study shows that certain parameters can be optimized to measure WM fMRI activation. As T2 weighting increased, ASE spiral showed increasing sensitivity to this activation. It remains to be seen whether similar activation can be reliably detected in other regions of the corpus callosum (or even other WM structures). Nonetheless, the findings provide strong evidence for continued investigation into the possibility of WM fMRI and its role in visualizing functional connectivity within the brain.

2.6 ACKNOWLEDGEMENTS

CHAPTER 3 FUNCTIONAL MAPPING IN THE CORPUS CALLOSUM: A 4T FMRI STUDY OF WHITE MATTER

This chapter includes work published in **Gawryluk, J.R**., D'Arcy, R.C., Mazerolle, E.L., Brewer, K.D. and Beyea, S.D. (2011). Functional mapping in the corpus callosum: a 4T fMRI study of white matter. NeuroImage; 54: 10-15.

Student contributions to the manuscript include: helping to design the experiment, recruit participants, collect data, analyze the data, intepret the results, and write the manuscript.

3.1   ABSTRACT

Introduction: The idea of fMRI activation in WM is controversial. Our recent work has used two different approaches to investigate whether there is evidence for WM fMRI. The first approach used words and faces to elicit interhemispheric transfer activation in the posterior corpus callosum (Sperry task). The second approach used checkerboard stimuli to elicit similar activation in the anterior corpus callosum (Poffenberger task). Using these different tasks, it has been possible to detect WM activation in different regions. In the current study, we report the results of a critical experiment: demonstrating that callosal activation can be experimentally manipulated within the same set of individuals. Methods: All subjects completed both the Sperry and Poffenberger tasks. Functional MRI data were acquired at 4 T, using an asymmetric spin echo spiral sequence. Data were analyzed with FSL using a model-based approach. Analyses focused on group and individual activations in WM. Results and discussion: Corpus callosum

activation was elicited for both tasks, with activation varying according to task type. A statistical contrast of the two tasks revealed posterior callosal activation for the Sperry task and anterior callosal activation for the Poffenberger task. The Sperry task showed activation in the isthmus and middle body of the corpus callosum at the group level and in 100% of subjects. The Poffenberger task showed activation in the genu and middle body of the corpus callosum at the group level and in 94% of subjects. The WM activation replicated prior results, with the additional strength of functional mapping within the same group of individuals.

3.2   INTRODUCTION

WM comprises approximately 50% of brain volume (Black, 2007), yet the notion of using fMRI to examine these regions remains relatively unexamined and highly controversial. There are two main reasons for the controversy: 1) BOLD signals rely in part on relatively small fluctuations in cerebral blood volume and flow, which are 3-6 times lower in WM (Helenius et al., 2003; Preibisch and Haase, 2001; Rostrup et al., 2000; van der Zande et al., 2005; Wise et al., 2004); and 2) the primary source of fMRI signal is thought to arise from post-synaptic potentials (Logothetis et al., 2001). To put the situation in context, of the 254 287 fMRI studies that have been published to date (according to a PubMed search for 'fMRI' at the time this paper was written), there are only nine reporting activation in WM to our knowledge (D'Arcy et al., 2006; Gawryluk et al., 2009; Mazerolle et al., 2010; Mazerolle et al., 2008; Mosier and Bereznaya, 2001; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Yarkoni et al., 2009). Approximately half of these studies detected WM activation incidentally.

Many of the fMRI studies that report WM activation used tasks designed to elicit interhemispheric transfer (IHT; e.g., Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005). The typical IHT task (Poffenberger, 1912) rapidly presents visual stimuli to each hemifield and requires a motor response from either the ipsilateral (no cross) or contralateral (motor cross) hand (e.g., Tettamanti et al., 2002). Another IHT task is modeled after so-called "split-brain" patients (Gazzaniga et al., 1965), using visual hemifield presentation of lateralized stimuli (words and faces) (e.g., D'Arcy et al., 2006).

Given the early evidence in support of functional activation in WM, our group followed up with two prospective studies of WM fMRI. In the first study, we used high field imaging (4T) and a Sperry task to elicit WM activation in the corpus callosum (Mazerolle et al., 2008). The results revealed activation in the isthmus of the corpus callosum in 20% of the individual subjects and at the group level. In the second study, we replicated the demonstration of WM activation using a Poffenberger task (Gawryluk et al., 2009). This time the results detected activation in the anterior corpus callosum, for 100% of the individual subjects and at the group level.

The increase in sensitivity was due largely to the use of an imaging technique called asymmetric spin echo (ASE) spiral (Brewer et al., 2009). ASE spiral acquires three images (per slice per volume) with increasing T2 weighting but equal T2* weighting. Previous studies demonstrated that T2 weighting at high field is sensitive to GM activation (Kim and Uğurbil, 1997). We have shown that increased T_2 weighting combined with 4T MRI is sensitive to WM fMRI activation (Gawryluk et al., 2009). Given these results, ASE spiral acquisition at high field may lead to increased detection of WM fMRI activation when compared with other methods.

Notably, the Mazerolle et al. (2008) and Gawryluk et al. (2009) studies detected activation in different regions of the corpus callosum – both of which were functionally consistent with the tasks. The posterior callosal activation observed for the Sperry task was thought to connect parietal regions involved in integrating high level sensory information (Witelson, 1989; Zarei et al., 2006). The anterior callosal activation observed for the Poffenberger task was thought to connect pre-motor regions associated with the subject's response (Iacoboni and Zaidel, 2004; Meyer et al., 1995; Stančák Jr et al., 2000; Zarei et al., 2006). Previous work using the Poffenberger task has identified a more anterior cluster in the genu of the corpus callosum, which was also attributed to pre-motor interhemispheric transfer, although recent tractography studies suggest the genu is structurally connected to pre-frontal regions (e.g., Zarei et al., 2006).

These results suggest that functional mapping in WM may be possible. This observation needed to be confirmed using a within-subjects design. Accordingly, we sought to answer the following question: Can two different tasks be used to map different callosal regions within the same subjects? To answer this question, we employed the Sperry and Poffenberger tasks. In order to continue optimizing our sensitivity to fMRI activation in WM, we used the 4T ASE spiral method, weighting the combined data towards the third image (with the most T_2 weighting). It was hypothesized that: 1) both tasks would elicit WM fMRI activation at the group and individual levels; 2) the Sperry task would elicit relatively more activation in the posterior corpus callosum and 3) the Poffenberger task would yield relatively more activation in the anterior corpus callosum.

3.3 MATERIALS AND METHODS

3.3.1 PARTICIPANTS

Seventeen healthy, right handed subjects (8 females) participated in the study. The mean age of participants was 26.05 ± 4.79 years. The study was approved by the local ethics boards. Each participant provided written informed consent prior to their participation.

3.3.2 EXPERIMENTAL DESIGN

Each participant completed the Poffenberger task followed by the Sperry task[1]. The Sperry task utilized a block design (eight 22 s blocks with eight stimuli/block, alternated with 18 s rest blocks) to present words (left hemisphere stimuli) and faces (right hemisphere stimuli) to the left and right visual fields. The stimuli were either real (i.e., typical faces or words) or pseudo (i.e., faces with rearranged features or non-words). Participants were asked to indicate if a given stimulus was a real or pseudo face or a real or pseudo word (four button forced response). Response hand was always crossed (i.e.,

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[1] Relative differences in task difficulty precluded counterbalancing, however, we verified that this was not an experimental concern. The Poffenberger task was always given first because it was significantly easier than the Sperry task ($P = 0.001$; see Behavioral Results section). Pilot testing showed that the overall activation was markedly reduced if the Poffenberger task was presented after the Sperry task. Notably, using this fixed task order did not appear to negatively affect either task, as the mean accuracy was consistent with previous work (Mazerolle et al., 2008; Gawryluk et al., 2009).

left hand for words and right hand for faces). This combination resulted in two different IHT conditions: a motor cross and a visual-motor cross. Each block of stimuli contained only one condition; block order was randomized.

The Poffenberger task used a block design (ten 12 s blocks with eight stimuli/block, alternated with 18 s rest blocks) to present small checkerboard stimuli randomly to the left and right visual fields. Instructions were given prior to each block indicating whether the responses were to be made with the same or opposite hand as the side of the visual stimulus (two button forced response). Varying response hand in this way created two different IHT conditions: motor cross and no cross. Each block of stimuli contained only one condition; block order was randomized.

Participants were instructed to maintain central fixation throughout the experiment. All stimuli were presented laterally (>2.3 degrees from fixation) to initially stimulate one hemisphere, and rapidly (words/faces: 150 ms and checkerboards: 100 ms) to avoid saccades. The tasks were presented visually through back-projection to a screen mounted inside the bore (and viewed through a mirror mounted on the head coil) using E-prime (Psychology Software Tools, Inc). Each subject performed a short practice of each task with feedback to ensure compliance.

3.3.3   FUNCTIONAL MRI ACQUISITION

Data were acquired from a 4 T Varian INOVA whole body MRI system. Gradients were provided by a body coil (Tesla Engineering Ltd.) operating at a maximum of 35.5 mT/m at 120 T/m/s, and driven by 950 V amplifiers (PCI). The RF coil employed was a TEM head coil (Bioengineering Inc.) driven by a 7 kW amplifier (Herley Inc.).

Functional MRI data were acquired using the ASE spiral sequence (Brewer et al., 2009). The ASE spiral sequence collects three images (with increasing T2 weighting but equal T2* weighting) per slice per volume. The number of slices was limited to 17 (4 mm axial slices, with no gap) in order to satisfy the time parameters required to collect the three ASE spiral images. Slices were prescribed to cover a slab extending from the ventral boundary of the corpus callosum to the cortex above. The parameters for functional imaging were as follows: 64 x 64 matrix (220 x 220 mm), 1 shot, TR = 2 s, TR/TE/TE* = 2000/68/27 ms (where TE is the spin-echo centre and TE* is the asymmetric echo times). A 3D MP FLASH whole brain anatomical image (72 2 mm axial slices) was also collected, with TR/TI/TE = 10/500/5 ms.

3.3.4   FUNCTIONAL MRI DATA ANALYSES

The three ASE images were combined using an inverted signal weighted averaging algorithm to increase T2 weighting (based on the findings of Gawryluk et al., 2009). Pre-statistics processing included the following steps: motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 6 mm, mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering (100 s cutoff). Statistical analyses were performed using fMRI expert analysis tool (FEAT) version 5.3 in FMRIB Software Library (FSL). A model-based approach (General Linear Model) was taken using a gamma HRF and its temporal derivative, convolved with the block design of the two tasks. Time-series statistical analyses were carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Statistical analyses were done with

motion parameters as covariates[2]. Except where otherwise stated, Z statistic images were first developed using a threshold for clusters determined by $Z > 2.0$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley et al., 1992). Subsequently, activation maps were displayed in MRIcro ($Z > 2.5$). Images were registered to the high-resolution T1-weighted anatomical image (7 DOF) before being normalized to standard MNI space (12 DOF) using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Registration was manually verified and optimized as needed.

Data were examined at both the group and individual levels. At the group level, the tasks were analyzed for activation versus rest. The main comparison of interest consisted of a statistical contrast of the Sperry and Poffenberger tasks at the group level, using a region of interest (ROI) approach focused on the corpus callosum to increase sensitivity ($P < 0.005$ uncorrected, displayed using $Z > 2.5$). For all group level analyses, local maxima (at least 5mm apart) in callosal WM were extracted for clusters with $Z > 2.5$ and extent > 2.

Results at the individual level were subsequently examined using activation versus rest contrasts. A region of interest (ROI) approach focused on the corpus callosum. The corpus callosum was masked within Featquery (FMRIB's Software Library) to determine the presence, size, and strength of activation in the ROI. Spatial

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[2] The inclusion of motion parameters in the analysis improved activation sensitivity when included in the model and reduced motion artifact (thereby increasing confidence that the white matter activation observed was not due to motion artifact).

coordinates (standard MNI space) were obtained for the maximally active voxel in callosal WM in each task.

3.4 *RESULTS*

3.4.1 FUNCTIONAL MRI RESULTS
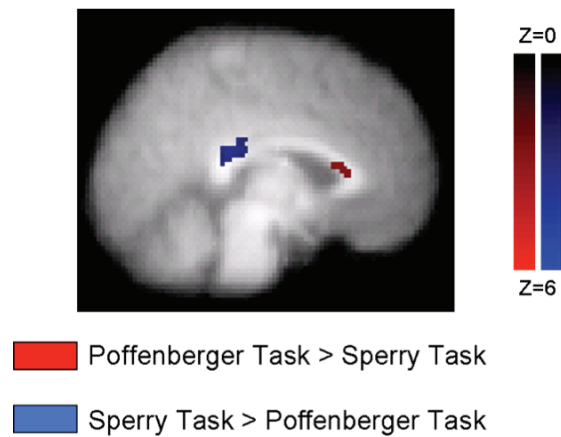
Figure 3.1 Group activation showing statistical difference between the Poffenberger and Sperry Tasks. The Poffenberger Task > Sperry Task (displayed in red) shows activation in the anterior corpus callosum. The Sperry Task > Poffenberger Task (displayed in blue) shows activation in the posterior corpus callosum. Activation intensity is displayed in terms of Z-scores (N=17).

3.4.2 COMPARISON OF THE SPERRY AND POFFENBERGER TASKS AT THE GROUP LEVEL

For all group level analyses, corpus callosum activation is summarized in Table 1.

Table 3.1 Summary of group level corpus callosum activation results.

	MNI coordinates (mm)			
	x	y	z	Z max
Poffenberger task > Sperry task	-2	20	12	3.04
Sperry task > Poffenberger task	6	-36	22	4.06
	2	-2	26	2.99
Poffenberger task > rest	4	24	0	3.36
Sperry task > rest	2	12	20	3.86
	6	-30	22	3.45
	-4	-36	14	3.12
Sperry task, motor cross	10	20	16	3.56
	-2	-36	14	3.26
	-4	-28	16	3.19
Sperry task, visual-motor cross	4	-30	20	3.74
	0	12	18	3.04
Poffenberger task, cross	2	10	18	3.02
	6	20	16	2.94
	-2	14	16	2.71
	-4	24	0	2.86
	2	20	12	2.54
Poffenberger task, no cross	-	-	-	-

When the tasks were statistically compared to one another, activation was present in different regions of the corpus callosum. Specifically, the Sperry task showed greater activation in the posterior corpus callosum when contrasted with the Poffenberger task. The reverse pattern was also observed. The Poffenberger task showed greater activation in the anterior corpus callosum when contrasted to the Sperry task (Figure 1).
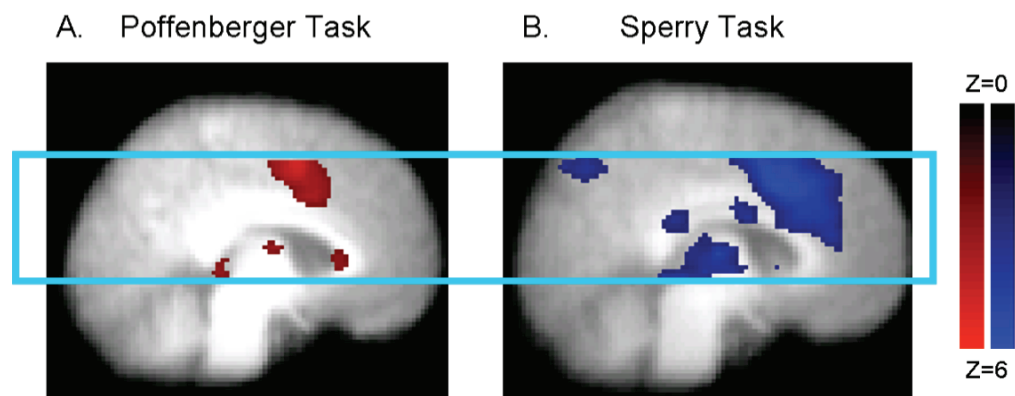
Figure 3.2 Group activation for the Poffenberger Task (A: left) and the Sperry Task (B: right). Activation maps show both WM activation in the corpus callosum and corresponding GM activation within the selected imaging slab (light blue box). All other details as per Fig. 1.

3.4.3 EXAMINATION OF THE SPERRY AND POFFENBERGER TASKS AT THE GROUP LEVEL

Separately, the tasks showed group level activation in different regions of the corpus callosum (Figure 2). The Sperry task revealed activation clusters in the isthmus of the corpus callosum as well as in the middle body of the corpus callosum. Corresponding GM task-related activation was present in bilateral occipital (precuneus, lingual gyrus), bilateral parietal (precuneus, supramarginal gyrus), bilateral temporal (fusiform gyrus,

inferior temporal gyrus, insula), bilateral frontal (middle frontal gyrus, inferior frontal gyrus) regions as well as in the thalamus and anterior cingulate.

The Poffenberger task showed activation in the genu of the corpus callosum. Corresponding GM activation was visible in bilateral occipital (lingual gyrus), bilateral parietal (precuneus, supramarginal gyrus), bilateral temporal (superior temporal gyrus, inferior temporal gyrus, insula), bilateral frontal (middle frontal gyrus, inferior frontal gyrus) regions as well as in the thalamus and anterior and posterior cingulate.
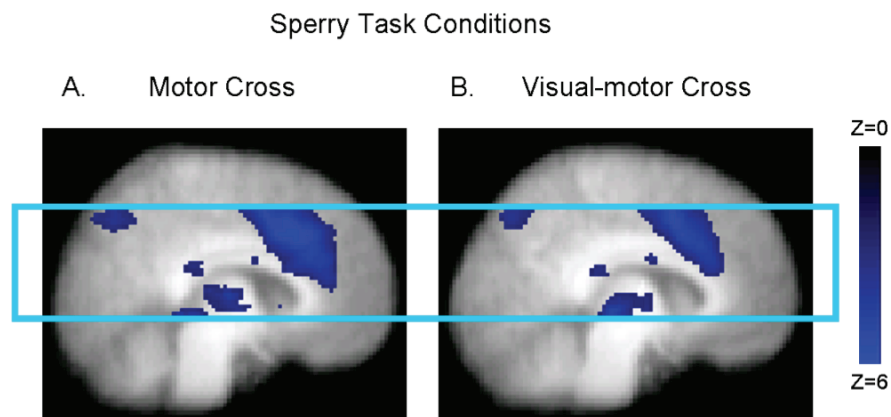
Figure 3.3 Sperry Task group activation showing similar clusters in both Motor Cross (A) and Visual-motor Cross (B) conditions. The posterior isthmus activation was specific to the Sperry Task, whereas, the middle body activation was also present in the Poffenberger Task. All other details as in Fig 3.2.
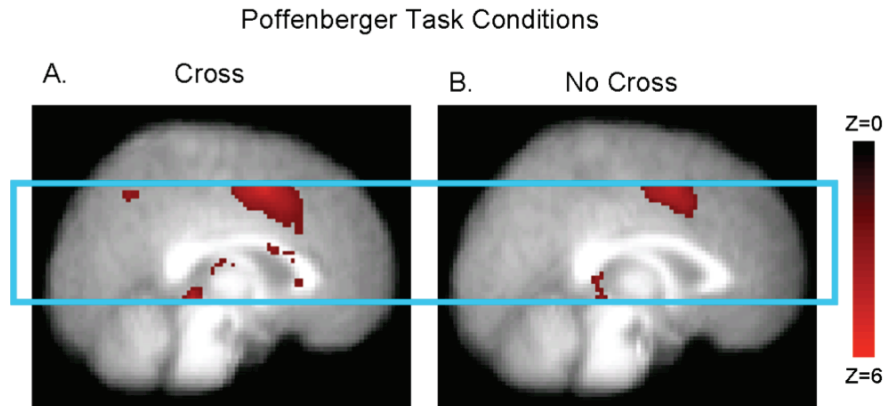
Figure 3.4 Poffenberger Task group activation showing anterior and middle body clusters in the Crossed condition (A). While there was no cluster in the Uncrossed condition (B), similar activation was detected at lower thresholds. The pattern of results is consistent with prior observations of no 'true' uncrossed condition (Gawryluk et al., 2009; Mazerolle et al., 2008). All other details as in Fig 3.2.

3.4.4 EXAMINATION OF THE SPERRY AND POFFENBERGER CONDITIONS AT THE GROUP LEVEL

The results of group level conditional analyses were also examined. In the Sperry task, the motor cross and visual-motor cross conditions (compared to rest) showed activation in the isthmus and middle body of the corpus callosum (Figure 3.3), as well as in the GM regions observed in the task versus rest analysis.

In the Poffenberger task, the motor cross condition revealed activation in the genu and middle body of the corpus callosum (Figure 3.4). The no cross condition did not show any activation in the corpus callosum. However, activation was present in the genu and middle body when analyzed at a lower threshold ($Z = 2.0$, $P = 0.1$).
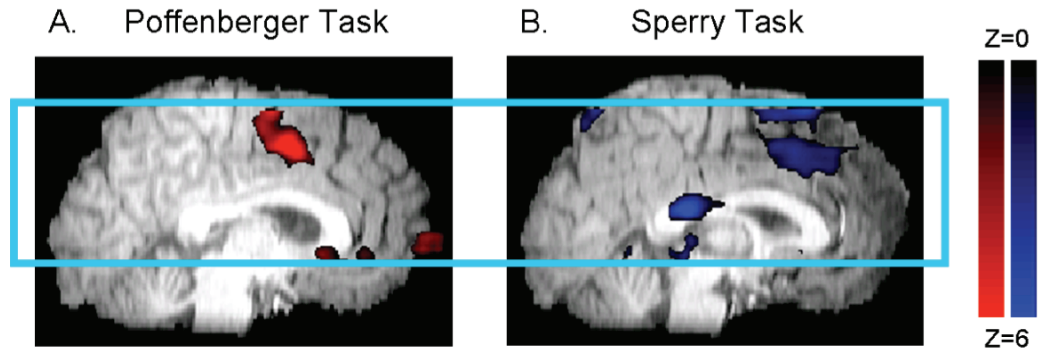
Figure 3.5 Individual activation for the Poffenberger Task (A: left) and the Sperry Task (B: right). Images show WM activation clusters clearly centered on the corpus callosum. All other details as in Fig 3.2.

3.4.5   *EXAMINATION OF THE SPERRY AND POFFENBERGER TASKS AT THE INDIVIDUAL LEVEL*

At the individual level, the Sperry task elicited WM activation in 17/17 participants. The Poffenberger task yielded WM activation in 16/17 participants. Table 2 shows the extent of activation, maximum Z score and co-ordinates of the maximally active voxel in the corpus callosum for each participant during each task. Figure 3.5 shows activation in a representative subject during each task. The average maximum Z score during the Sperry task was 5.23 (SD = 1.45) and the average maximum Z score during the Poffenberger task was 4.56 (SD = 1.53).

Table 3.2 Individual level results during the A. Sperry Task and B. Poffenberger Task: Cluster extent, intensity and MNI space co-ordinates of the maximally active voxel in the corpus callosum.

A. **Sperry Task**

Subject	Number of Voxels in the Corpus Callosum (z>2.5)	Maximum z Value in the Corpus Callosum	Coordinates of Maximum z Voxel (mm)		
			x	y	z
1	7	4.15	-8	17	24
2	208	6.31	6	10	20
3	105	3.86	0	-2	26
4	2	2.64	-8	-4	28
5	96	5.61	5	24	6
6	141	5.54	1	-30	18
7	83	7.33	13	20	27
8	30	4.61	-16	-46	10
9	27	3.38	-2	-38	12
10	78	5.70	12	22	20
11	35	4.17	6	4	26
12	50	5.90	4	-34	14
13	60	3.42	8	-38	16
14	48	5.46	-12	14	26
15	114	3.25	-2	-32	18
16	56	3.38	0	22	0
17	18	3.51	-8	0	28

B. <u>Poffenberger Task</u>

Subject	Number of Voxels in the Corpus Callosum (z>2.5)	Maximum z Value in the Corpus Callosum	Coordinates of Maximum z Voxel (mm)		
			x	y	z
1	0	0			
2	98	5.04	17	24	9
3	2	2.85	-2	26	2
4	2	3.37	-10	24	16
5	48	3.65	2	-16	26
6	89	4.06	-6	22	14
7	9	3.21	22	-46	8
8	144	4.19	0	26	-2
9	80	3.78	10	32	2
10	31	3.06	-2	18	16
11	2	2.94	4	8	22
12	13	2.99	-8	28	4
13	68	3.57	13	20	26
14	127	5.93	-10	10	26
15	59	4.13	-14	8	26
16	100	4.10	0	14	160
17	35	6.93	-13	20	25

3.4.6 BEHAVIORAL RESULTS

Analyses of behavioral data demonstrated that participants performed the Sperry task with a mean accuracy of 81.8%. The mean reaction time for the visual-motor cross condition (807.7 ms, SD = 93.9 ms) was shorter than the motor cross condition (819.4 ms, SD = 112.1 ms). However, this difference was not significant (p = 0.258).

The Poffenberger task was completed with a mean accuracy of 97.5%[3]. The mean reaction time of the motor cross condition (413.9 ms, SD = 73.8 ms) was longer than the mean reaction time in the uncrossed condition (351.7 ms, SD = 53.6 ms). The mean crossed-uncrossed difference was 62.2 ms, which was statistically significant (p < 0.001).

3.5 *DISCUSSION*

The current study examined whether different interhemispheric transfer tasks could be used to functionally map patterns of activation in the corpus callosum. As predicted, the Sperry and Poffenberger tasks reliably detected WM activation at both the group and individual level (Hypothesis 1). The Sperry task elicited activation in the posterior corpus callosum (Hypothesis 2). The Poffenberger task elicited activation in the anterior corpus callosum (Hypothesis 3). Both tasks elicited activation in the middle body of the corpus callosum.

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[3] A separate analysis using a paired samples t-test showed that the Sperry task was significantly more difficult than the Poffenberger task (P = 0.001).

Functional mapping of different callosal regions was demonstrated at the group level. Importantly, when the tasks were statistically compared, the Sperry task showed greater activation in the posterior corpus callosum, whereas the Poffenberger task showed greater activation in the anterior corpus callosum (Figure 1). This finding is highly consistent with the differences observed between tasks across previous studies (Gawryluk et al., 2009; Mazerolle et al., 2008). These results suggest that it is possible to functionally map WM using a within subjects design. This finding represents a critical experimental test of WM activation.

The Sperry task elicited WM activation in the isthmus of the corpus callosum (Figure 2; Figure 3), replicating prior WM (and GM) results (Mazerolle et al., 2008). This WM activation is consistent with connections between parietal areas that serve to integrate high-level sensory information (Witelson, 1989; Zarei et al., 2006). Indeed, we used a subset of the same data to examine diffusion based tractography (Mazerolle et al., 2010) [4]. The results linked the WM activation in the isthmus to GM activation in the parietal lobe (Mazerolle et al., 2010).

In addition to the isthmus cluster, WM activation was also detected in the middle body of the corpus callosum for the Sperry task (Figure 2; Figure 3). This region is thought to be associated with pre-motor cortical areas (Iacoboni and Zaidel, 2004; Meyer

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[4] Due to optimization of acquisition parameters, diffusion imaging was limited to a subset of subjects in which the initial data were not included.

et al., 1995; Stančák Jr et al., 2000; Zarei et al., 2006). Given the motor component of the Sperry task, this WM activation is consistent with the task response requirements. Notably, the tractography results discussed above have also linked this cluster to GM activation in the pre-motor cortex (Mazerolle et al., 2010).

By comparison, the Poffenberger task yielded WM activation in the genu (Figure 3; Figure 4), highly consistent with previous research (Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005). The genu is thought to be associated with the pre-frontal cortex (Zarei et al., 2006). On-going tractography analyses have linked the WM activation in the genu to GM activation in the inferior frontal lobes (Mazerolle et al., 2009). This finding is not consistent with previous interpretations, which have linked genu activation to pre-motor interhemispheric transfer (Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005). Future studies are required to further examine the functional significance of genu activation.

Interestingly, conditional analyses of the Poffenberger task (Figure 4; motor cross versus rest) also revealed a second corpus callosum cluster located in the middle body, replicating prior results (Gawryluk et al., 2009) and consistent with the middle body cluster in the Sperry task (above)[5]. The results indicated a degree of overlap in WM activation, which is likely related to the motor responses common to both tasks.

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[5] At liberal thresholds, the Poffenberger no cross condition also revealed activation in the genu and middle body of the corpus callosum, consistent with previous work (Gawryluk et al., 2009).

Similar to prior work using the ASE spiral sequence, there was improved sensitivity to WM activation. At the individual level, callosal activation was elicited in 100% of participants for the Sperry task and 94% of participants for the Poffenberger task (Figure 5). The proportion of subjects with WM activation was similar to the prior Poffenberger task results using the ASE spiral sequence (Gawryluk et al., 2009), and showed improved sensitivity for the Sperry task (compared to 20% in the previous study; Mazerolle et al., 2008). The increased sensitivity of ASE spiral may have also accounted for detecting more clusters in WM.

Indeed, the use of ASE spiral likely represents a major factor accounting for the detection of WM activation. We previously found that the percent signal change and extent of activation in WM increase with T2 weighting (the third ASE image has the most sensitivity to WM activation; Gawryluk et al., 2009). It is possible that the known extravascular diffusion effects related to T2 weighting (Duong et al., 2003; Yacoub et al., 2003) are different in GM and WM, leading to increased sensitivity to WM activation in the third ASE spiral image. Another possibility is that the combination of three fMRI images leads to general increases in the signal-to-noise and contrast-to-noise ratios that augment the sensitivity of ASE spiral across tissue types. Along with ASE spiral, a number of other experimental factors may also play a role in enhancing sensitivity to fMRI activity in WM (e.g., power, analysis parameters, etc.).

One caveat of the current study relates to the fact that the tasks were not counterbalanced. It is possible that the lack of counterbalancing confounded task differences with other effects (e.g., fatigue or practice). While future work is needed to rule this out, the fact that the results replicated those of previous studies, in which these tasks were used in isolation, suggests that order did not influence the findings.

3.5.1 CONCLUSIONS

Functional MRI has been used to advance both basic and clinical science. However, the inability to study WM function is a significant limitation. The current study replicates prior work, and demonstrates that WM can be functionally mapped in the corpus callosum using fMRI. Upcoming studies examine whether fMRI activation can be detected in other WM structures and whether this technical advance can be utilized for diagnostic/assessment methods in WM diseases.

3.6 ACKNOWLEDGMENTS

CHAPTER 4 INVESTIGATION OF FMRI ACTIVATION IN THE INTERNAL CAPSULE

This chapter includes work published in **Gawryluk J.R.**, Mazerolle E.L., Brewer K.D., Beyea S.D. and D'Arcy R.C. (2011). Investigation of fMRI activation in the internal capsule. BMC Neuroscience; 12:56.

Student contributions to the manuscript include: helping to design the experiment, recruit participants, collect data, analyze the data, intepret the results, and write the manuscript.

4.1 *ABSTRACT*

Functional MRI in WM has long been considered controversial. Recently, this viewpoint has been challenged by an emerging body of evidence demonstrating WM activation in the corpus callosum. The current study aimed to determine whether WM activation could be detected outside of the corpus callosum, in the internal capsule. Data were acquired from a 4 T MRI using an asymmetric spin echo spiral sequence. A motor task was selected to elicit activation in the posterior limb of the internal capsule. WM fMRI activation was examined at the individual and group levels. Analyses revealed that activation was present in the posterior limb of the internal capsule in 80% of participants. These results provide further support for WM fMRI activation. The ability to visualize functional activation in tracts has strong implications for the basic scientific study of connectivity and the clinical assessment of WM disease.

4.2 BACKGROUND

WM represents approximately half of the tissue in the brain (Black, 2007). The idea of WM activation in fMRI represents an important advance for both basic and clinical studies. Enabling the measurement of functional connectivity more directly than current fMRI approaches, WM fMRI could provide valuable insight into the dynamics of distributed neural systems and WM diseases.

However, WM fMRI is a controversial idea and, up until recently, has been largely disregarded in the literature. The majority of fMRI studies have restricted their focus to GM for two reasons; 1) the BOLD signal relies on cerebral blood volume and flow which are 3-6 times lower in WM (Helenius et al., 2003; Preibisch and Haase, 2001; Rostrup et al., 2000; van der Zande et al., 2005; Wise et al., 2004), and 2) the primary source of fMRI signal is thought to arise from post-synaptic potentials as opposed to action potentials (Logothetis et al., 2001). Despite these arguments, WM tissue is involved in functional processes that may lead to detectable fMRI signal. Indeed, an increasing number of fMRI studies have shown WM activation (Baudewig et al., 2008; D'Arcy et al., 2006; Gawryluk et al., 2009; Gawryluk et al., 2011a; Mazerolle et al., 2010; Mazerolle et al., 2008; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Yarkoni et al., 2009).

Most of the WM fMRI reports have employed tasks that exploit the lateralized nature of the visual and motor systems (opposite response hand to visual hemifield presentation creates a so-called 'crossed' condition) to study interhemispheric transfer and related information processing phenomena. Recently, our group reported the first prospective WM fMRI studies at 4T using tasks designed to elicit interhemispheric

transfer across the corpus callosum. Mazerolle et al. used a visual Sperry task (word/face) to detect activation in the isthmus of the corpus callosum (Gazzaniga et al., 1965; Mazerolle et al., 2008). These results were observed at the group level and in 20% of the individual subjects (N=24, p<0.005, uncorrected). Gawryluk et al. used a Poffenberger task (visual/motor) to elicit activation in the anterior corpus callosum (Gawryluk et al., 2009; Poffenberger, 1912). These results were present at the group level and, notably, in 100% of the individual subjects (N=10, p<0.05 corrected).

A key factor that accounted for the sensitivity difference between the two studies related to the method of acquisition. Gawryluk et al. (2009) sought to enhance the detection of WM fMRI using an imaging sequence called asymmetric spin echo (ASE) spiral (Brewer et al., 2009). ASE spiral acquires three images (per slice per volume) with increasing T2 weighting but equal T2* weighting. Sensitivity to WM fMRI activation increased with increasing T2 weighting, with the third ASE spiral image (with the highest T2 weighting) demonstrating a significant increase in percent signal change relative to the first ASE spiral image (with the lowest T2 weighting). Moreover, the extent of active voxels in WM increased as a function of T2 weighting. The results provided valuable insight into optimizing fMRI acquisition for the detection of WM activation. Indeed, in a subsequent within-subjects study that administered both the Sperry and Poffenberger tasks using the ASE spiral method of acquisition, corpus callosum activation was observed in 100% and 94% of participants, respectively (Gawryluk et al., 2011a). These results provide further evidence of the sensitivity of ASE spiral to the detection of WM fMRI.

There is additional evidence favoring the detection of fMRI signal in WM. First, WM activation appears to improve when motion is included as a regressor in the model (Gawryluk et al., 2011a; Mazerolle et al., 2008); this would not be expected if the activation resulted from motion artifact. Second, recent work has shown that WM activation varies according to task type, indicating that it can be functionally manipulated (Gawryluk et al., 2011a). Third, as Mazerolle et al. demonstrated, diffusion tensor imaging (DTI) based tractography data can be used to confirm structural connections between active regions in GM and WM (Mazerolle et al., 2010).

Taken together, the research to-date has reported WM activation in the corpus callosum. However, in these previous studies, we cautioned that it is important to verify WM activity in other structures (Gawryluk et al., 2009; Gawryluk et al., 2011a; Mazerolle et al., 2008). This is particularly important if the intent is to develop future applications in both basic science (e.g. the study of functional connectivity) as well as clinical practice (e.g. the assessment of WM diseases). To extend the current findings, we examined the possibility of detecting fMRI activation in another WM structure, namely the internal capsule.

To date, the only evidence for WM fMRI in a fibre tract other than the corpus callosum comes from an abstract by Maldjian et al. (Maldjian et al., 1999). The protocol involved two motor tasks with data collected at 1.5 and 4 T. WM activation was observed in the posterior limb of the internal capsule (PLIC) at 4 T only.

Given that more evidence is needed to characterize controversial WM activation in pathways outside the corpus callosum, the current study sought to answer the

following question: Can WM fMRI activation be detected in the PLIC using a basic

motor paradigm at 4 T? Accordingly, it was hypothesized that it is possible to detect WM

fMRI activation in the PLIC at both the individual and group level.

4.3   METHODS

4.3.1   PARTICIPANTS

Ten healthy, right handed subjects (five females) participated in the study. The

mean age of the participants was 26.4 (SD = 5.2). The study was approved by the local

ethics boards and each participant gave their informed consent prior to their participation.

4.3.2   EXPERIMENTAL DESIGN

The task was optimized based on the Maldjian et al. (1999) study. Each

participant performed a finger tapping task while holding a foam ball in each hand. All

task instructions were presented visually via back-projection to a screen mounted inside

the bore (and viewed through a mirror mounted on the head coil) using E-prime

(Psychology Software Tools, Inc). The instructions indicated on and off blocks as well as

which hand to tap with (order of left and right was randomized). The task consisted of 8

blocks (20s on, 20s off). Participants focused on a central fixation point during the rest

phases. Each subject performed a short practice to ensure task compliance.

4.3.3   IMAGING PROTOCOL

Data were acquired from a 4 T Varian INOVA whole body MRI system.

Gradients were provided by a body coil (Tesla Engineering Ltd.) operating at a maximum

of 35.5 mT/m at 120 T/m/s, and driven by 950 V amplifiers (PCI). The RF coil used was

a TEM head coil (Bioengineering Inc.). All subjects underwent the same imaging

protocol consisting of fMRI acquisition and a high-resolution T1 weighted scan. All images were obtained within one session that was approximately 60 minutes in duration.

4.3.4 FMRI ACQUISITION

FMRI was conducted using the ASE spiral sequence (Brewer et al., 2009). The ASE spiral sequence collects three images (each with differing contrast) per slice per volume. Due to the parameters needed to collect three images per slice per volume, the number of slices was limited to 17 (4 mm axial slices, with no gap, interleaved). Slices were prescribed to cover the region extending from the internal capsule to the primary motor cortex using a 64 x 64 matrix (220 x 220 mm), with 1 shot and a volume repetition time of 2 s (170 volumes). The sequence had an asymmetric echo time of 27 ms, and a spin-echo centre of 68 ms.

4.3.5 STRUCTURAL IMAGE ACQUISITION

Following the fMRI scans, a 3D MP FLASH T1 weighted whole brain anatomical scan (72 2 mm axial slices) was collected for registration purposes. The parameters were as follows: a repetition time of 10 ms, an inversion time of 500 ms, and an acquisition echo time of 5 ms.

4.3.6 FMRI DATA ANALYSES

Prior to data analyses, the three ASE images were combined using an inverted signal weighted averaging algorithm. This approach was taken based on the results of our previous study, which indicated that ASE spiral is more sensitive to WM fMRI activation due to the T2 weighting of the third image (Gawryluk et al., 2009).

Statistical analyses were performed using a model-based approach (General

Linear Model) in FMRIB Software Library (FSL) using fMRI expert analysis tool (FEAT) version 5.3 (FMRIB's Software Library). Pre-statistics processing steps included motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, mean-based intensity normalization of all volumes by the same factor, and highpass temporal filtering (100 s cutoff). Time-series statistical analyses were carried out using FILM with local autocorrelation correction, motion included as a regressor, and a temporal derivative included in the model (Woolrich et al., 2001). Activation was modeled as two boxcar functions representing the blocks of right and left finger tapping separately, convolved with a gamma function. Contrasts were calculated to statistically compare each finger tapping condition to rest. Z statistic images were developed using a threshold for clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley et al., 1992).

Registration was of particular importance in this study, given our small region of interest in the posterior limb of the internal capsule. To ensure the best possible registration, a variety of approaches were compared (e.g. functional images were registered to high resolution anatomical images as well as to standard images with different contrasts). The optimal registration method was subsequently employed; images were registered to the SPM EPI template (12 DOF) before being registered to the standard MNI152 image (12 DOF) using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The two-step registration approach is standard in FSL; in this case, using an image of comparable contrast to the functional data (the SPM EPI template) for the initial registration, improved the registration to standard space. Additionally, the accuracy

of registration was manually confirmed for each subject (by JG and EM

(neuroscientists)). Data were analyzed at the individual and group levels. The JHU

ICBM-DTI White Matter Labels of the left and right PLIC were then combined with

activation maps for each participant. PLIC activation was also manually verified for each

subject (by JG and EM).

4.4   RESULTS
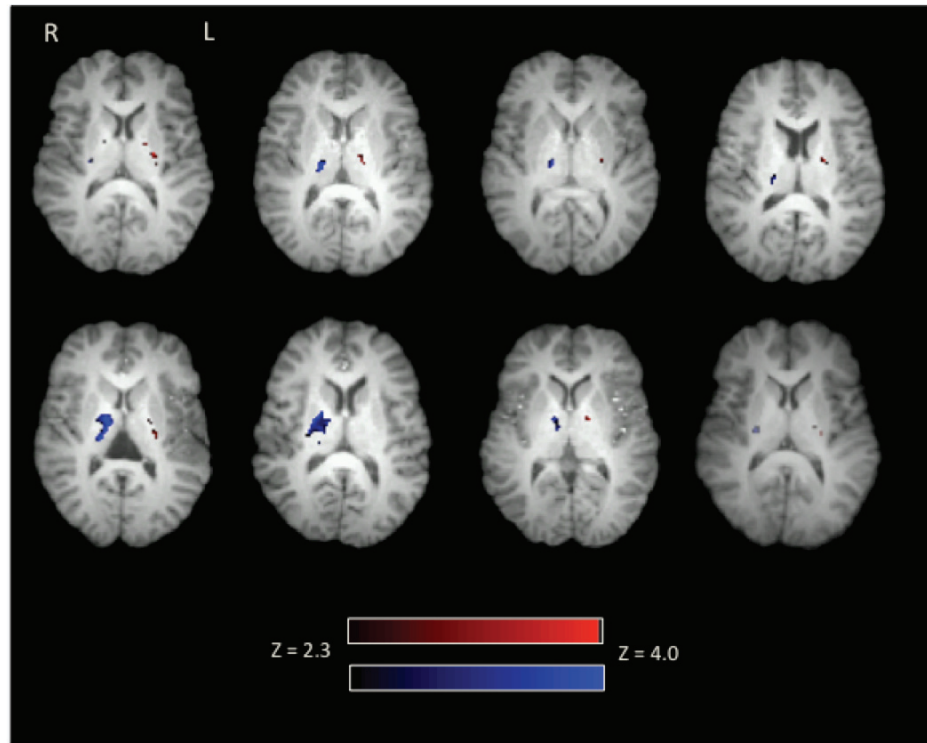
Figure 4.1 Individual level activation during right and left finger tapping. Eight out of ten participants showed activation in the PLIC. Left finger tapping related activation (displayed in blue) is present in the right posterior limb of the internal capsule. Right finger tapping related activation (displayed in red) is present in the left posterior limb of the internal capsule. Of the eight participants with PLIC activation, 100% had activation in the right PLIC and 87.5% showed activation in the left PLIC. Activation intensity is displayed in terms of Z-scores with a Z threshold of 2.3.

At the individual level, PLIC activation was present in 80% of participants (8/10). The left finger tapping condition elicited activation in the right PLIC in 100% of these participants (8/8). The right finger tapping condition elicited activation in the left PLIC in 87.5% of these participants (7/8). Figure 1 shows activation in the PLIC in each subject

for each condition. Table 1 reports the maximum Z score and peak coordinates in the

PLIC for each participant.

Table 4.1 The maximum Z score and peak co-ordinates (MNI space) in the posterior limb of the internal capsule at the individual and group levels during right finger tapping (left hemisphere) and left finger tapping (right hemisphere).

Subject	Hemisphere	Maximum Z score	Co-ordinates of maximum (MNI)
1	Left	3.63	-24 -6 14
	Right	3.62	26 -14 8
2	Left	3.64	-14 -12 8
	Right	3.66	14 -12 8
3	Left	2.85	-16 -2 6
	Right	4.23	18 -20 2
4	Left	3.83	-28 -16 16
	Right	3.80	20 -22 16
5	Left	4.10	-24 -26 14
	Right	5.00	14 -10 6
6	Right	4.05	20 -2 10
7	Left	4.28	-14 -2 0
	Right	4.72	18 -18 4
8	Left	3.31	-22 -12 -2
	Right	3.84	26 -14 6
GROUP	Right	3.15	20 -22 14

The task also showed group level activation in the PLIC (Figure 2; Table 1). The left finger tapping condition produced activation in the right PLIC and to a lesser extent the left PLIC. Conversely, the right finger tapping condition did not reveal PLIC activation
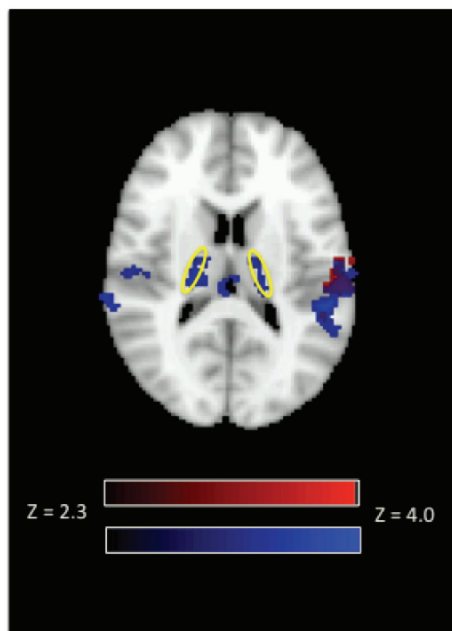
Figure 4.2 Group activation (N =10) during right finger tapping (displayed in red) and left finger tapping (displayed in blue). WM activation is present in the right and left posterior limb of the internal capsule during left hand finger tapping (blue). Activation is displayed with a Z threshold of 2.3.

Additional group level WM activation was present in the superior longitudinal fasciculus (bilaterally) for both conditions. GM task related activation was present in frontal (precentral gyrus, middle frontal gyrus), parietal (postcentral gyrus, superior

parietal lobule, inferior parietal lobule, precuneus), temporal (superior temporal gyrus), and subcortical (basil ganglia, thalamus) regions and in the insula in the left hemisphere for the right finger tapping condition and bilaterally for the left finger tapping condition. The left tapping condition also elicited limbic (cingulate) activation. Figure 3 shows the above group results.
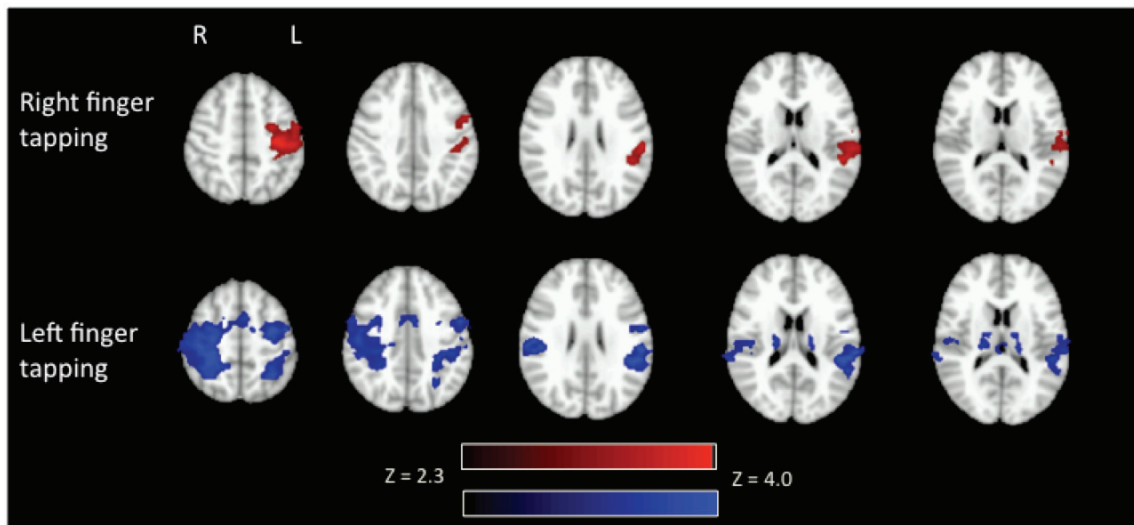
Figure 4.3 Group activation (N =10) in white and GM during right finger tapping (above) and left finger tapping (below). Activation related to right finger tapping is displayed in red and activation related to left finger tapping is displayed in blue. Activation is present in the left primary motor cortex during right finger tapping. Activation is present in the right and left posterior limb of the internal capsule and right primary motor cortex during left finger tapping. Activation is displayed with a Z threshold of 2.3.

4.5 DISCUSSION

The current study examined whether WM fMRI activation could be reliably detected in the internal capsule using a basic motor task and 4 T imaging. As predicted, WM fMRI activation was detected in the PLIC at both the individual and group level.

These findings correspond with fMRI results obtained by Maldjian et al. (1999). As mentioned, Maldjian et al. collected data at 1.5 and 4 T and observed activation in the PLIC at 4 T only, emphasizing the importance of high field strength to the detection of WM fMRI (Maldjian et al., 1999).

The current findings are also consistent with known neuroanatomy. The PLIC contains corticospinal fibers and is thought to directly connect to the primary motor cortex (Nolte, 2002). Such connections have previously been demonstrated in healthy subjects using a combination of fMRI activation in the primary motor cortex and DTI tractography (Guye et al., 2003). Given this, the finding of WM fMRI activation in the PLIC is thought to be functionally consistent with the motor task employed. The most pronounced activation in the internal capsule was present in the hemisphere contralateral to the engaged hand (Figure 2). This pattern of activation (bilateral: contralateral > ipsilateral) matches that typically seen in the primary motor cortices for a finger tapping task.

One potential concern with imaging a structure as small as the internal capsule is partial volume effects resulting from limitations in resolution. Although the current study used higher resolution than previous work (thinner slices), resolution remains a limitation

to be addressed in future research. To address concerns about partial voluming, we examined the individual level data for consistent localization to the PLIC using a double rater approach. Using this method, WM activation in the PLIC was present in 80% of participants (Figure 1). This proportion of subjects with WM activation is highly consistent with previous results (Gawryluk et al., 2009; Gawryluk et al., 2011a). This is likely due to the use of ASE spiral imaging in combination with high field MRI.

Interestingly, of participants with activation in the PLIC, 87.5% showed activation in the left hemisphere during right finger tapping and 100% showed activation in the right hemisphere during left finger tapping. Additionally, at the group level, PLIC activation was only observed during left finger tapping. Given that all participants were right handed, this difference may reflect task demand related to hand dominance.

At the individual level, activation in the PLIC showed some variability in location (Figure 1; Table 1). Logically, one might question why activation was not visible along the entire corticospinal tract. Presumably, activation in WM is detected near the vasculature supplying the region. Donzelli et al. (1998), examined the perforating branches of the middle cerebral artery in 21 human brains. They found that the supplied territory included the dorsal and ventrorostral regions of the PLIC and that there was variability between hemispheres/subjects (Donzelli et al., 1998). Consequently, based on neuroanatomical findings, activation in a WM tract may be expected in only some regions along a tract or section of a tract (based on blood supply), and these regions may vary. In the current study, we focused on the PLIC as an area of interest because it is "the location of the descending corticospinal tract fibers related to hand and arm function" (Maldjian et al., 1999).

67

Despite increasing evidence, the detection of fMRI in WM remains controversial. However, there is no direct evidence against WM fMRI (Tettamanti et al., 2002). In fact, fluorodeoxyglucose autoradiography in rats has been used to detect activity-dependent metabolic changes in WM (Weber et al., 2002). There is also evidence that in addition to local field potentials, spiking activity is correlated with fMRI activation (albeit to a lesser extent) (Iacoboni, 2006; Nir et al., 2008; Smith et al., 2002). One possible neurophysiologic source of fMRI signal changes in WM is increased activity of ATP-dependent Na+/K+ pumps, required to restore ionic gradients that are disrupted by axonal conduction (Kida and Hyder, 2005) (Waxman and Ritchie, 1993). Such energy-dependent events could cause changes in WM regional hemodynamics that could be detected with fMRI. Further investigation of the physiological basis and possible imaging mechanism underlying this phenomenon are ongoing.

4.6 CONCLUSIONS

Despite the fact that WM comprises half of the brain, few studies have attempted to measure fMRI activity in this tissue. Recently, we reported activation in the corpus callosum (Gawryluk et al., 2009; Gawryluk et al., 2011a; Mazerolle et al., 2010; Mazerolle et al., 2008). The current study provides evidence of WM fMRI activation in the internal capsule. These results represent an important avenue to advance in studies of functional connectivity as well as the clinical assessment of WM disease/disorder.

4.7 ACKNOWLEDGMENTS AND FUNDING

CHAPTER 5   FUNCTIONAL MRI SUPPORTS WHITE MATTER INVOLVEMENT IN THE SYMBOL DIGIT MODALITIES TEST

This chapter includes work submitted to **Gawryluk J.R**., Mazerolle E.L., Beyea, S.D., and D'Arcy, R.C. Functional MRI supports white matter involvement in the Symbol Digit Modalities Test. The Journal of Experimental and Clinical Neuropsychology.

Student contributions to the manuscript include: helping to design the experiment, recruit participants, collect data, analyze the data, intepret the results, and write the manuscript.

5.1   ABSTRACT

Advances in functional magnetic resonance imaging (fMRI) are providing new insight into the neuroanatomical basis of neuropsychological tests. Recent evidence shows that fMRI can detect activation in WM. An important next step is to examine whether WM activation can be linked to tests associated with WM function. We used an adapted Symbol Digit Modalities Test (SDMT) in a 4T fMRI study. Results from 17 healthy individuals revealed WM activation in the corpus callosum and internal capsule. The findings link advances in fMRI to an established clinical test of WM function.

5.2   INTRODUCTION

5.2.1   BACKGROUND

The ability to measure fMRI activation in WM has potential to advance the clinical investigation of WM disorders (e.g., MS, diffuse axonal injury resulting from

brain trauma). A key step in this respect is to examine whether neuropsychological tests that are sensitive to WM dysfunction can in fact elicit WM fMRI activation.

To date, imaging methods have documented structural changes in WM and have attempted to link such changes to behavior (Anzola et al., 1990; Charil et al., 2003; Ranjeva et al., 2006; Sperling et al., 2001). Yet, in many cases, structural measures of WM integrity do not correlate to functional deficits experienced by the patient (i.e., the clinico-radiological paradox; e.g., Pelletier et al., 2009). Functional MRI can provide a more direct assessment, however, the concept of WM activation is highly controversial (Logothetis and Wandell, 2004; Weis et al., 2011). The prevailing assumptions that go against WM fMRI activation relate to two main issues: 1) fMRI signal in WM is thought to be near or below detection thresholds because the cerebral blood flow/volume are lower in WM than GM (Helenius et al., 2003; Preibisch and Haase, 2001; Rostrup et al., 2000; van der Zande et al., 2005; Wise et al., 2004); and 2) fMRI signal is thought to arise primarily from post-synaptic potentials in GM (Logothetis et al., 2001). Importantly, increased magnetic field strength improves the detection of fMRI activation and WM tissue has metabolic demands that must be met (Tettamanti et al., 2002). Indeed, a rising number of studies from our group and others report WM activation (Baudewig et al., 2008; D'Arcy et al., 2006; Fabri et al., 2011; Gawryluk et al., 2009; Gawryluk et al., 2011a; Gawryluk et al., 2011b; Maldjian et al., 1999; Mazerolle et al., 2010; Mazerolle et al., 2008; Newman et al., 2010; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005; Weis et al., 2011; Yarkoni et al., 2009; Zeffiro et al., 2007).

Recently, we published a series of prospective WM fMRI studies at 4T using tasks designed to elicit interhemispheric transfer across the corpus callosum. Mazerolle et al. (2008) used a visual word/face task and detected activation in the isthmus of the corpus callosum. Subsequently, we used a simple visual/motor checkerboard task to confirm callosal activation. The results demonstrated that WM activation was detected in the anterior corpus callosum (Gawryluk et al., 2009).

Notably, the Mazerolle et al. (2008) and Gawryluk et al. (2009) detected activation in different regions of the corpus callosum, suggesting that task type may be useful for mapping functional differentiation in WM. To follow up, we confirmed that varying task type elicited activation differences in the anterior and posterior callosal regions, within the same subjects (Gawryluk et al., 2011a). Specifically, the word/face task showed activation in the posterior corpus callosum and the visual/motor checkerboard task showed activation near the genu. The results demonstrated that it is possible to dissociate different functional regions of the corpus callosum. Importantly, diffusion based tractography demonstrated that the WM activation clusters observed in each task were connected to corresponding areas of GM activation (Mazerolle et al., 2010).

Other groups have now reported similar findings. Fabri et al. (2011) recently confirmed the concept of functional mapping in the corpus callosum. Specifically, they used tactile, gustatory, visual, and motor stimulation to investigate the topography of the corpus callosum. The results showed anterior activation for taste, middle activation for motor, middle, and posterior activation for tactile stimuli and splenium activation for visual stimuli.

The above findings in the corpus callosum provide strong support for WM fMRI. However, it is important to verify WM activity in other structures as well. Yarkoni et al. (2009) used reaction time data to analyze a series of fMRI experiments and reported WM activation in the right lateral genu of the corpus callosum as well as in the posterior corona radiata (bilaterally). To extend the evidence of WM fMRI outside the corpus callosum, we investigated whether activation could be reliably detected in the internal capsule (Gawryluk et al., 2011b). A simple motor task elicited activation in the posterior limb of the internal capsule in 80% of participants. These results served to provide further support for WM fMRI.

5.2.2 *THE CLINICAL ASSESSMENT OF WHITE MATTER FUNCTION*

The ability to detect WM fMRI activation has clear implications for the evaluation of WM disease or damage. In order to prepare for clinical applications, research on WM fMRI must be linked to well known clinical tests. Neuropsychological testing has shown that patients with WM disease (e.g. MS) present with impairments on measures of attention, memory, and executive function (Chiaravalloti and DeLuca, 2008; Hoffmann et al., 2007; Rogers and Panegyres, 2007; Smith et al., 2011; Wishart et al., 2001). The most common and profound cognitive deficits associated with WM disorder are evident on measures of information processing speed (Chiaravalloti and DeLuca, 2008; Hoffmann et al., 2007; Rogers and Panegyres, 2007; Smith et al., 2011). Accordingly, one of the most common tests for assessing WM disorders is the SDMT (Hoffmann et al., 2007).

Briefly, the SDMT is a standardized clinical measure that is used to assess a wide range of neuropsychological disorders (including brain injury and MS). Indeed, the

SDMT is considered to be highly sensitive to WM dysfunction (Chiaravalloti and

DeLuca, 2008; Felmingham et al., 2004; Hoffmann et al., 2007; Rogers and Panegyres,

2007). It consists of a legend depicting nine symbols with the numbers 1-9 written

beneath. Below the legend there is a series of symbols paired with blank boxes. During

written administration, the patient is asked to use the legend to fill in as many missing

numbers as possible within 90 seconds (Smith, 1982).

5.2.3 *ADAPTATION OF A CLINICAL MEASURE FOR USE WITH FMRI*

Our group has adapted a wide range of neuropsychological tests for use in brain

imaging (Bolster et al., 2011; Connolly and D'Arcy, 2000; Connolly et al., 1999;

Connolly et al., 2006; D'Arcy et al., 2000; D'Arcy et al., 2003; Marchand et al., 2002).

Similarly, the SDMT has been modified for use with fMRI (e.g., Genova et al.,

2009). In addition to the GM activation, at least one study has published figures depicting

evidence of WM activation using the SDMT. While not reported in text, Genova et al.

(Genova et al., 2009) showed greater activation in the anterior corpus callosum and

internal capsule for healthy controls relative to MS patients (see Genova et al., 2009). In

fact, the corpus callosum and internal capsule are both regions that are functionally

consistent with the task demands. Although the SDMT is not an interhemispheric transfer

task per se, it is likely that information is transferred because both hemispheres are

involved in the task. Furthermore, previous DTI studies on MS patients have shown that

low fractional anisotropy values in the corpus callosum correlate with impaired

performance on the SDMT (Yu et al., 2012). Activation in the posterior limb of the

internal capsule is also likely to be task related given the involvement of the corticospinal

tract in hand movement and the required motor response. Even when present in the data,

WM activation is often not reported. Rather, the result is often either ignored or dismissed as an artifact.

5.2.4   THE CURRENT EXPERIMENT

The current study used a clinical measure of information processing to study WM fMRI activation in specific regions of healthy controls. We administered a modified version of the SDMT (Genova et al., 2009). We hypothesized that the SDMT would elicit activation in the corpus callosum and internal capsule at the individual level.

5.3   MATERIALS AND METHODS

5.3.1   PARTICIPANTS

Twenty healthy adults were enrolled in the study. Three participants were excluded for technical reasons (two for excessive movement and one for task non-compliance). The remaining 17 participants (9 F) had a mean age of 27.23 years (SD = 3.36). Fifteen participants were right-handed and two were left-handed. Local ethics boards approved the study. Individuals with contraindications for MRI were excluded, as were individuals on psychotropic medications or with neurological damage. We also set a priori exclusion criteria for individuals who demonstrated head motion that exceeded one voxel and for individuals who were unable to complete the task.

5.3.2   STIMULI AND PROCEDURE

The main objective in modifying standardized clinical tests for research purposes is to keep the adapted version as close to the clinical administration as possible (Connolly and D'Arcy, 2000). During the clinical written SDMT, the patient is asked to use a legend to fill in numbers that match with symbol/number pairs in a legend with a 90 second limit

(Smith, 1982). The SDMT had recently been adapted for use with fMRI (e.g., Genova et al., 2009; Kohl et al., 2009). As in previous studies, the modified SDMT presented a legend involving the same symbol/number combinations as used in the clinical version. During active blocks, participants were shown a symbol/number combination below the legend and asked to respond whether the stimulus was a "match" or "not a match" with the legend using a hand held response pad. During rest blocks, participants fixated on the centre of the screen.

The task and instructions were presented visually through back-projection to a screen mounted inside the bore (and viewed through a mirror mounted on the head coil) using E-Prime (Psychology Software Tools, Inc). The task consisted of five active blocks (36 s) and five rest blocks (18 s), yielding a time of approximately five minutes. All subjects performed the clinical paper-and-pencil SDMT and a short practice of the adapted task prior to imaging. The SDMT was administered 15-20 minutes into the imaging session and fatigue was not shown to be an issue on a self-report exit questionnaire administered immediately following the session.

5.3.3   DATA ACQUISITION

Data were acquired from a 4 T Varian INOVA whole body MRI system. Gradients were provided by a body coil (Tesla Engineering Ltd.) operating at a maximum of 35.5 mT/m at 120 T/m/s, and driven by 950 V amplifiers (PCI). The RF coil used was a TEM head coil (Bioengineering Inc.). All images were obtained within one 60-minute session.

Functional MRI was conducted using an asymmetric spin-echo (ASE) spiral sequence that collects three images per slice per volume (Brewer et al., 2009). The three ASE spiral images have equal T2* weighting, but increasing T2 weighting. Prior work has shown that increased T2 weighting improves sensitivity to WM fMRI activation (Gawryluk et al., 2009). Accordingly, the three ASE images were combined using an inverted signal weighted averaging algorithm (that lead the combined images to be weighted towards the third image). A total of 26 slices were acquired, which allowed for whole brain coverage with the following parameters: 5 mm axial slices, 0.5 mm gap, 64 x 64 matrix (220 x 220 mm), 1 shot, TR = 3 s, TI = 1400 ms, TE = 68 ms, and TE* = 28 ms (where TE is the spin echo center and TE* is the asymmetric echo time).

5.3.4   *DATA ANALYSES*

Motion correction was carried out using SPM software (Friston et al., 1995). Other pre-statistics processing steps were performed in FMRIB Software Library (FSL) using fMRI expert analysis tool (FEAT) version 5.3 (Smith et al., 2004; Woolrich et al., 2009). These steps included non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 6 mm, mean-based intensity normalisation of all volumes by the same factor, and highpass temporal filtering (100 s cutoff). Statistical analyses were performed using a model-based approach (General Linear Model). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Z statistic images were reported using a corrected threshold for clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley et al., 1992). Functional data was registered to the subject's anatomical (no search, DOF = 7; Jenkinson et al., 2002; Jenkinson and

Smith, 2001).

The local maxima of clusters in the corpus callosum and internal capsule were also determined to ensure that the cluster was centered in white matter. Subsequently, activation maps were displayed in FSLView (Z > 2.5). The analyses focused on individual level results in order to capture variability that is relevant to future patient studies/applications. To verify WM fMRI activation, individual data were examined against both the anatomic underlay and the raw functional images (task versus rest). Subsequently, masks of the corpus callosum and internal capsule (based off of the JHU WM labels atlas) were tailored to each individual and used to examine these regions of interest (ROIs).

5.4   RESULTS

5.4.1   FUNCTIONAL MRI RESULTS

WM activation was present in 88% of participants (15/17). The activation was in either the corpus callosum (anterior and/or posterior) or internal capsule (left and/or right). Fifteen participants showed activation in the corpus callosum (7 anterior, 5 posterior, 3 both anterior and posterior). Eight of these participants also showed activation in the internal capsule.

Figure 1 shows the results of the ROI analyses for a representative subject overlaid on the subject's anatomical as well as the raw fMRI data. Table 1 details the extent and maximum intensity of activation in the corpus callosum and internal capsule for each subject.
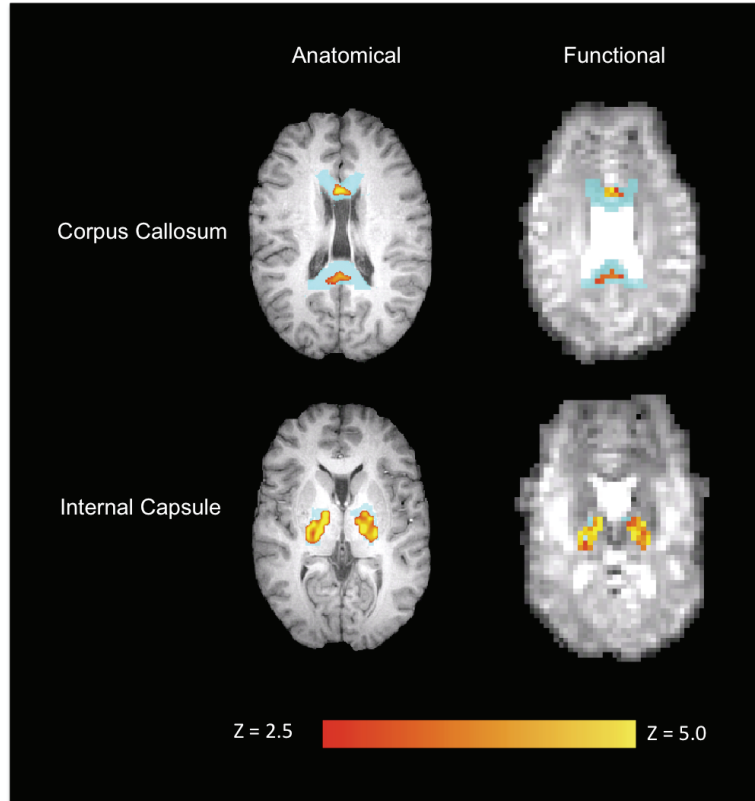
Figure 5.1 Corpus callosum (top) and internal capsule (bottom) ROI results overlaid on anatomical (left) and raw functional (right) data for a single subject (S5) during the SDMT. The ROI mask is shown in blue. Images are in radiological view. Activation related to the task is displayed in red-yellow with a Z threshold of 2.5.

Table 5.1 The extent and maximum intensity of activation in the corpus callosum (CC) and internal capsule (IC), behavioral scores and demographic data for each subject and averaged across individuals.

Subject	Number voxels CC	max z CC	Number voxels IC	max z IC	fMRI-SDMT ACC (%)	fMRI-SDMT RT (ms)	Written SDMT	Handedness	Age (years, months)	Sex
1	15	3.19	28	5.78	97	1635.30	83/83	Right	24y, 8m	M
2	55	5.87	29	4.13	93	1119.22	58/58	Right	27y 5m	M
3	14	4.60	21	3.06	97	1588.90	53/54	Right	29y,11m	F
4	21	4.26	18	4.75	93	1447.65	49/51	Right	26y, 9m	M
5	47	4.51	158	5.31	97	1172.05	74/75	Right	30y, 6m	M
6	31	6.99	17	5.00	97	1108.13	76/78	Right	31y, 1m	F
7	126	8.04	12	4.34	87	1618.68	62/63	Right	20y, 2m	F
8	30	3.86	12	3.61	97	1541.50	56/60	Left	27y, 9m	M
9	17	3.85	none	none	93	1351.02	61/63	Right	25y,10m	F
10	12	3.91	none	none	90	1365.45	72/72	Right	21y, 7m	F
11	29	4.52	none	none	77	1695.98	57/57	Right	32y, 1m	M
12	21	3.91	none	none	90	1321.63	91/93	Right	26y, 8m	M
13	7	3.74	none	none	93	1427.95	65/66	Right	31y, 5m	F
14	41	4.60	none	none	87	1502.47	59/59	Right	28y, 2m	M
15	50	5.78	none	none	83	1494.47	49/49	Right	25y,10m	F
GROUP	34.40	4.78	36.88	4.50	91.40	1426.03	64/65	14 R, 1 L	27y, 6m	7F, 8M
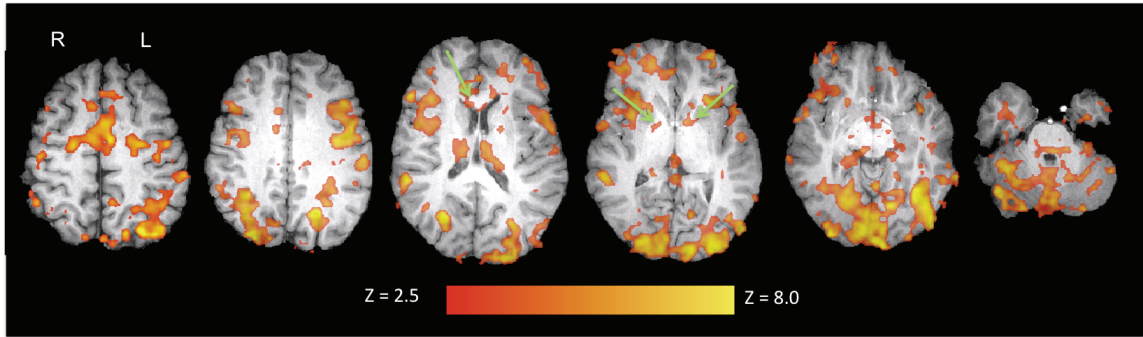
Figure 5.2 Activation in white and gray matter during the adapted SDMT overlaid on anatomical data for a representative individual (S3). Activation clusters in the corpus callosum and internal capsule are pointed out in green. Images are in radiological view. Activation related to the task is displayed in red-yellow with a Z threshold of 2.5.

Gray matter activation was observed at the individual level in occipital, parietal, temporal and frontal regions (including regions associated with motor activation), as well as in the cerebellum. Figure 2 shows whole brain activation results for a representative individual (overlaid on the subject's anatomical). Figures 3 and 4 show the results of the ROI analysis for each subject with significant callosal activation and internal capsule activation, respectively.
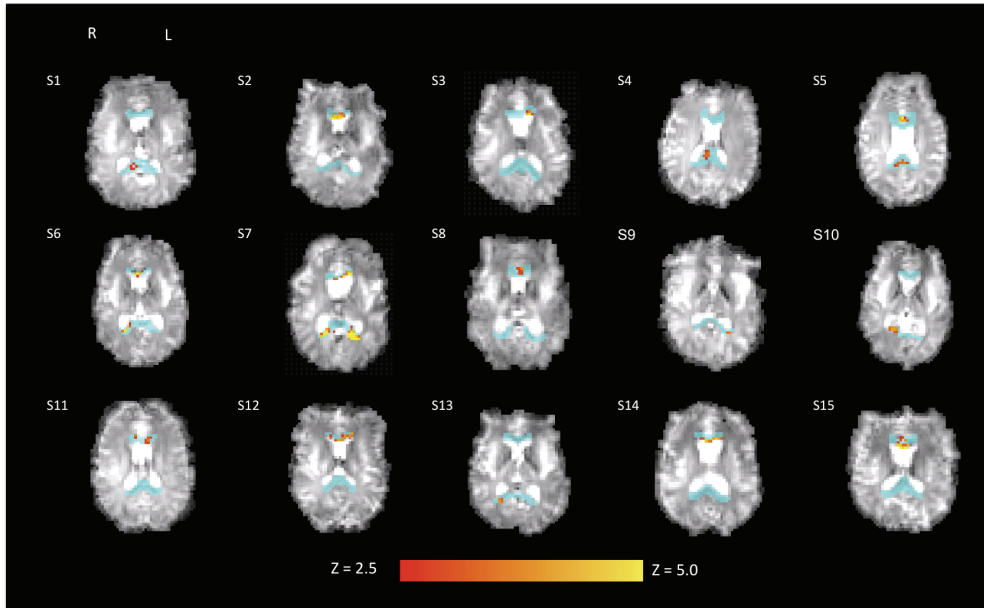
Figure 5.3 Corpus callosum ROI results overlaid on raw functional data for each individual during the adapted SDMT. Fifteen of 17 subjects showed activation in the corpus callosum. The ROI mask is shown in blue. Corpus callosum activation is displayed in red-yellow with a Z threshold of 2.5.
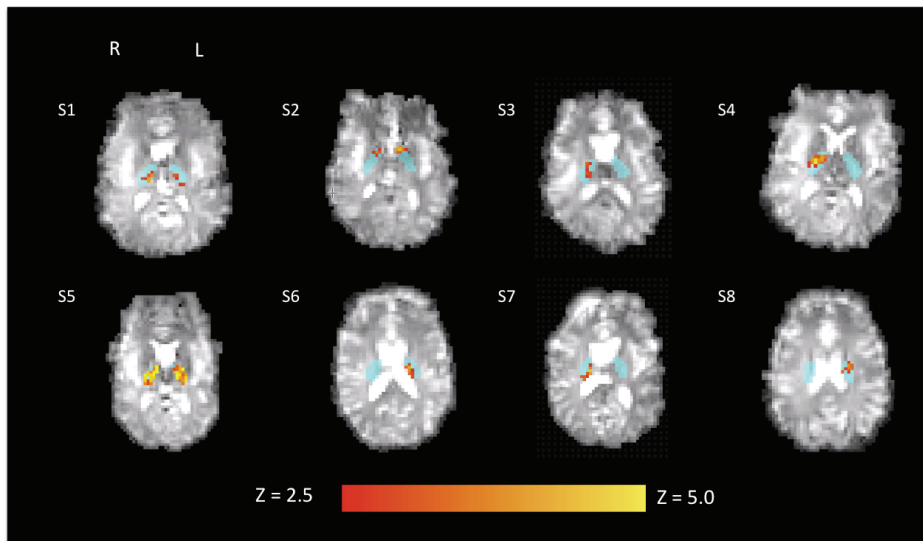
Figure 5.4 Internal capsule ROI results overlaid on raw functional data for each individual during the adapted SDMT. Eight of 17 subjects showed activation in the internal capsule. The ROI mask is shown in blue. Internal capsule activation is displayed in red-yellow with a Z threshold of 2.5.

5.4.2 BEHAVIORAL RESULTS

Analyses of behavioral data demonstrated that participants performed the fMRI adapted SDMT with a mean accuracy of 91.71% (SD = 5.59%). The mean reaction time was 1432.00 ms (SD = 175.55 ms). The clinical written SDMT revealed that all participants' scores were in the normal range (mean = 62.88, SD = 12.33).

5.5 DISCUSSION

The current study evaluated whether the adapted SDMT could elicit WM fMRI activation in healthy controls. As predicted, activation was observed in the corpus callosum or internal capsule, for 88% of individuals.

These findings are consistent with previous fMRI results for the SDMT that were shown but not reported. Importantly, the gray matter activation observed in the current study is also consistent with previous studies, which revealed activation in occipital, parietal, and frontal regions (including motor cortex), as well as the cerebellum (Forn et al., 2009; Genova et al., 2009). Genova et al. (2009) used the adapted SDMT to compare patients with MS to healthy controls. The results for a between-groups t-test indicated that the patients had significantly less activation in the anterior corpus callosum and internal capsule (Genova et al., 2009).

While the current results show individual variability in WM activation, the clusters were generally consistent with the SDMT task requirements. For instance, the anterior corpus callosum is known to connect to pre-frontal and motor cortical areas, which fit with both the decision making component and motor response required (Iacoboni and Zaidel, 2004; Meyer et al., 1995; Stančák Jr et al., 2000; Zarei et al., 2006).

The posterior corpus callosum is thought to link parietal areas involved in sensory integration related to the visual-perceptual task demands (Mazerolle et al., 2008; Zarei et al., 2006). Activation in the internal capsule, which contains corticospinal fibers and is thought to directly connect to the primary motor cortex (Nolte, 2002), is also consistent with the motor component of the task.

Although WM represents approximately 50% of the tissue in the brain (Black, 2007), fMRI has rarely been investigated in this tissue. As mentioned, the idea of WM fMRI activation is controversial and such results are often ignored (Logothetis and Wandell, 2004; Weis et al., 2011). While we have shown that WM fMRI activation can be detected using a neuropsychological test, the underlying basis of the phenomena remains to be determined. There are a number of possible factors that may contribute to the detection of fMRI signal in WM: 1) ion pumps (e.g., Na^+/K^+) in unmyelinated axons and at the nodes of Ranvier in myelinated axons have metabolic requirements; 2) astrocytes, which are known to exist in WM (Orthmann-Murphy et al., 2008; Sun et al., 2010), have been proposed to be functionally entrained to metabolic requirements related to neurotransmitter reuptake/recycling and regulating "cerebral blood delivery" (Figley and Stroman, 2011); and 3) tissue-specific hemodynamic differences can influence MR contrast mechanisms related to the relative contribution of conventional T2* versus T2/diffusion effects.

It remains possible that data acquisition methods can be optimized for detection of WM fMRI activation. For example, we employed the ASE spiral sequence (which can provide increased sensitivity to WM activation; Gawryluk et al., 2009) and used 4T MRI. However, there are other studies that have used standard imaging sequences and reported

white matter activation at 1.5T (e.g., Fabri et al., 2011). Part of the difficulty in interpreting how and when white matter activation is detected is that some groups report these findings and others do not (e.g., Genova et al., 2009). This variability makes it difficult to assess when and with what types of parameters investigators are detecting white matter activation.

One limitation of the current study relates to the investigation of the relationship between the clinical and adapted SDMT. There are differences that exist between the tasks (e.g., with the legend replaced on each trial, the working memory component has been removed from the adapted version). In addition, it remains difficult to compare the two versions of the task given that the scoring of the tasks is inherently different. The current study used an adapted version of the SDMT that has been used in the literature (to confirm an unreported finding). Given the potential for this task to be of clinical use, future efforts may focus on validation or standardization.

5.5.1 *IMPLICATIONS AND FUTURE DIRECTIONS*

The current study is the first to investigate WM fMRI activation using a clinical measure. The SDMT was implemented because it is commonly used in clinical settings to detect WM dysfunction (Hoffmann et al., 2007). Given that the fMRI adapted SDMT demonstrated WM activation in predicted regions, it shows potential as a clinical assessment tool. The individual variability that was observed might reflect true differences in the strategies that participants employ to perform the task. Alternatively, it is possible that the variability represents differences in underlying vasculature (Gawryluk et al., 2011). Variability in activation is not detected when testing is limited to traditional behaviorally-based measures and will be a key consideration in future patient

studies/applications. Given the individual variability noted in the current study, the SDMT fMRI task may be best suited to tracking progression/changes in WM function over the course of diseases (i.e., longitudinal evaluations of patients). This idea is supported by previous studies that have demonstrated that the SDMT can be used to predict "clinically meaningful cognitive decline" (Morrow et al., 2010) and that it is the "most sensitive" test to measure cognitive decline longitudinally in patients with MS (Amato et al., 2010). The next step in this line of research is to use the fMRI adapted SDMT to test patients with WM disorder to further explore the clinical value of this technique.

5.6 *ACKNOWLEDGMENTS*

CHAPTER 6 DISCUSSION

6.1   OVERVIEW

This section will begin with an overview of the manuscripts presented in this thesis,

followed by a discussion of the limitations of this work. Given the controversy

surrounding the detection of fMRI activation in WM, there are common questions and

concerns that arise in the investigation of this phenomenon; these will be presented in

question and answer format. Finally, future directions for basic and clinical research on

WM fMRI will be considered.

6.2   AN OVERVIEW OF THE CURRENT STUDIES

Each of the manuscripts included in this thesis investigate fMRI activation in

WM. As of 2009, when the first paper in this thesis was published, there was some

indication of (but limited evidence for), the ability to detect fMRI signal in WM tissue. A

small number of fMRI studies that mostly focused on GM activation had reported

activation in the anterior corpus callosum during interhemispheric transfer tasks. These

studies prompted the two initial studies by our group that lent support to the idea of WM

fMRI (D'Arcy et al., 2006; Mazerolle et al., 2008). Both of these studies used tasks that

exploited the lateralized nature of face processing (right hemisphere) and word

processing (left hemisphere) to elicit activation in the posterior corpus callosum.

Given these promising results, we developed two main objectives for the next

project (Gawryluk et al., 2009). The first aim was to use a Poffenberger inspired

checkerboard task that had previously been used in the literature (e.g, Tettamanti et al.,

2002) in order to investigate the possibility of detecting WM activation (in a greater

proportion of individuals and at the group level using a corrected threshold). The second aim was to determine whether certain imaging parameters are more sensitive to the detection of WM fMRI (given that commonly used fMRI parameters are optimized for detection of signal in GM). To investigate, we used an ASE spiral imaging sequence that collected three images per slice per volume with constant T2* weighting and increasing T2 weighting. Data were collected at 4 T to further improve sensitivity to the detection of WM fMRI. The results revealed activation in the anterior corpus callosum in 100% of subjects and at the group level (Z>2.5). We also found that increasing T2 contrast improved sensitivity as measured by percent signal change (the third ASE image was the most sensitive). The findings provided firm support for further investigation of WM fMRI and offered some guidance in moving forward with the ASE spiral sequence.

A key observation derived from Mazerolle et al. (2008) and Gawryluk et al. (2009) was that two differing interhemispheric transfer tasks elicited activation in two distinct regions of the corpus callosum. Consequently, we conducted a critical follow up study that investigated whether it was possible to elicit activation in the corpus callosum in different regions dependent on the task, within the same subjects.

In order to functionally map the corpus callosum within subjects, data were collected at 4 T using the ASE spiral method of acquisition (weighted towards the third image). The results showed corpus callosum activation for both tasks; activation varied according to task type such that the Sperry (face/word) task elicited greater posterior activation and the Poffenberger (checkerboard) task elicited greater anterior activation in the corpus callosum (Gawryluk et al., 2011a). This study lent further support to WM fMRI and indicated the possibility of mapping functional differentiation in WM tissue.

Given the accumulating evidence for the ability to detect fMRI activation in the corpus callosum, we thought it an important step (for the future development of clinical applications) to examine the possibility of detecting activation in other WM structures. The only evidence that previously existed for WM activation outside the corpus callosum came from an abstract presented by Maldjian et al. (1999) in which activation was reported in the internal capsule at 4 T.

To further explore WM activation outside of the corpus callosum, we optimized a motor task based on the results of Madjian et al. (1999) and examined activation in the posterior limb of the internal capsule at 4 T, again using ASE (weighted towards the third image). The results revealed activation in the posterior limb of the internal capsule in 80% of participants (Gawryluk et al., 2011b).

Taken together, our results provided the support necessary to move forward with a proof of concept study on the clinical potential of WM fMRI. In order to prepare WM fMRI for clinical use, we sought to link the advances we had made with a well known/commonly used clinical measure that is sensitive to WM dysfunction. The SDMT met these criteria and had previously elicited activation in the corpus callosum and internal capsule that went unreported (Genova et al., 2009). We administered a computerized version of the SDMT to healthy controls during 4 T fMRI. The results revealed WM activation in the corpus callosum and/or internal capsule in 88% of individuals. This study provided initial evidence that clinical methods can be combined with fMRI to assess WM function (Gawryluk et al., submitted).

6.3   *LIMITATIONS IN THE CURRENT WORK*

There are several limitations to the current work that should be addressed. One limitation is that two of the studies used a small sample size (e.g. N=10). Notably, these studies elicited WM activation in 80-100% of participants (Gawryluk et al., 2009; Gawryluk et al., 2011b). Additionally, the results of the optimization study using ASE have since been replicated using the data set that was collected for the functional mapping paper (N=17), which lends further credibility to the findings (McWhinney et al., provisionally accepted). It is also worth noting that the two studies with higher sample sizes (N=17) show a consistent proportion of subjects with WM activation (88-100%) (Gawryluk et al., 2011a; Gawryluk et al., submitted).

Another concern relates to partial volume effects. Partial voluming can occur when a voxel exists at the interface of WM and GM, which renders the source of the signal indistinguishable. This can be complicated by the use of low resolution (large) voxels (which offer benefits in SNR) as well as data pre-processing steps such as spatial smoothing. Although partial voluming is a valid concern, there are a few key pieces of evidence that the activation we view in WM is not a result of GM signal. First, as discussed in each manuscript, the areas in which we observe activation in WM are functionally consistent with the nature of the task. For example, activation in the posterior limb of the internal capsule was observed during a motor task, as would be expected (Gawryluk et al., 2011b). Second, in each case that a cluster was large enough to cover both WM and GM, we confirmed activation in WM by increasing the threshold to ensure that the centre of the cluster (i.e. local max) was on the WM structure of interest. Recent work by our group has provided further evidence that WM activation is

not a result of partial volume effects. We took an analysis approach that used very conservative masks of GM and WM (thereby reducing/eliminating partial voluming) on a data set that showed whole brain activation (from a breath hold task). It was determined that the activation seen in WM was independent of that in GM (Mazerolle et al., 2011). Therefore, although partial volume effects should always be considered, it is unlikely that the presented WM activation is a result of partial voluming.

In terms of translating WM fMRI research into clinical applications, there are two main limitations. The first limitation relates to test validation, and applies to all fMRI adaptations of clinical tests. Specifically, it is difficult to show that adapted tests are directly comparable to their clinical counterparts because the format and scoring of the tests often differ. A potential solution is to standardize the computer version of tasks on large samples of controls/patients.

The second limitation in preparing WM fMRI for clinical use relates to the ability to detect activation in WM diffusely. The set of tasks employed in the current series of studies focused on fMRI activation in specific WM regions. Our approach is representative in that no single neuropsychological task is able to independently assess cognitive function across brain regions. To optimize clinical relevance, a battery approach should be developed in which a series of short tasks are administered to examine activation in a variety of WM regions. Given that certain tasks (e.g., the SDMT) can be used to assess specific regions (e.g., the corpus callosum and internal capsule), such measures may be used to evaluate changes in activation over time. With further development and testing of these approaches, WM fMRI has the potential to enhance the current assessment of WM disorder.

6.4 COMMON QUESTIONS ABOUT WHITE MATTER FMRI

6.4.1 WHAT IS THE UNDERLYING PHYSIOLOGICAL MECHANISM(S) RESPONSIBLE FOR WHITE MATTER ACTIVATION?

Although more research on the physiological basis of fMRI in WM (as well as GM) is required, it may be reasonable to expect measurable task related activity in these regions. Logothetis et al. (2001) demonstrated that a BOLD response can be derived from post-synaptic potentials; however, this does not preclude the possibility that action potentials create a measureable hemodynamic response. Indeed, there are indications that local spiking activity is coupled to a local vascular response (Nir et al., 2008). There is also evidence that WM tissue has metabolic demands that must be met. For example, fluorodeoxyglucose autoradiography in rats has been used to detect activity-dependent metabolic changes in WM. Specifically, Weber et al. (2002) reported increased glucose uptake in the corpus callosum during electrical stimulation of a connected cortical region. Such metabolic changes could initiate a measurable hemodynamic response, although this has not been explicitly demonstrated. At the molecular level, fMRI signal changes in WM could result from increased blood-oxygen levels associated with the activity of ATP-dependent Na+/K+ pumps, required to restore ionic gradients (Kida and Hyder, 2005; Waxman and Ritchie, 1993). Another possibility is that astrocytes in WM demand oxygenated blood to meet metabolic requirements related to neurotransmitter reuptake/recycling (Figley and Stroman, 2011).

6.4.2 WHAT UNDERLYING MRI CHARACTERISTICS ARE RESPONSIBLE FOR WHITE MATTER ACTIVATION?

Conventionally, fMRI signal has only been considered to be detectable in GM. As a result, the imaging parameters employed in functional activation studies have largely been optimized for detection of fMRI signal in GM regions. Given that WM fMRI is a relatively new area of investigation, the MRI mechanisms responsible for this phenomenon are not well understood. Although further research on optimizing WM fMRI is needed, potential avenues for exploration include examining the role of 1) field strength and 2) T2 weighted imaging.

In terms of field strength, there is a large body of evidence demonstrating increased sensitivity to GM activation at higher field strengths (e.g., Duong et al., 2003). There is also recent evidence that sensitivity to WM activation increases with field strength (Mazerolle et al., in prep). Indeed, all four of the studies contained in this thesis detected WM activation, perhaps in part because they were performed on a 4T MRI system. The relationship between field strength and sensitivity to fMRI activation can be explained by the fact that sensitivity to magnetic susceptibility effects (including, but not limited to those created by the magnetic differences between oxy- and deoxy-hemoglobin) scale with magnetic field strength.

The use of T2 weighted fMRI imaging sequences may also increase sensitivity to WM activation. Specifically, the first study presented in this thesis demonstrated that increased T2 weighting (combined with T2* weighting) increased sensitivity to WM activation. We speculated that our finding might have resulted from the combination of high field imaging with a T2 weighted technique. The BOLD signal is known to reflect

both intra- and extra- vascular components from large and small vessels. Duong et al. (2003) demonstrated that "spin-echo acquisition suppresses extra vascular BOLD from large veins and reflects predominantly blood $T2$ changes and extra vascular BOLD signal from small blood vessels." It is possible that T2 weighted imaging may be particularly useful for studying WM, which is supported by small vessels (as opposed to large draining veins). We also posited that T2 weighting may increase sensitivity to activation across tissue types due to increased CNR. Further investigation into the relationship between T2 weighted imaging and WM fMRI activation is underway (McWhinney et al., provisionally accepted).

6.4.3   IS ASE SPIRAL MORE SENSITIVE TO WHITE MATTER ACTIVATION AND DO OTHER GROUPS FIND ACTIVATION WITHOUT IT?

ASE spiral collects three images per slice per volume with different contrast such that the T2* weighting is constant and T2 weighting increases with each image (Brewer et al., 2009). In the optimization study, we discovered that the third image, with the highest T2 weighting, was found to have significantly higher average percent signal change in the maximum z voxel than both the first image (which is comparable to a traditional spiral in acquisition) and second image. These findings suggest that ASE can offer increased sensitivity to WM activation because of the T2 weighting in the third image. However, it is still possible to detect WM activation with other sequences. Some studies that elicit activation in WM report these results (e.g., Tettamanti et al., 2002) while others do not (e.g, Genova et al., 2009) This variability makes it difficult to assess when and with what types of parameters investigators are detecting WM activation. To better characterize the effects of T2 weighted imaging and other parameters on sensitivity to WM activation, a study that compares a variety of imaging sequences is required.

6.4.4 WHY ISN'T ACTIVATION PRESENT ALONG THE ENTIRE TRACT?

As with GM, it is assumed that activation in WM is detected near the vasculature supplying the area. Therefore, it is possible that activation in a WM tract may only be expected in the regions along a tract or section of a tract that receive the greatest blood supply. Related to this, the vasculature in the brain can vary at the individual level (Donzelli et al., 1998), which might be responsible for some of the between subject differences we see at the individual level in activation in well-characterized tracts, such as the internal capsule.

6.4.5 COULD WHITE MATTER ACTIVATION BE DUE TO MOTION ARTIFACT?

We have routinely done the following to reduce the impact of motion:

1) Excluded participants with motion that exceeded one voxel

2) Included motion as a regressor in the analysis.

In fact, we have found that WM activation improved when motion was included as a regressor in the model (data not shown). This observation would not be expected if the activation resulted from motion artifact.

6.4.6 WHY IS ACTIVATION PRESENT IN BOTH 'CROSSED' AND 'UNCROSSED' CONDITIONS?

Our group has consistently detected activation in the corpus callosum with interhsmispheric transer tasks (i.e., the Poffenberger and Sperry tasks) in both crossed and uncrossed conditions (Gawryluk et al., 2009; Mazerolle et al., 2008). This has been a concern because it may take away from the claim that the WM activation we report is related to the experimental conditions. However, it is likely that interhemispheric transfer

takes place in both conditions but is greater in the crossed condition relative to the uncrossed condition. Notably, there were task related differences observed in the functional mapping experiment and lateralization differences observed in the internal capsule experiment that are highly supportive of task related WM activation (Gawryluk et al., 2011a; Gawryluk et al., 2011b).

6.4.7 WHAT KIND OF DIFFERENCES/CHANGES WOULD YOU EXPECT TO OBSERVE IN PATIENT GROUPS?

It is possible that injury or lesions associated with WM disorder could lead to decreased activation (i.e. less recruitment of oxygenated blood to injured regions) or increased activation (i.e. more recruitment of oxygenated blood to the injured area to compensate for the damage) at the lesion site or in alternate compensatory areas. To date, there are no published studies of WM activation in patient groups. However, the study by Genova et al. (2009) contrasted patients with MS and healthy controls on the SDMT and showed (but did not report) less activation in the corpus callosum and internal capsule in patients than controls. Based on these results, one might expect less WM activation in patients with WM lesions or damage.

6.5   DIRECTIONS FOR FUTURE RESEARCH ON WM FMRI

The avenues for future research on WM fMRI can be conceptualized as either basic or clinical in nature.

6.5.1   FUTURE DIRECTIONS FOR BASIC RESEARCH

Basic research is required to determine the physiological basis of WM fMRI signal and to further optimize the detection of this signal. One way to investigate the physiological underpinnings of fMRI signal in WM would involve the use of animal

models. Specifically, MRI compatible electrodes could be used to stimulate WM directly while measuring hemodynamic components (blood volume/flow) affecting fMRI activation. This technique could examine changes during WM activity and the relationship between rate of firing and the hemodynamic response (Mazerolle et al., unpublished).

Human studies could also provide information regarding the neurophysiology of WM in the regions that activation is observed. For example, fMRI activation in WM could be examined in relation to fractional anisotropy (FA) – a DTI derived measure that is thought to reflect the myelination of WM tissue (with higher FA values representing more myelinated tissue; Harsan et al., 2006). Perhaps there is a relationship between the areas along a tract that WM fMRI activation is observed and the myelination of the tissue (this could potentially help answer the question about why activation is not visualized along an entire tract). Interestingly, previous studies have found positive correlations between FA and behavioral measures such as the SDMT (Segura et al., 2010).

Basic research could also focus on analysis techniques to further optimize our sensitivity to the detection of WM fMRI activation. For example, it may be possible to increase sensitivity to WM activation by basing features of the analysis, such as the hemodynamic response function on the characteristics of WM. Although there is evidence that the hemodynamic response function in the corpus callosum resembles the canonical hemodynamic response function (Fraser et al., provisionally accepted), more work is needed to evaluate the hemodynamic response function in various WM regions. Additionally, various fMRI analysis software packages handle data differently (e.g., motion correction, thresholding options; Oakes et al., 2005). Future work could compare

different analysis options and determine the selections that are most sensitive to activation in WM.

Another way in which detection of WM activation could be optimized (or at least made more accessible) is through MRI sequence comparisons. The presented optimization study used ASE spiral and discovered that increased T2 weighting lead to enhanced detection of WM activation (Gawryluk et al., 2009). Future studies could compare a more commonly used fMRI sequence such as gradient echo EPI (that is mostly T2* weighted) to an EPI sequence with a spin echo (that is mostly T2 weighted) and the ASE spiral sequence. If all T2 weighted sequences are more sensitive to WM activation, the implication would be that enhanced detection of WM signal would be accessible across labs (as compared to the ASE spiral sequence developed by our group) and potentially lead to more visualization/reporting of WM results.

Once WM fMRI is better understood and accepted, it can potentially enhance our understanding of brain connectivity. Current efforts identify the structural connections between various GM regions (using diffusion based imaging) or use functional connectivity analyses. However, WM fMRI may allow for a more direct assessment of the role these connections play in a given task.

6.5.2   *FUTURE DIRECTIONS FOR CLINICAL RESEARCH*

In terms of preparing WM fMRI for clinical applications, the main challenge will be in developing a comprehensive approach. The tasks used in the presented set of manuscripts elicited activation in the corpus callosum and internal capsule. Although these structures are often involved in WM disorder, an ideal and thorough assessment of

WM function should be able to evaluate multiple regions. Such an evaluation would likely require a battery approach in which a variety of short tasks could be administered to study specified areas of interest. It is also possible to use different tasks to assess the same white matter structure. For example corpus callosum activation could be evaluated using either cognitive tasks (such as the Sperry task used in the functional mapping study) or simple sensory tasks (such as those used by Fabri et al., 2011) that elicit interhemispheric transfer. Tests developed for a battery should also be studied in a large group of individuals to document the variability associated with a given task. Future work on the tasks that have been developed thus far, could focus on within-subject reliability (i.e. does the same task activate the same WM region in an individual over multiple administrations?). This question becomes highly relevant when assessing patients with WM disorder over time (because of the need to detect real change versus variability).

WM fMRI can provide valuable insight into a number of disorders and conditions. It could potentially be used to measure differences/changes in patients with MS, track plasticity in WM following diffuse axonal injury, study degenerative disorders (e.g., amyotrophic lateral sclerosis, Alzheimer's disease), or investigate changes in WM function associated with epilepsy and neurosurgery. WM is involved in all brain activity and in many neurological disorders. Until recently, WM tissue had only been examined using structural measures that do not always correlate well with measures of function (Pelletier et al., 2009). The advances presented in this thesis provide evidence for a more direct method of studying and evaluating WM function with fMRI.

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REFERENCES

Anzola, G.P., Bevilacqua, L., Cappa, S.F., Capra, R., Faglia, L., Farina, E., Frisoni, G., Mariani, C., Pasolini, M.P., Vignolo, L.A., 1990. Neuropsychological assessment in patients with relapsing-remitting multiple sclerosis and mild functional impairment: correlation with magnetic resonance imaging. J Neurol Neurosurg Psychiatry 53, 142.

Baudewig, J., Bohm, J., Dechent, P., Rothenberger, A., Roessner, V., 2008. Interhemispheric transfer visualized by fMRI: Are there BOLD signal changes in white matter? , Proceedings of the 14th Annual Meeting of the Organization for Human Brain Mapping, Melbourne, Australia: #618.

Black, S.E., 2007. Imaging white matter and the burden of small vessel disease. Brain Cogn 63, 191 - 196.

Blume, W.T., 1984. Corpus callosum section for seizure control: rationale and review of experimental and clinical data. Cleve Clin Q 51, 319-332.

Bolster, R.B., D'Arcy, R.C.N., Song, X., Runke, D.S., Ryner, L., 2011. Detection versus location judgments in a hidden pattern task: Functional MRI and behavioral correlates. J Clin Exp Neuropsychol 33, 765-775.

Bonzano, L., Tacchino, A., Roccatagliata, L., Abbruzzese, G., Mancardi, G.L., Bove, M., 2008. Callosal contributions to simultaneous bimanual finger movements. J Neurosci 28, 3227-3233.

Boxerman, J.L., Hamberg, L.M., Rosen, B.R., Weisskoff, R.M., 1995. MR contrast due to intravascular magnetic susceptibility perturbations. Magn Reson Med 34, 555-566.

Brewer, K.D., Rioux, J.A., D'Arcy, R.C.N., Bowen, C.V., Beyea, S.D., 2009. Asymmetric spin-echo (ASE) spiral improves BOLD fMRI in inhomogeneous regions. NMR in Biomedicine 22, 654-662.

Brown, M.A., Semelka, R.C., 2010. MRI: basic principles and applications, 4 ed. Wiley-Blackwell, Hoboken.

Burde, R.M., Feldon, S.E., 1992. The extraocular muscles. In: Hart, W.M.J. (Ed.), Adler's Physiology of the Eye. CV Mosby, St. Louis.

Charil, A., Zijdenbos, A.P., Taylor, J., Boelman, C., Worsley, K.J., Evans, A.C., Dagher, A., 2003. Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. NeuroImage 19, 532-544.

Chiaravalloti, N.D., DeLuca, J., 2008. Cognitive impairment in multiple sclerosis. Lancet Neurol 7, 1139-1151.

Connolly, J.F., D'Arcy, R.C.N., 2000. Innovations in neuropsychological assessment using event-related brain potentials. Int J Psychophysiol 37, 31-47.

Connolly, J.F., Major, A., Allen, S., D'Arcy, R.C.N., 1999. Performance on WISC-III and WAIS-R NI vocabulary subtests assessed with event-related brain potentials: an innovative method of assessment. J Clin Exp Neuropsychol 21, 444-464.

Connolly, J.F., Marchand, Y., Major, A., D'Arcy, R.C.N., 2006. Event-related Brain Potentials as a Measure of Performance on WISC-III and WAIS-R NI Similarities Subtests. J Clin Exp Neuropsychol 28, 1327-1345.

D'Arcy, R.C.N., Connolly, J.F., Eskes, G.A., 2000. Evaluation of reading comprehension with neuropsychological and event-related brain potential (ERP) methods. J Int Neuropsychol Soc 6, 556-567.

D'Arcy, R.C.N., Hamilton, A., Jarmasz, M., Sullivan, S., Stroink, G., 2006. Exploratory data analysis reveals visuovisual interhemispheric transfer in functional magnetic resonance imaging. Magn Reson Med 55, 952-958.

D'Arcy, R.C.N., Marchand, Y., Eskes, G.A., Harrison, E.R., Phillips, S.J., Major, A., Connolly, J.F., 2003. Electrophysiological assessment of language function following stroke. Clin Neurophysiol 114, 662-672.

D'Arcy, R.C.N., Mazerolle, E.L., Pelot, N., 2008. Tracking inter-hemispheric transfer with high-density event-related brain potentials., Proceedings of the 14th Annual Meeting of the Organization for Human Brain Mapping, Melbourne, Australia.

Dolan, R.J., 2008. Neuroimaging of cognition: past, present, and future. Neuron 60, 496-502.

Donzelli, R., Marinkovic, S., Brigante, L., de Divitlis, O., Nikodijevic, I., Schonauer, C., Maiuri, F., 1998. Territories of the perforating (lenticulostriate) branches of the middle cerebral artery. Surg Radiol Anat 20, 393 - 398.

Duong, T.Q., Yacoub, E., Adriany, G., Hu, X., Uğurbil, K., Kim, S.G., 2003. Microvascular BOLD contribution at 4 and 7 T in the human brain: Gradient echo and spin echo fMRI with suppression of blood effects. Magn Reson Med 49, 1019-1027.

Fabri, M., Polonara, G., Mascioli, G., Salvolini, U., Manzoni, T., 2011. Topographical organization of human corpus callosum: An fMRI mapping study. Brain Res 1370, 99-111.

Felmingham, K.L., Baguley, I.J., Green, A.M., 2004. Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. Neuropsychology 18, 564-571.

Figley, C.R., Stroman, P.W., 2011. The role(s) of astrocytes and astrocyte activity in neurometabolism, neurovascular coupling, and the production of functional neuroimaging signals. Eur J Neurosci 33, 577-588.

Forn, C., Belloch, V., Bustamante, J.-C., Garbin, G., Parcet-Ibars, M.À., Sanjuan, A., Ventura, N., Ávila, C., 2009. A Symbol Digit Modalities Test version suitable for functional MRI studies. Neurosci Lett 456, 11-14.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., Frackowiak, R.S.J., 1995. Spatial registration and normalization of images. Hum Brain Mapp 3, 165-189.

Gawryluk, J.R., Brewer, K.D., Beyea, S.D., D'Arcy, R.C.N., 2009. Optimizing the detection of white matter fMRI using asymmetric spin echo spiral. NeuroImage 45, 83 - 88.

Gawryluk, J.R., D'Arcy, R.C.N., Mazerolle, E.L., Brewer, K.D., Beyea, S.D., 2011a. Functional mapping in the corpus callosum: A 4T fMRI study of white matter. NeuroImage 54, 10-15.

Gawryluk, J.R., Mazerolle, E.L., Brewer, K.D., Beyea, S.D., D'Arcy, R.C.N., 2011b. Investigation of fMRI activation in the internal capsule. BMC Neurosci 12, 56.

Gazzaniga, M.S., Bogen, J.E., Sperry, R.W., 1965. Observations on visual perception after disconnexion of the cerebral hemispheres in man. Brain 88, 221 - 236.

Gazzaniga, M.S., Smylie, C.S., 1983. Facial recognition and brain asymmetries: Clues to underlying mechanisms. Ann Neurol 13, 536-540.

Genova, H.M., Hillary, F.G., Wylie, G., Rypma, B., Deluca, J., 2009. Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. J Int Neuropsychol Soc 15, 383-393.

Glover, G.H., Law, C.S., 2001. Spiral in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. Magn Reson Med 46, 515-522.

Guye, M., Parker, G.J., Symms, M., Boulby, P., Wheeler-Kingshott, C.A., Salek-Haddadi, A., Barker, G.J., Duncan, J.S., 2003. Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo. NeuroImage 19, 1349 - 1360.

Haller, S., Bartsch, A.J., 2009. Pitfalls in fMRI. Eur Radiol 19, 2689-2706.

Hardyck, C., Dronkers, N., Chiarello, C., Simpson, G.V., 1985. The eyes have it: Exposure times and saccadic movements in visual half-field experiments. Brain Cogn 4, 430-438.

Harsan, L.A., Poulet, P., Guignard, B., Steibel, J., Parizel, N., Loureiro de Sousa, P., Boehm, N., Grucker, D., Ghandour, M.S., 2006. Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. J Neurosci Res 83, 392-402.

Helenius, J., Perkiö, J., Soinne, L., Østergaard, L., Carano, R.A.D., Salonen, O., Savolainen, S., Kaste, M., Aronen, H.J., Tatlisumak, T., 2003. Cerebral hemodynamics in a healthy population measured by dynamic susceptibility contrast MR imaging. Acta Radiol 44, 538-546.

Hoffmann, S., Tittgemeyer, M., Von Cramon, D.Y., 2007. Cognitive impairment in multiple sclerosis. Curr Opin Neurol 20, 275-280.

Iacoboni, M., 2006. Visuo-motor integration and control in the human posterior parietal cortex: evidence from TMS and fMRI. Neuropsychologia 44, 2691 - 2699.

Iacoboni, M., Zaidel, E., 2004. Interhemispheric visuo-motor integration in humans: the role of the superior parietal cortex. Neuropsychologia 42, 419-425.

Jang, S.H., 2009. A review of corticospinal tract location at corona radiata and posterior limb of the internal capsule in human brain. NeuroRehabilitation 24, 279-283.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825-841.

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med Image Anal 5, 143-156.

Jezzard, P., Clare, S., 2001. Principles of nuclear magnetic resonance and MRI. In: Jezzard, P., Matthews, P.M., Smith, S. (Eds.), Functional MRI: an introduction to methods. Oxford University Press, Oxford, pp. 67-92.

Kida, I., Hyder, F., 2005. Physiology of Functional Magnetic Resonance Imaging: Energetics and Function. In: Prasad, P. (Ed.), Magnetic Resonance Imaging: Methods and Biologic Applications. Humana Press, Totowa, pp. 175 - 195.

Kim, S.G., Uğurbil, K., 1997. Functional magnetic resonance imaging of the human brain. J Neurosci Methods 74, 229-243.

Kim, S.G., Uğurbil, K., 2003. High-resolution functional magnetic resonance imaging of the animal brain. Methods 30, 28-41.

Kim, Y.-H., Kim, D.-S., Hong, J.H., Park, C.H., Hua, N., Bickart, K.C., Byun, W.M., Jang, S.H., 2008. Corticospinal tract location in internal capsule of human brain: diffusion tensor tractography and functional MRI study. Neuroreport 19, 817-820.

Kohl, A.D., Wylie, G.R., Genova, H.M., Hillary, F.G., DeLuca, J., 2009. The neural correlates of cognitive fatigue in traumatic brain injury using functional MRI. Brain Inj 23, 420-432.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150-157.

Logothetis, N.K., Wandell, B.A., 2004. Interpreting the BOLD Signal. Annu Rev Physiol 66, 735-769.

Maldjian, J.A., Gottschalk, A., Detre, J.A., Alsop, D., 1999. Basal Ganglia and white matter activation using functional MRI at 4 Tesla. Proceedings of the 7th Annual Meeting of the International Society of Magnetic Resonance in Medicine, Philadelphia, USA.

Marchand, Y., D'Arcy, R.C.N., Connolly, J.F., 2002. Linking neurophysiological and neuropsychological measures for aphasia assessment. Clin Neurophysiol 113, 1715-1722.

Martuzzi, R., Murray, M.M., Maeder, P.P., Fornari, E., Thiran, J.P., Clarke, S., Michel, C.M., Meuli, R.A., 2006. Visuo-motor pathways in humans revealed by event-related fMRI. Exp Brain Res 170, 472-487.

Marzi, C.A., 1999. The Poffenberger paradigm: a first, simple, behavioural tool to study interhemispheric transmission in humans. Brain Res Bull 50, 421-422.

Marzi, C.A., Bisiacchi, P., Nicoletti, R., 1991. Is interhemispheric transfer of visuomotor information asymmetric? Evidence from a meta-analysis. Neuropsychologia 29, 1163-1177.

Matthews, P.M., 2001. An introduction to functional magnetic resonance imaging of the brain. In: Jezzard, P., Matthews, P.M., Smith, S.M. (Eds.), Functional MRI: an introduction to methods. Oxford University Press, Oxford, pp. 3-34.

Mazerolle, E.L., Beyea, S.D., Gawryluk, J.R., Brewer, K.D., Bowen, C.V., D'Arcy, R.C.N., 2010. Confirming white matter fMRI activation in the corpus callosum: Co-localization with DTI tractography. NeuroImage 50, 616-621.

Mazerolle, E.L., Brewer, K.D., Beyea, S.D., Gawryluk, J.R., Bowen, C.V., DeBay, D.R., Feindel, K., Rioux, J.A., Rasmusson, D.D., Semba, K., D'Arcy, R.C.N., 2011. Hemodynamic changes in white matter during a breath-hold task do not result from partial volume effects: Implications for white matter fMRI. Proceedings of the 17th Annual Meeting of the Organization for Human Brain Mapping, Quebec City, Canada.

Mazerolle, E.L., D'Arcy, R.C.N., Beyea, S.D., 2008. Detecting functional magnetic resonance imaging activation in white matter: Interhemispheric transfer across the corpus callosum. BMC Neurosci 9, 84.

Mazerolle, E.L., Gawryluk, J.R., Brewer, K.D., D'Arcy, R.C.N., Bowen, C.V., Beyea, S.D., 2009. Co-localization of white matter fMRI and tractography in the corpus callosum., Proceedings of the 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, USA.

Meyer, B.U., Röricht, S., von Einsiedel, H.G., Kruggel, F., Weindl, A., 1995. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118, 429-440.

Morrow, S.A., Drake, A., Zivadinov, R., Munschauer, F., Weinstock-Guttman, B., Benedict, R.H.B., 2010. Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline. Clin Neuropsychol 24, 1131-1145.

Mosier, K., Bereznaya, I., 2001. Parallel cortical networks for volitional control of swallowing in humans. Exp Brain Res 140, 280-289.

Newman, A.J., Supalla, T., Hauser, P., Newport, E.L., Bavelier, D., 2010. Dissociating neural subsystems for grammar by contrasting word order and inflection. Proc Natl Acad Sci USA 107, 7539-7544.

Nir, Y., Dinstein, I., Malach, R., Heeger, D.J., 2008. BOLD and spiking activity. Nat Neurosci 11, 523 - 524.

Nolte, J., 2002. The Human Brain: An Introduction to Its Functional Anatomy. Mosby Year Book Inc., Missouri.

Oakes, T.R., Johnstone, T., Ores Walsh, K.S., Greischar, L.L., Alexander, A.L., Fox, A.S., Davidson, R.J., 2005. Comparison of fMRI motion correction software tools. NeuroImage 28, 529-543.

Ogawa, S., Tank, D.W., Menon, R., Ellermann, J.M., Kim, S.G., Merkle, H., Ugurbil, K., 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 89, 5951-5955.

Omura, K., Tsukamoto, T., Kotani, Y., Ohgami, Y., Minami, M., Inoue, Y., 2004. Different mechanisms involved in interhemispheric transfer of visuomotor information. Neuroreport 15, 2707-2711.

Orthmann-Murphy, J.L., Abrams, C.K., Scherer, S.S., 2008. Gap Junctions Couple Astrocytes and Oligodendrocytes. J Mol Neurosci 35, 101-116.

Pelletier, J., Audoin, B., Reuter, F., Ranjeva, J., 2009. Plasticity in MS: from Functional Imaging to Rehabilitation. Int MS J 16, 26-31.

Poffenberger, A.T., 1912. Reaction time to retinal stimulation with special reference to the time lost in conduction through nervous centers. Arch Psychol 23, 1-73.

Preibisch, C., Haase, A., 2001. Perfusion imaging using spin labeling methods: contrast-to-noise comparison in functional MRI applications. Magn Res Med 46, 172-182.

Ranjeva, J.P., Audoin, B., Au Duong, M.V., Confort-Gouny, S., Malikova, I., Viout, P., Soulier, E., Pelletier, J., Cozzone, P.J., 2006. Structural and functional surrogates of cognitive impairment at the very early stage of multiple sclerosis. J Neurol Sci 245, 161-167.

Rayner, K., 1998. Eye movements in reading and information processing: 20 years of research. Psychol Bull 124, 372-422.

Rogers, J.M., Panegyres, P.K., 2007. Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. J Clin Neurosci 14, 919-927.

Rosen, B.R., Buckner, R.L., Dale, A.M., 1998. Event-related functional MRI: past, present, and future. Proc Natl Acad Sci USA 95, 773-780.

Rostrup, E., Law, I., Blinkenberg, M., Larsson, H.B.W., Born, A.P., Holm, S., Paulson, O., 2000. Regional differences in the CBF and BOLD responses to hypercapnia: a combined PET and fMRI study. NeuroImage 11, 87-97.

Saron, C.D., Foxe, J.J., Schroeder, C.E., Vaughan Jr., H.G., 2003. Complexities of interhemispheric communication in sensorimotor tasks revealed by highdensity event-related potential mapping. MIT Press, Cambridge.

Segura, B., Jurado, M., Freixenet, N., Bargalló, N., Junqué, C., Arboix, A., 2010. White matter fractional anisotropy is related to processing speed in metabolic syndrome patients: a case-control study. BMC Neurol 10, 64.

Smith, A., 1982. Symbol Digit Modalities Test. Western Psychological Services, Los Angeles.

Smith, A.J., Blumenfeld, H., Behar, K.L., Rothman, D.L., Shulman, R.G., Hyder, F., 2002. Cerebral energetics and spiking frequency: the neurophysiological basis of fMRI. Proc Natl Acad Sci USA 99, 10765 - 10770.

Smith, A.M., Walker, L.A.S., Freedman, M.S., Berrigan, L.I., St. Pierre, J., Hogan, M.J., Cameron, I., 2011. Activation patterns in multiple sclerosis on the Computerized Tests of Information Processing. J Neurol Sci 312, 131-137.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp 17, 143-155.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23, S208-S219.

Sperling, R.A., Guttmann, C.R.G., Hohol, M.J., Warfield, S.K., Jakab, M., Parente, M., Diamond, E.L., Daffner, K.R., Olek, M.J., Orav, E.J., 2001. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. Arch Neurol 58, 115.

Stančák Jr, A., Lücking, C.H., Kristeva-Feige, R., 2000. Lateralization of movement-related potentials and the size of corpus callosum. Neuroreport 11, 329-332.

Sun, D., Lye-Barthel, M., Masland, R.H., Jakobs, T.C., 2010. Structural Remodeling of Fibrous Astrocytes after Axonal Injury. J Neurosci 30, 14008-14019.

Tettamanti, M., Paulesu, E., Scifo, P., Maravita, A., Fazio, F., Perani, D., Marzi, C., 2002. Interhemispheric transmission of visuomotor information in humans: fMRI evidence. J Neurophysiol 88, 1051-1058.

van der Zande, F.H.R., Hofman, P.A.M., Backes, W.H., 2005. Mapping hypercapnia-induced cerebrovascular reactivity using BOLD fMRI. Neuroradiology 47, 114 - 120.

Waxman, S.G., Ritchie, J.M., 1993. Molecular dissection of the myelinated axon. Ann Neurol 33, 121 - 136.

Weber, B., Fouad, K., Burger, C., Buck, A., 2002. White matter glucose metabolism during intracortical electrostimulation: a quantitative [^{18}F]Fluorodeoxyglucose autoradiography study in the rat. NeuroImage 16, 993 - 998.

Weber, B., Treyer, V., Oberholzer, N., Jaermann, T., Boesiger, P., Brugger, P., Regard, M., Buck, A., Savazzi, S., Marzi, C.A., 2005. Attention and interhemispheric transfer: a behavioral and fMRI study. J Cogn Neurosci 17, 113-123.

Weis, S., Leube, D., Erb, M., Heun, R., Grodd, W., Kircher, T., 2011. Functional Neuroanatomy of Sustained Memory Encoding Performance in Healthy Aging and in Alzheimer's Disease. Int J Neurosci 121, 384-392.

Wise, R.G., Ide, K., Poulin, M.J., Tracey, I., 2004. Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. NeuroImage 21, 1652-1664.

Wishart, H.A., Flashman, L., Saykin, A.J., 2001. The neuropsychology of multiple sclerosis: contributions of neuroimaging research. Curr Psychiatry Rep 3, 373-378.

Witelson, S.F., 1989. Hand and sex differences in the isthmus and genu of the human corpus callosum. Brain 112, 799.

Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. NeuroImage 45, S173-S186.

Woolrich, M.W., Ripley, B.D., Brady, J.M., Smith, S.M., 2001. Temporal Autocorrelation in Univariate Linear Modelling of FMRI Data. NeuroImage 14, 1370 - 1386.

Worsley, K.J., Evans, A.C., Marrett, S., Neelin, P., 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 12, 900 - 918.

Yacoub, E., Duong, T.Q., Van De Moortele, P.F., Lindquist, M., Adriany, G., Kim, S.G., Uğurbil, K., Hu, X., 2003. Spin-echo fMRI in humans using high spatial resolutions and high magnetic fields. Magn Reson Imaging 49, 655-664.

Yarkoni, T., Barch, D.M., Gray, J.R., Conturo, T.E., Braver, T.S., 2009. BOLD correlates of trial-by-trial reaction time variability in gray and white matter a multi-study fMRI analysis. PLoS One 4, e4257.

Zarei, M., Johansen-Berg, H., Smith, S., Ciccarelli, O., Thompson, A.J., Matthews, P.M., 2006. Functional anatomy of interhemispheric cortical connections in the human brain. J Anat 209, 311-320.

Zeffiro, T., Vasios, C., Belliveau, J., 2007. Neural mechanisms of visuomotor interhemispheric transfer: the Poffenberger paradigm., Proceedings of the 13th Annual Meeting of the Organization for Human Brain Mapping, Chicago, USA.