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Investigating Reading Processes Using Diffusion Tensor Imaging

by

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Abstract

Recent evidence from diffusion tensor imaging (DTI) studies reported that the structural integrity [fractional anisotropy (FA)] of white matter (WM) tracts in the ventral and dorsal regions of the brain is correlated with reading ability. It has thus been hypothesized that WM pathways in these regions may support reading tasks that rely on corresponding cortical regions. This project investigated the relationship between behavioural measurements of reading and FA of WM tracts obtained using tractography, region of interest (ROI) analysis, and a hybrid tract-based spatial statistics (TBSS) – voxelwise approach. Reaction times (RTs) for overt reading of exception words (ventral), regular words (ventral and dorsal), pseudohomophones (dorsal), and non-words (dorsal) by healthy participants were correlated with the FA of WM tracts thought to underlie the dorsal and ventral processing streams. This study found mixed support for the hypothesis of a relationship between dorsal and ventral processing streams and the underlying WM tracts.

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List of Abbreviations

ACR: Anterior corona radiata

AF: Arcuate fasciculus

CBT: Corticobulbar tract

CR: Corona radiata

CS: Centrum semiovale

CST: Corticospinal tract

DTI: Diffusion Tensor Imaging

ESL: English as a second language

EXC: Exception word

FA: Fractional anisotropy

fMRI: Functional magnetic resonance imaging

ILF: Inferior longitudinal fasciculus

IFOF: Inferior fronto-occipital fasciculus

MRI: Magnetic resonance imaging

ms: millisecond

NW: Non-word

PH: Pseudohomophone

PLIC: Posterior limb of the internal capsule

REG: Regular word

ROI: Region of Interest

RT: Reaction time

SCR: Superior corona radiata

SLF: Superior longitudinal fasciculus

SS: Sagittal stratum

TBSS: Tract-based spatial statistics

T_E: Echo time

T_R: Repetition time

UF: Uncinate fasciculus

VBA: Voxel based analysis

VOI: Volume of interest

VWFA: Visual word form area

WM: White matter

1. Introduction

Today's society is highly dependent on written communication. As such, impairments in reading could have a major impact on daily interactions and the quality of life. Well-developed models of reading are important for furthering our understanding of reading processes. While there has been a lot of research investigating the functional framework of basic reading, there have been relatively few studies exploring the structural framework. Understanding the relationships between structural measurements of the brain and reading processes will aid in the development of more comprehensive models of reading and reading impairment.

1.1 The Dual Route Model of Reading

Current models of the neurophysiology of basic reading processes derived from functional magnetic resonance imaging (fMRI) studies suggest that reading involves two cortical streams, dorsal (occipital-parietal-frontal) and ventral (occipital-temporal-frontal) processing streams (Pugh et al., 2000; Borowsky et al., 2006; Steinbrink et al., 2008). The dorsal stream projects dorso-posteriorly (Hickok & Poeppel, 2004), and includes the posterior portions of the superior temporal, supermarginal and angular gyri of the temporal-parietal region (Borowsky et al., 2006). The dorsal stream is thought to support rule-based (sublexical) analyses of words, which are necessary for integrating orthographic features of printed words with their phonological, morphological, and lexical-semantic information (Pugh et al., 2000; Borowsky et al., 2006; Steinbrink et al., 2008). The dorsal stream is thought to be the dominate stream during reading development (Steinbrink et al., 2008). Increased activation of the dorsal stream has been found during phonological and semantic analyses, which are both relevant to learning (Pugh et al., 2000). It is thought that the dorsal processing stream aids beginning readers via sublexical mapping of letter to sound correspondences, thus allowing words to be decoded phonetically (Borowsky et al., 2006).

The ventral stream projects ventro-laterally (Hickok & Poeppel, 2004), and includes the medial extrastriate, left inferior occipito-temporal regions, and fusiform gyrus in the occipital lobe and the inferior and medial temporal gyri in the temporal lobe (Borowsky et al., 2006). The ventral stream is hypothesized to be a memory-based word identification system (Steinbrink et al., 2008, Pugh et al., 2000), which supports lexically based (whole word) reading, such as when accessing familiar words that are encoded in lexical memory (Borowsky et al., 2006). It is thought to be a fast, but late developing word-form system that underlies fluency in word recognition (Steinbrink et al., 2008, Pugh et al., 2000). Increased activation of the ventral stream has been shown to predict reading skill (Pugh et al., 2000). It is thought that skilled readers tend to rely on this stream after words have been established in long-term memory (Pugh et al., 2000). Pugh et al. (2000) proposed that the development of this lexically based system is dependant upon the analytical processing of words in the dorsal stream.

Reading of different word types is thought to rely on different processing streams. For example, non-words (e.g., boak) have familiar phonological representations while lacking whole word representation and should require the sublexical analysis performed by the dorsal processing stream, as they are unfamiliar letter strings that need to be sounded out. Like non-words, pseudohomophones (e.g., beek) have the familiar phonological- representations but also sound like real words. However, pseudohomophones lack the whole word orthographic- representation (Borowsky et al., 2006). As such, reading of pseudohomophones should require the sublexical analysis performed by the dorsal processing stream because they need to be sounded out and additionally, would activate lexical representations as their phonology is familiar (Borowsky et al., 2006). On the other hand, exception words (e.g., yacht) could not be pronounced using sublexical analysis because the pronunciations of these words do not follow the regular letter-to-sound correspondence found in English (Borowsky et al., 2006). Thus, reading of exception words necessitates lexically based reading using the ventral processing stream, where the phonological representation of a word is retrieved from memory using the orthographic representation of the whole word (Borowsky et al., 2006). Reading of regular words, which possess the typical correspondence between orthographic and phonological representation, likely involves the activation of both processing streams depending on the frequency of their occurrence. More frequently occurring regular words (e.g., cat) would likely be stored in memory due to their high frequency of occurrence and accessed through the ventral stream. Conversely, regular words that occur infrequently (e.g., munch) or are new to the reader would likely be analysed sublexically by the dorsal stream because they are unlikely to be stored in the memory-based ventral processing stream.

1.2 White Matter Pathways and Reading Processes

Recent fMRI studies have defined the brain regions that are associated with the dorsal and ventral processing streams. However, these studies could not provide any information on the underlying connectivity of these regions. As Turken and Dronkers (2011) noted, what determines the contribution of each brain region in a functional network is the pattern of their connectivity and the interactions between different regions within that network (Mesulam, 1990, 1998, 2005; Schmahmann & Pandya, 2008). As such, it is necessary to be able to delineate the white matter pathways, which connect the brain regions that compose the language network in order to elucidate how each region is integrated into the overall network and language processing (Turken & Dronkers, 2011). In addition, better knowledge of the white matter pathways underlying language processing will lead to improved understanding of the consequences of brain injury that cause disruption to the white matter pathways (Turken & Dronkers, 2011).

Numerous studies have been conducted for the purpose of obtaining a better understanding of the white matter pathways underlying language processing. Those studies have employed a variety of different methods, such as surgical resection (Epelbaum et al., 2008; Papagno et al., 2011), subcortical stimulation (Mandonnet et al., 2007; Duffau et al., 2009), and diffusion tensor imaging (DTI) (Klingberg et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005; Niogi & McCandliss, 2006; Gold et al., 2007; Qiu et al., 2008; Steinbrink et al., 2008; Odegard et al., 2009; Rollins et al., 2009; Carter et al., 2009; Palmer et al., 2010; Rimrodt et al., 2010; Yeatman et al., 2011; Vandermosten et al., 2012). A summary of the previous work will be described in the next section.

1.3 Surgical Resection Studies

Surgical resection studies, which involve studying patients subsequent to the removal of a portion of their brain, has provided some valuable insights to the white matter tracts underlying language processes. For example, Epelbaum and colleagues (2008) observed the progressive and selective degeneration of the left inferior longitudinal fasciculus (ILF) through analysis of diffusion images in a case study of a patient who developed pure alexia (i.e., able to perform letter-by-letter reading, but not whole word reading) following a small surgical lesion that damaged the left ILF just behind the visual word form area (VWFA). The VWFA, located in the left occipito-temporal region, is a part of the left ventral visual stream involved in whole-word identification (Szwed et al., 2011; Epelbaum et al., 2008). Even though the VWFA remained anatomically intact, it was no longer activated during fast word presentation following the surgery (Epelbaum et al., 2008). Epelbaum et al. (2008) speculated that the lesion to ILF resulted in the disconnection of the VWFA from visual input, leading to alexia. The results of this case study suggested that the left ILF plays a critical role in normal reading, and that the disruption of this tract is one of the causes of pure alexia (Epelbaum et al., 2008).

Another study by Papagno et al. (2011) examined patients following the removal of a left frontal or temporal glioma. Some of the patients had portions of their UF removed while others did not. Three months after surgery, Papagno et al. (2011) found that patients who had undergone resection of portions of their UF performed significantly worse than patients with intact UF at naming of objects and famous faces. Identification of objects and words recruits similar ventral stream networks since they both involve retrieval from memory. Although these investigators may not have tested word recognition explicitly; it could be assumed that removal of UF would also impair word naming. The results of this study suggest that the left UF may play an important role in the retrieval of word forms during naming (Papagno et al., 2011).

1.4 Subcortical Stimulation Studies

Subcortical stimulation involves the use of direct electrical stimulation on the subcortical regions of individuals undergoing neurosurgery in order to induce a temporary inhibition of the stimulated white matter region. This procedure allows for correlations between neuroanatomy and function to be performed (Mandonnet et al., 2007; Duffau et al., 2009). In a study involving patients undergoing surgery for left temporal lobe glioma, Mandonnet et al. (2007) found that subcortical stimulation of the left arcuate fasciculus (AF) during a picture-naming task generated phonological paraphasia, whereby a word (e.g., apple) is substituted by a non-word with phonological similarities (e.g., ipple). In contrast, stimulation of the left inferior fronto-occipital fasciculus (IFOF) elicited semantic paraphasia, whereby a word (e.g., chair) is substituted by that of another word that is related in meaning (e.g., table). However, stimulation of the left ILF during the naming task did not elicit any language disturbances (Mandonnet et al., 2007). Mandonnet et al. (2007) suggested that the results of the study did not mean that the ILF is not part of the language networks in healthy individuals, but rather that the growing glioma in the patients may have lead to the redistribution of the language function of the ILF. A subsequent study by Duffau et al. (2009) replicated the results of the study by Mandonnet at al. (2007) and found that subcortical stimulation of the left uncinate fasciculus (UF) during a naming task did not elicit any language disturbances. Mandonnet et al. (2007) and Duffau et al. (2009) hypothesized that the ventral processing stream may consist of two parallel pathways: a direct pathway composed of the IFOF, which links the posterior temporal regions and orbitofrontal region, as well as an indirect pathway composed of the ILF, which connects the posterior occipito-temporal areas and the anterior temporal pole, and the UF, which connects the anterior temporal lobe to the orbitofrontal area.

1.5 Diffusion Tensor Imaging Studies

Diffusion Tensor Imaging (DTI) is a Magnetic Resonance Imaging (MRI) technique used to measure the diffusion of water molecules in brain tissue, as well as the magnitude and direction of diffusion in three dimensions (Basser et al., 1994; Le Bihan et al., 2001; Hunsche et al., 2001; Bammer et al., 2002; Beaulieu, 2002). In white matter, water diffuses more readily along the orientation of axonal fibres than in other directions due to restriction from structural components of the fibres such as the myelin sheath and the axonal membrane (Moseley et al., 1990; Beaulieu, 2002; Niogi & McCandliss, 2006). Diffusion anisotropy is a measure that quantifies the degree of directionality of diffusion in the three dimensions (van Gelderen et al., 1994; Basser, 1995; Basser & Pierpaoli, 1996; Conturo et al., 1996). Fractional anisotropy (FA) is a normalized measure of diffusion anisotropy. It is the standard deviation of the three eigenvalues (λ_1, λ_2, λ_3) normalized to the magnitude of the diffusion tensor (Klingberg et al., 2000).

$$\mathrm{FA} = \sqrt{\frac{3}{2}}\frac{\sqrt{(\lambda_1-\hat{\lambda})^2+(\lambda_2-\hat{\lambda})^2+(\lambda_3-\hat{\lambda})^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$$

Where $\hat{\lambda} = (\lambda_1+\lambda_2+\lambda_3)/3$

Values of FA can range between zero and one; high values of FA suggest the presence of highly directional diffusion (Deutsch et al., 2005; Niogi & McCandliss, 2006; Odegard et al., 2009). This information can be used to infer the integrity and microstructure of white matter in vivo, with higher values of FA indicating better structural integrity (Klingberg et al., 2000; Deutsch et al., 2005; Niogi & McCandliss, 2006).

Diffusion-tensor data can be analyzed using a variety of different methods. These methods include voxel based analysis (VBA), tract-based spatial statistics (TBSS), region of interest (ROI) analysis, and three-dimensional tract reconstruction (tractography) (Basser & Pierpaoli, 1996; Richards et al., 2008; Qiu et al., 2008; Snook et al., 2007; Mukherjee et al., 2008). The aforementioned means of investigating diffusion-tensor data all possess their strengths and weaknesses, making the most accurate and precise method of investigating diffusion-tensor data a controversial issue.

Voxel based correlational analysis has been one of the more popular methods of analyzing diffusion-tensor data. This analysis looks for voxels in the brain that demonstrates a correlation between FA and other variables of interest. Depending on the study, the researchers may look for correlation with voxels anywhere in the brain or voxels within a predefined volume of interest (VOI) based on the results of previous studies (Klingberg et al., 2000; Deutsch et al., 2005). This method has provided some compelling evidence linking the structural integrity of white matter with functional performance. A landmark study by Klingberg et al. (2000) using VBA found that white matter FA in the left hemisphere temporo-parietal region was significantly correlated with reading scores of reading impaired adults and the control group. More specifically, adults with dyslexia demonstrated decreased FA in the left hemisphere temporo-parietal region when compared to the adults in the control group (Klingberg et al., 2000). DTI analysis showed that axons in the temporo-parietal region were predominately anterior-posterior in direction; the location and the orientation of the fibres suggest that the white matter is composed of the left superior longitudinal fasciculus (SLF) (Klingberg et al., 2000). In another study with adult participants, Steinbrink et al. (2008) found a correlation between reading ability and FA of the temporo-parietal white matter regions associated with the left SLF, as well as fronto-temporal regions associated with the left ILF and the IFOF. Adults with dyslexia were found to have decreased FA in regions associated with the left SLF, ILF and IFOF compared to adults in the control group (Steinbrink et al., 2008). Like the results of the study by Klingberg et al. (2000), the principal diffusion was in an anterior-posterior direction (Steinbrink et al., 2008). Steinbrink et al., (2008) also found that higher anisotropy values in the fronto-temporal part of the SLF of the left hemisphere were associated with faster pseudoword reading.

While it is tempting to assume that the white matter differences found between adults with and without dyslexia is the cause of poorer reading performance in adults with dyslexia, it is also conceivable that the differences were the result of differences in the development of white matter due to the use of compensatory reading strategies by dyslexic adults (Beaulieu et al., 2005; Ben-Shachar et al., 2007). As such, studies using VBA to analyse diffusion-tensor data have been replicated using child participants, in attempts to discern the precise nature of the relationship between FA in localized white matter regions and reading skill (Ben-Shachar et al., 2007). For example, a study by Deutsch et al. (2005) also found that white matter structure in the left temporo-parietal region differs between normal and poor readers between the ages of 7-13; with lower FA associated with poorer performance scores in reading, spelling, and rapid naming. However, contrary to the studies with adult participants, the principal diffusion of the white matter in this study was found to be oriented in the inferior-superior direction (Deutsch et al., 2005). The gross position of the fibres suggested that the left temporo-parietal region identified by Deutsch et al. (2005) was at the border between the AF and projection fibres of the corona radiata. Deutsch et al. (2005) noted that the white matter fibres going through the region could be the part of the AF that curve downward as they project to the temporal lobe; nonetheless the researchers did not eliminate the possibility that the fibres could be projection fibres of the corona radiata. An independent study by Beaulieu et al. (2005) also found a strong, positive correlation between children's reading performance and FA in the left temporo-parietal white matter. The principal direction of diffusion was oriented in the inferior-superior direction, and the fibres were located in an area consistent with the left posterior limb of the internal capsule (PLIC) (Beaulieu et al., 2005). However, Beaulieu et al. (2005) noted the possibility that other white matter fibres crossing at this level, such as the adjacent SLF, could be responsible for the correlation with reading ability. In a study with children who were treated with neurosurgery and cranial irradiation for brain tumours, Palmer et al., (2010) found that average readers had significantly higher FA than below average readers within the left and right PLIC and the temporo-occipital region. The correlations found in children between reading ability and FA in localized white matter regions reduced the likelihood that white matter changes between adults with and without dyslexia are caused by different experiences with reading.

The potential limitations of the studies using VBA include large multiple comparisons and potential artefacts or loss of sensitivity introduced through smoothing and spatial normalization (Niogi & McCandliss, 2006). Qiu et al. (2008) also observed that registration methods with low dimensional transformation could limit VBA resulting in limited accuracy of the correspondence of anatomical points between individuals as a result of the heterogeneous signal intensity of the FA map.

Tract-based spatial statistics (TBSS), an automated observer-independent method of aligning FA images from multiple subjects for group-wise comparisons of diffusion-tensor data, is a method that can overcome some of the limitations encountered with conventional methods (Rollins et al., 2009; Qiu et al., 2008). Tract-based spatial statistics uses a nonlinear registration method and projects the centre of fibre tracts of individual subjects into a common white matter skeleton to prevent issues with residual misregistration (Qiu et al., 2008). In addition, this method of analysis does not require image smoothing and uses nonparametric statistical test with a correction of multiple comparisons in order to deliver better localization ability (Qiu et al., 2008). Using TBSS, Qiu et al., (2008) found that in Chinese ESL speakers, the mean diffusivity of the superior corona radiata correlated significantly with English reading scores. In a study investigating the relationship between white matter and reading abilities in reading impaired and non-reading impaired children, Odegard et al. (2009) found positive correlations between FA values and real word as well as pseudoword decoding in the left superior corona radiata. Correlations between FA values and decoding skills were observed within clusters of voxels along tracts primarily oriented in the superior-inferior direction; however no correlation between FA of the PLIC and reading ability were found (Odegard et al., 2009). In another study, Gebauer et al. (2012) found that children with spelling impairments had lower FA values than control subjects in the left superior corona radiata, but found no group differences in the left temporo-parietal white matter.

Region of Interest analysis involves looking for correlations between the FA of manually traced ROIs on diffusion-tensor images and other variables of interest. Tisserand et al. (2002) suggested that while voxel based approaches are quick, reproducible among groups, and applicable to large datasets, the most accurate method for analysis is an anatomically based manual ROI approach. Several studies have used ROI analysis to examine the correlation between the structural integrity of white matter and language processes. Niogi and McCandliss (2006) assessed the FA values of a restricted set of a priori defined anatomical ROIs using unmodified diffusion-tensor data. Results from previous studies were used to select the ROIs: centrum semiovale (CS), superior corona radiata (SCR), SLF, PLIC, anterior corona radiata (ACR) (Niogi & McCandliss, 2006). Strong correlations were found between FA in a left temporo-parietal white matter region and standardized reading scores of typically developing children (Niogi & McCandliss, 2006). FA values in two left temporo-parietal regions, the left SCR and the left CS, were each highly correlated with standardized word identification skills (Niogi & McCandliss, 2006). Rollins et al. (2009) compared the FA values of the SLF, IFOF-ILF, and PLIC between normal-reading children and children with simple developmental dyslexia. No difference in mean FA of the SLF was observed between the two groups (Rollins et al., 2009). However, the mean FA of the IFO-ILF and PLIC were observed to be higher in the group with dyslexia than the control group up to around 11 years of age, after which the mean FA values were lower in the group with dyslexia than the control group (Rollins et al., 2009).

Unfortunately, ROI analysis is subject to sampling error and lack of sensitivity to changes that occur outside the ROI (Qiu et al., 2008, Snook et al., 2007; Mukherjee et al., 2008). As such several studies have combined VBA and ROI analysis when examining the relationship between white matter integrity and language processes. In a study by Gold et al. (2007), VBA and ROI analysis were used to explore whether the reaction time (RT) of a lexical decision task (using low-frequency words and orthographically legal non-words, which are thought to activate the dorsal stream) correlates with FA values in the white matter of healthy young adults (Gold et al., 2007). The results indicated that lexical decision RT was negatively correlated with FA of left hemisphere white matter in inferior parietal and frontal language regions; regions that are implicated in the mapping of letter to sound correspondences (transformation of orthographic information to phonological codes) (Gold et al., 2007). These white matter regions were associated with the left superior longitudinal fasciculus (SLF) and possibly other smaller association fibres (Gold et al., 2007). Another study by Carter et al. (2009) found that children with dyslexia have decreased FA in the left temporo-parietal white matter associated with the left posterior SLF. A study by Rimrodt et al. (2010) also found decreased FA of the left temporo-parietal area in children with dyslexia.

Tractography is another method of analyzing diffusion-tensor data. It uses the bulk-averaged tissue properties in each voxel and mathematical modeling to infer the dominant fibre orientation in each voxel (Wakana et al., 2004; Mukherjee et al., 2008). Despite some problems associated with using tractography, which include image noise, insensitivity to crossing fibres, limited spatial resolution during image acquisition and inherent mathematical uncertainty, it remains the only method of investigating white matter pathways and brain connectivity in vivo (Mori et al., 1999; Richards et al., 2008; Ben-Shachar et al., 2007). In a tractography study using children with typical reading abilities, Yeatman et al. (2011) reported a correlation between phonological awareness and white matter diffusivity in the left AF. In addition, another study by Vandermosten et al. (2012) found that adults with dyslexia had significantly reduced FA in the left AF than adults in the control group. Furthermore, the study also found a relationship between phoneme awareness and the FA of the left AF, as well as a relationship between orthographic processing and FA in the left IFOF (Vandermosten et al., 2012). The results of these two tractography studies suggest that the AF underlies the dorsal processing stream and the IFOF underlies the ventral processing stream.

The results of studies examining the link between white matter and reading have been somewhat conflicting. Overall, five different white matter tracts have been identified as being potentially important for language processes. In the ventral region, the three tracts identified are the left inferior fronto-occipital fasciculus (IFOF), the left inferior longitudinal fasciculus (ILF), and the left uncinate fasciculus (UF) (Catani & Mesulam, 2008). These three tracts help to connect the frontal, temporal, and occipital lobes and are thought to play a critical role in semantic processing (Shaywitz et al., 1998; Makris et al., 2005; Mandonnet et al., 2007). The IFOF is a large white matter tract that directly connects the occipital and frontal cortex via the extreme capsule (Catani, 2007; Yeatman et al., 2012; Vandermosten et al., 2012). While the relevance of this fasciculus to language is not fully understood, it is thought that it may be involved in reading and writing (Catani & Mesulam, 2008; Steinbrink et al., 2008). The ILF is a ventral associative bundle, which joins the occipital and anterior temporal lobe (Catani et al., 2003; Steinbrink et al., 2008; Agosta et al., 2010; Yeatman et al., 2012). It is thought to play an important role in visual object recognition and in linking object representations to their lexical labels by mediating the fast transfer of visual signals to anterior temporal regions (Mummery et al., 1999; Steinbrink et al., 2008). Finally, the UF is a tract that interconnects the anterior temporal lobe to the orbitofrontal cortex (Catani et al., 2002; Schmahmann et al., 2007). It is thought to play an important role in lexical retrieval, semantic associations, and aspects of naming (Grossman et al., 2004; Lu et al., 2002).

In the dorsal region, the white matter tracts that have been identified as being potentially important for language processes are the left corona radiata (CR), the left posterior limb of the internal capsule (PLIC), the centrum semiovale (CS) and the left superior longitudinal fasciculus (SLF), more specifically the arcuate fasciculus (AF) portion of the SLF. The CR is a white matter tract that projects from the thalamus to the sensory cortices (Odegard et al., 2009). Fibres of the CR pass through the internal capsule ventrally and continue dorsally as the CS, and as such the PLIC, CR and CS can be considered as part of the same white tract. Due to the fact that the corona radiata does not seem to connect commonly identified brain regions involved when reading, integrating it into current theories of reading have not been an easy task (Odegard et al., 2009). The SLF is one of the major cortical association fibre pathways in the human brain; it connects perisylvian frontal, parietal, and temporal association areas (Wakana et al., 2004; Makris et al., 2005; Gold et al., 2007; Agosta et al., 2010). It can be divided into four components; the most important portion for language processing is thought to be the AF, which consists of long arched fibres that link Broca's area in the frontal lobe with Wernicke's area in the temporal lobe (Geschwind, 1970; Petrides & Pandya, 1984; Catani et al., 2005; Makris et al., 2005; Parker et al., 2005; Powell et al., 2006; Schmahmann et al., 2007; Bernal & Altman, 2010).

The majority of previous studies investigating the relationship between reading and the structural integrity of white matter tracts focused on reading ability and included participants both with and without dyslexia (see: Klingberg et al., 2000; Deutsch et al., 2005; Niogi & McCandliss, 2006; Steinbrink et al., 2008; Odegard et al., 2009; Rollins et al., 2009; Carter et al., 2009; Vandermosten et al., 2012); few studies thus far included only normal readers (see: Beaulieu et al., 2005; Gold et al., 2007; Yeatman et al., 2011) and none have explored basic reading process such as reading speed. The purpose of this study was to investigate the relationship between reading speed and the structural data of white matter tracts in the brain of healthy adult participants. Specifically, the current study examined whether or not there is a correlation between the FA of white matter tracts hypothesized to underlie the dorsal and ventral processing streams and the reaction times for overt reading of exception words, regular words, and pseudohomophones. Three different methods of analyzing DTI data were used. Tractography analysis was used to investigate the correlation between RT for overt reading of different types of stimuli and the mean FA of entire white-matter tracts in the left hemisphere. Region of interest (ROI) analysis was used to examine the correlation between reading speed and the FA of manually traced areas of pre-defined white matter tracts in the left hemisphere. Finally, an exploratory hybrid analysis composed of TBSS and VBA was used to explore white matter regions in the brain that correlate with reading speed.

Based on the dual route model of reading and previous research on the connection between the structural integrity of the left hemisphere white matter and reading; it is hypothesized that there is a relationship between stimuli that typically activate the ventral stream (exception words) and the underlying white matter tracts in the ventral region (the left IFOF, ILF and UF) and that there is a relationship between stimuli that typically activate the dorsal stream (pseudohomophones, non-words) and the underlying white matter tracts in the dorsal region (the left PLIC and AF). Regular words, which can rely on either system, were hypothesized to be associated with both dorsal and ventral white matter tracts.

2. Behavioural Data Acquisition

2.1 Participants

A total of 32 volunteers (21 female, 9 male) participated in this experiment. Participants included undergraduate and graduate students at the University of Alberta as well as individuals from the community. The participants ranged in age from 18 to 30 years (mean = 22.61±3.02), and 28 of the participants were right handed. Inclusion criteria consisted of normal or corrected to normal vision, no diagnosed language impairments, 18 years-of-age or older, able to go in the MRI, and English as a first language. Consent was obtained from the participants and the experiment was performed in compliance with institutional guidelines and with the approval of the University of Alberta Health Research Ethics Board.

2.2 Stimuli

A total of 756 stimuli organized by stimulus type, were presented. Stimuli consisted of 252 pronounceable non-words (NWs), 252 pseudohomophones (PHs), 126 exception words (EXCs), and 126 regular words (REGs). Stimuli were all monosyllabic and matched for initial onset, length, and orthographic neighbourhood.

2.3 Materials

Stimuli were presented on a computer monitor using EPrime software (Psychology Software Tools, Inc., http://www.pstnet.com). Voice onset was coded via a microphone and the experimenter used a button response to code accuracy on each trial.

2.4 Procedure

After giving written consent, participants were tested individually in a normally lit room. Letter strings were presented to the centre of a computer screen. Participants were instructed to name aloud the presented stimuli as quickly and as accurately as possible. The stimuli were presented in pure blocks (i.e., the participants named all the EXCs in one block, all the REGs in another, etc.). Stimuli were randomly presented in each block and the order of blocks was randomized across participants. Participants were given 1800 ms to name the stimuli. The experimenter used a mouse button click to code correct (left button) and incorrect (right button) responses on all trials.

2.5 Results

Mean correct reaction times (RTs) are displayed in Table 1; trials in which the response was made prior to 250 ms or after 1500 ms were excluded from analysis per the procedure established in previous literature as those responses were typically made in error (Hino & Lupker, 1998; 2000). A correlation between age and reaction time was run to rule out age as a confounding factor. The correlations were not significant for any of the stimulus types (see Table 2).

	Mean RT (ms)	RT SD
EXC	584	85
REG	560	85
NW	636	97
PH	656	114

Table 1. Mean reaction time (RT) and standard deviation (SD) for exception words (EXC), regular words (REG), non-words (NW), and pseudohomophones (PH).

	Age	p-value
EXC	-0.066	0.721
REG	-0.164	0.361
PH	-0.106	0.558
NW	-0.143	0.427

Table 2. Pearson's correlation coefficients of age with the reaction times for overt naming of exception words (EXC), regular words (REG), pseudohomophones (PH), and non-words (NW).

3. Diffusion Tensor Image Data Acquisition

All DTI imaging was conducted using a 1.5T Siemens Sonata MRI scanner and scans were acquired using a dual spin-echo single-shot echo-planar imaging sequence. Thirty non-collinear directions of diffusion-sensitizing gradients were acquired, diffusion sensitivity b = 1000 s/mm^2, 1 average, T_R = 6900 ms, T_E = 100 ms. Forty, 3 mm thick axial slices (no inter-slice gap) were obtained with an image matrix of 128 x 128 with 75% phase partial Fourier zero-filled to 256 x 256 and FoV 220 mm. Raw images were visually examined and no motion artefacts were found. Acquisition time was approximately 8 minutes.

4. Tractography Analysis of FA and RT Correlation

Three-dimensional tract reconstruction (tractography) for the tracts of interest in the left hemisphere were conducted for each participant on DTIstudio, using a multiple region of interest (ROI) approach and referencing the protocols outlined in Wakana et al. (2007) and Zisner and Phillips (2009a; b; c; d). Multiple ROI approach utilizes existing anatomical knowledge of tract trajectories in order to reconstruct said tracts; fibres which penetrate the manually defined ROIs are assigned to the specific tracts associated with those ROIs (Agosta et al., 2010; Wakana et al., 2007).

Tractography was performed using raw DTI images that have not been spatially normalized, smoothed, or manipulated in order to avoid potential artefacts or loss of sensitivity. An FA threshold of 0.25 was used to initiate and continue tracking; the maximum angle threshold was 70 degrees. With reference to the protocol outlined in Wakana et al. (2007), three types of ROI operations within DTIstudio were used for fibre tracking: “OR”, “AND”, and “NOT”. The “OR” function selects all the fibres that penetrates a particular ROI, the “AND” function selects only those fibres that penetrate the defined ROIs, and the “NOT” function removes any fibres that penetrate the defined ROI. After the reconstruction of the tract, DTIstudio computed the mean FA value of each tract for each individual, which was then correlated with reaction time.

4.1 Arcuate Fasciculus (Fig. 1)

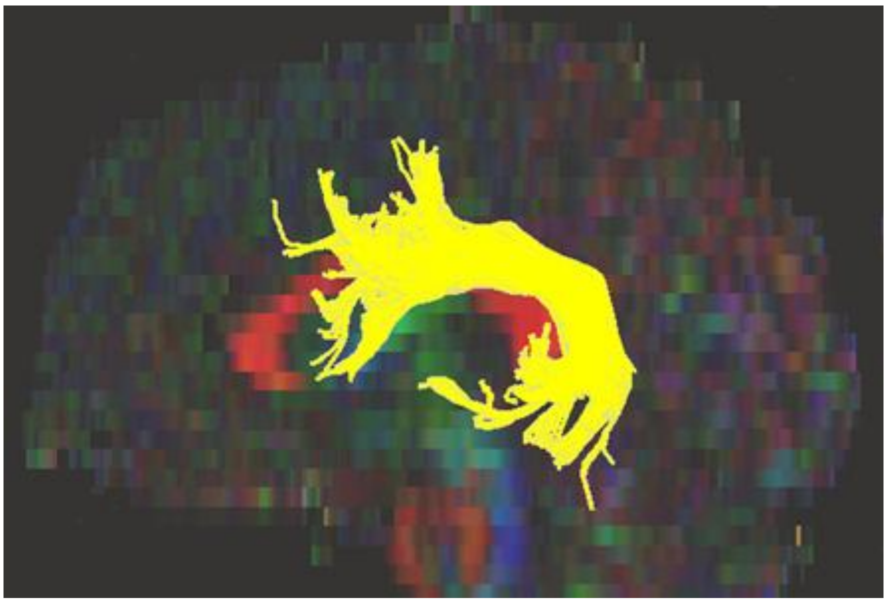


Fig. 1. Sagittal view of the arcuate fasciculus (AF).

Following the protocol outlined in Wakana et al. (2007) for the reconstruction of the left arcuate fasciculus (AF) (Fig. 1), the most inferior axial slice in which the fornix is visible was selected (Fig. 2a, the fornix is indicated by the white arrow). A coronal slice bisecting the posterior limb of the internal capsule (PLIC) was identified and the first ROI was drawn using the "OR" function to select all the fibres in the left parietal lobe (Fig. 2b) (Wakana et al., 2007). In the axial slice identified in Fig. 2a, a second ROI was drawn using the "AND" function to select the fibres located laterally to the sagittal stratum (SS) (Wakana et al., 2007). The "NOT" function was used to remove any fibres that did not appear to be part of the AF (i.e., fibres that crossed the midline).

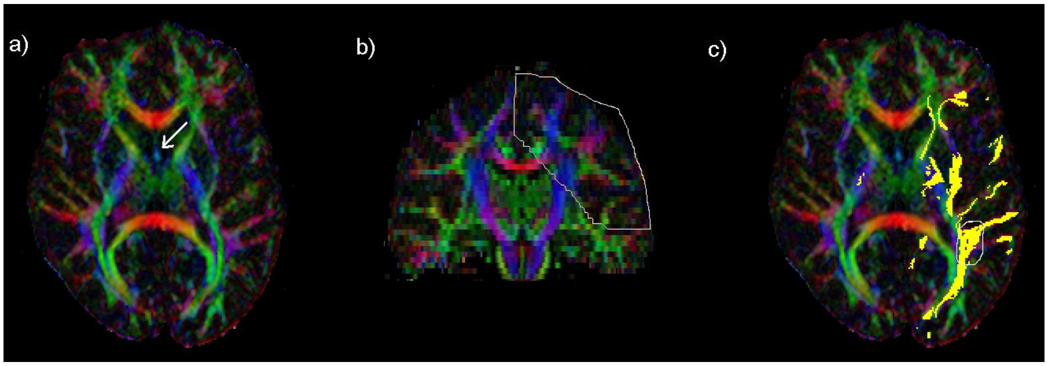


Fig. 2. Tractography method for reconstructing the left hemisphere arcuate fasciculus (AF). a) Most inferior axial slice containing the fornix (indicated by the white arrow. b) ROI 1: All fibres in the left parietal lobe of the coronal slice that bisects the posterior limb of the internal capsule. c) ROI 2: Fibres lateral to the sagittal stratium.

4.2 Posterior Limb of the Internal Capsule (Fig. 3)

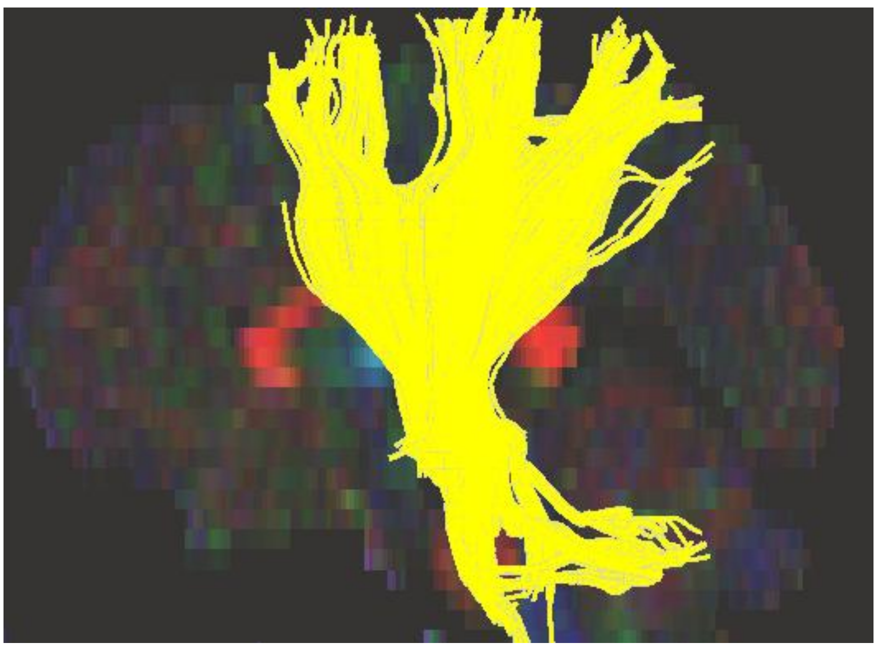


Fig. 3. Sagittal view of the posterior limb of the internal capsule (PLIC).

The posterior limb of the internal capsule (PLIC) is primarily composed of two different tracts: the corticospinal tract (CST) and the corticobulbar tract (CBT) (Wakana et al., 2004). With reference to the protocol outlined in Wakana et al., (2007) for the reconstruction of the CST, an axial slice showing the cerebral peduncle was selected (Fig. 4a). The first ROI was drawn using the “OR” function to select all the fibres in the left cerebral peduncle (Fig. 4b) (Wakana et al., 2007). An axial slice where the two hemispheres are not connected by the corpus callosum (Fig. 4c, the separation of the hemispheres is indicated by the white arrow) was selected. The second ROI was drawn using the “AND” function to select the fibres of the superior region of the left internal capsule in the parietal lobe. The “NOT” function was used to remove any fibres that did not appear to be part of the PLIC (i.e., fibres that crossed the midline).

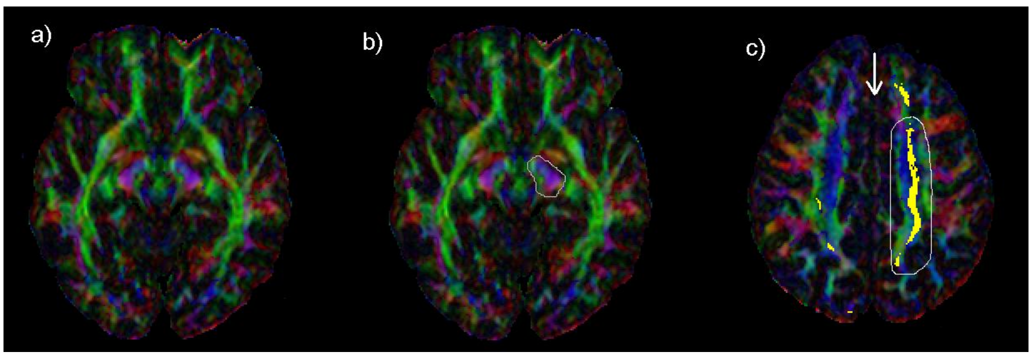


Fig. 4. Tractography method for reconstructing the left posterior limb of the internal capsule (PLIC). a) Axial slice containing the cerebral peduncle. b) ROI1: All fibres of the left cerebral peduncle. c) An axial slice in which the two hemispheres are separated (indicated by the white arrow) was selected. ROI2: Fibres of the superior region of left internal capsule in the parietal lobe.

4.3 Inferior Fronto-Occipital Fasciculus (Fig. 5)

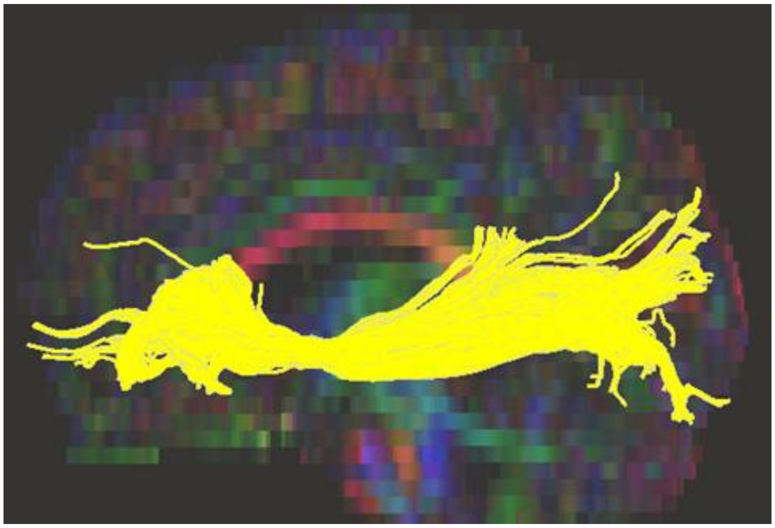


Fig. 5. Sagittal view of the inferior fronto-occipital fasciculus (IFOF).

With reference to the protocols outlined in Wakana et al., (2007) and Zisner and Phillips (2009b) for the reconstruction of the inferior fronto-occipital fasciculus (IFOF) (Fig. 5), the most posterior coronal slice in which the corpus callosum is visible was selected (Fig. 6a, the corpus callosum is indicated by the white arrow). The first ROI was drawn using the "OR" function to select all the fibres in the left temporal-parietal region (Fig. 6b). A coronal slice where the IFOF bunches and in which the temporal lobe is separated from the frontal lobe was selected (Zisner & Phillips, 2009b). A second ROI was drawn using the "AND" function to select the circular fibre bundle in the inferior portion of the frontal lobe of the coronal slice (Fig. 6c) (Zisner & Phillips, 2009b). The "NOT" function was used to remove any fibres that did not appear to be part of the IFOF (i.e., fibres that crossed the midline).

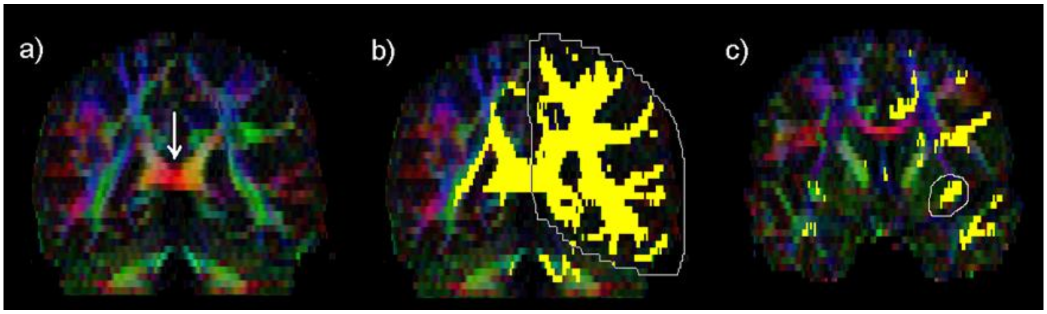


Fig. 6. Tractography method for reconstructing the left inferior fronto-occipital fasciculus (IFOF). a) The most posterior coronal slice in which the corpus callosum is visible (indicated by the white arrow). b) ROI1: All the fibres in the left temporal-parietal region. c) A coronal slice where the IFOF bunches was selected. ROI2: Circular fibre bundle in the inferior portion of the frontal lobe.

4.4 Inferior Longitudinal Fasciculus (Fig. 7)

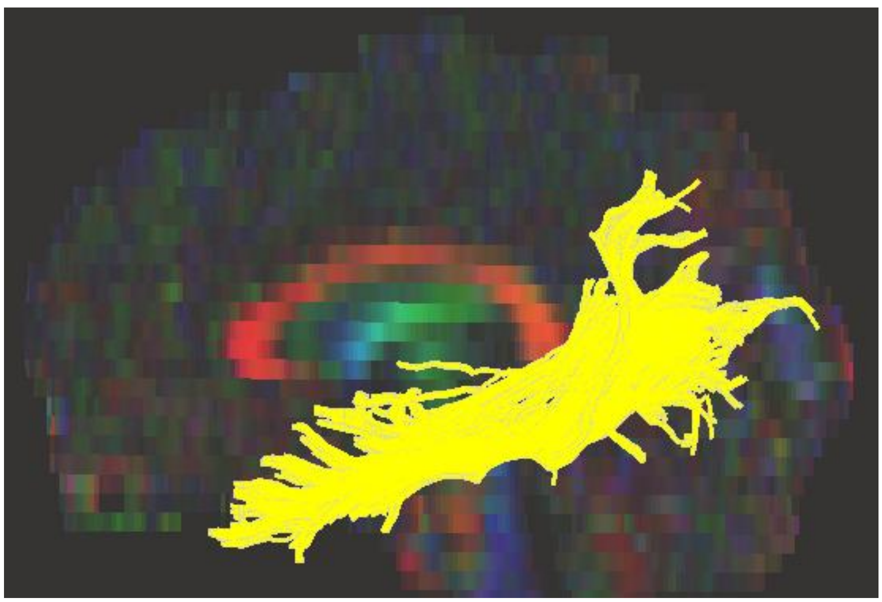


Fig. 7. Sagittal view of the inferior longitudinal fasciculus (ILF).

With reference to the protocols outlined in Wakana et al. (2007) and Zisner and Phillips (2009c) for the reconstruction of the inferior longitudinal fasciculus (ILF) (Fig. 7), the most posterior coronal slice in which the corpus callosum is visible was selected (Fig. 8a, the corpus callosum is indicated by the white arrow). The first ROI was drawn using the “OR” function to select all the fibres in the left temporal-parietal region (Fig. 8b) (Wakana et al., 2007; Zisner & Phillips 2009c). A coronal slice where the temporal lobe is disconnected from the frontal lobe was selected (Wakana et al., 2007; Zisner & Phillips 2009c). A second ROI was drawn using the "AND" function to select all the fibres in the temporal lobe (Fig. 8c) (Wakana et al., 2007; Zisner & Phillips 2009c). The "NOT" function was used to remove any fibres that did not appear to be part of the ILF (i.e., fibres that crossed the midline).

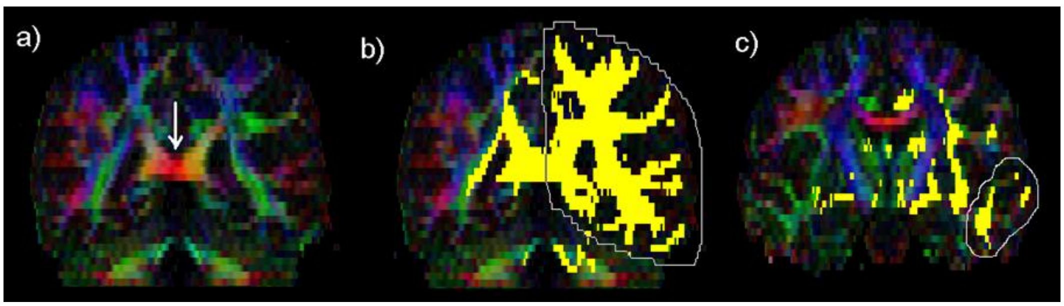


Fig. 8. Tractography method for reconstructing the left inferior longitudinal fasciculus. a) The most posterior coronal slice in which the corpus callosum is visible (indicated by the white arrow). b) ROI1: All the fibres in the left temporal-parietal region. c) A coronal slice where the temporal lobe is disconnected from the frontal lobe is selected. ROI2: All the fibres in the temporal lobe.

4.5 Uncinate Fasciculus (Fig. 9)

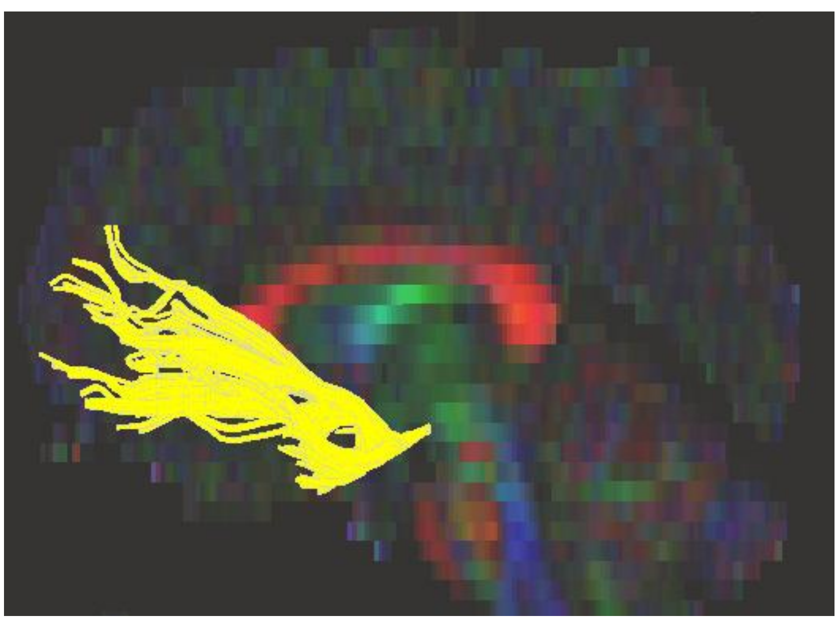


Fig. 9. Sagittal view of the uncinate fasciculus (UF).

Following the protocols outlined in Wakana et al. (2007) and Zisner and Phillips (2009d) for the reconstruction of the uncinate fasciculus (UF) (Fig. 9), the most posterior coronal slice in which the temporal lobe is separated from the frontal lobe was selected (Fig. 10a, the separation of the temporal and the frontal lobe is indicated by the white arrow). The first ROI was drawn using the "OR" function to select all the fibres in the left temporal lobe (Fig. 10b) (Wakana et al., 2007; Zisner & Phillips 2009d). A second ROI was drawn in the same coronal slice using the "AND" function to select all the fibres in the frontal lobe (Fig. 10c) (Wakana et al., 2007; Zisner & Phillips 2009d). The "NOT" function was used to remove any fibres that did not appear to be part of the UF (i.e., fibres that crossed the midline).

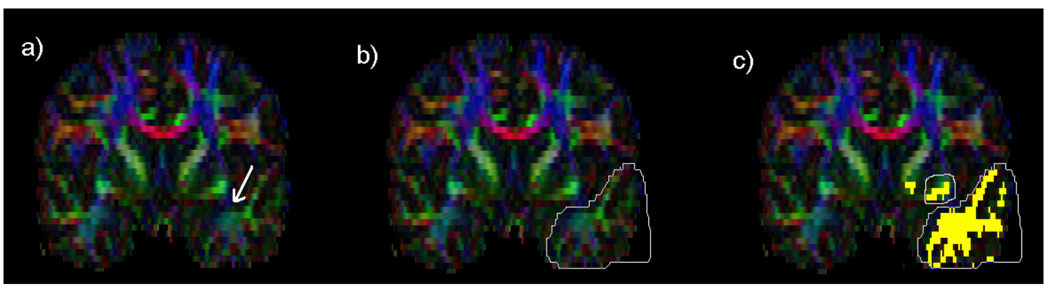


Fig. 10. Tractography method for reconstructing left uncinate fasciculus (UF). a) The most posterior coronal slice in which the temporal lobe is separated from the frontal lobe (indicated by the white arrow). b) ROI1: All the fibres in the left temporal lobe. c) ROI2: All the fibres in the frontal lobe.

4.6 Reliability of Tractography Analysis

Seven participants were randomly selected from the pool of participants and tractography was performed again to check the intra-rater reliability. Overall, it was found that the FA value obtained from the second tractography analysis correlated strongly with the FA value from the first tractography analysis: ILF (r $(5) = 0.996$, $p < 0.001$, two-tailed), IFOF (r $(5) = 0.997$, $p < 0.001$, two-tailed), UF

($r(5) = 0.969$, $p < 0.001$, two-tailed), AF ($r(5) = 0.991$, $p < 0.001$, two-tailed), and PLIC ($r(5) = 0.796$, $p = 0.032$, two-tailed). In addition, a paired-samples t-test was also conducted to evaluate whether the mean difference between the two sets of analyses were significantly different from zero. No significant difference was found between the FA value obtained from the first tractography analysis and the FA value obtained from the second tractography analysis: ILF ($t(6) = -0.055$, $p = 0.958$, two-tailed), IFOF ($t(6) = 0.823$, $p = 0.442$, two-tailed), UF ($t(6) = 0.326$, $p = 0.756$, two-tailed), AF ($t(6) = 1.329$, $p = 0.232$, two-tailed), and PLIC ($t(6) = 1.545$, $p = 0.173$, two-tailed).

5. Region of Interest Analysis of FA and RT Correlation

Region of Interest analysis was used to examine the correlation between reading speed and the FA of manually traced areas of pre-defined white matter tracts in the left hemisphere. ROI analysis was performed using raw DTI images that have not be normalized, smoothed, or manipulated in any way. ROIs for the tracts of interest were traced using DTIstudio, the boundaries of which were selected with reference to a human white matter atlas (Wakana et al., 2004). When the ROIs are traced using axial slices, they are traced from the superior slices to the inferior slices. When the ROIs are traced using the coronal slices, they are traced from the anterior slices to the posterior slices. The program, DTIstudio, computed the mean FA value for each manually traced ROI, which were then averaged to produce a single mean FA value for each tract/region of each subject. This FA value was then correlated with reaction time and the results of tractography analysis.

5.1 Arcuate Fasciculus

The ROIs for the left AF were traced in the left hemisphere white matter located laterally to the superior region of the internal capsule from the axial slice where the superior portion of the corpus callosum is just visible until the axial slice in which both thalami are clearly visible (Fig. 11). The manually traced ROIs for the AF may have contained sections of white matter associated with the superior region of the internal capsule.

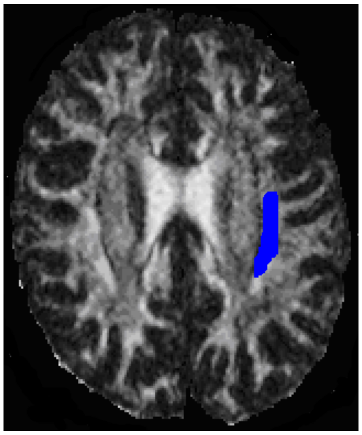


Fig. 11. Example of region of interest (ROI) for the left arcuate fasciculus (AF).

5.2 Posterior Limb of the Internal Capsule

The ROIs for the left PLIC were traced in the axial slices where the PLIC could be clearly identified (Fig. 12). The manually traced ROIs for the PLIC may have included miniscule portions of white matter associated with the genu of the internal capsule.

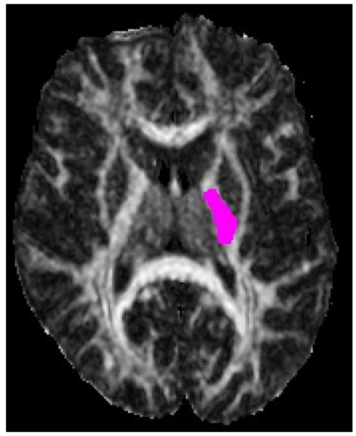


Fig. 12. Example of region of interest (ROI) for the left posterior limb of the internal capsule (PLIC).

5.3 Inferior Fronto-Occipital Fasciculus

The ROIs for the left IFOF were traced in the left hemisphere fronto-temporal white matter from the axial slice where the fornix is just visible until the axial slice where approximately one third of the frontal lobe was visible (Fig. 13). The manually traced ROIs for the IFOF may have incorporated a few sections of white matter associated with the UF, the stria terminalis, and the superior longitudinal fasciculus (SLF).

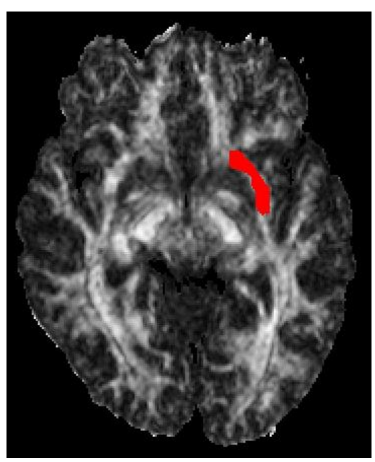


Fig. 13. Example of region of interest (ROI) for the left inferior fronto-occipital fasciculus (IFOF).

5.4 Inferior Longitudinal Fasciculus

The ROIs for the left ILF were traced in the left temporal lobe white matter from the axial slice where the frontal lobe is mostly visible until the axial slice where the entire temporal lobe is visible (Fig. 14). The manually traced ROIs for the ILF may have included small portions of white matter associated with the IFOF and the stria terminalis.

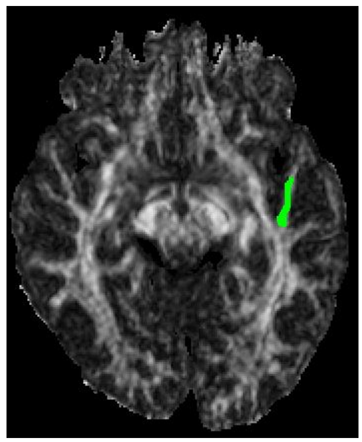


Fig. 14. Example of region of interest (ROI) for the left inferior longitudinal fasciculus (ILF).

5.5 Uncinate Fasciculus

The ROIs for the left UF were traced in the white matter bundle connecting the frontal lobe to the temporal lobe from the coronal slice where the anterior portion of the fornix is just visible until the coronal slice where the fornix can be clearly identified as a single intense structure (Fig. 15). The manually traced ROIs for the UF may have contained sections of white matter associated with the IFOF, the SLF and the ILF.

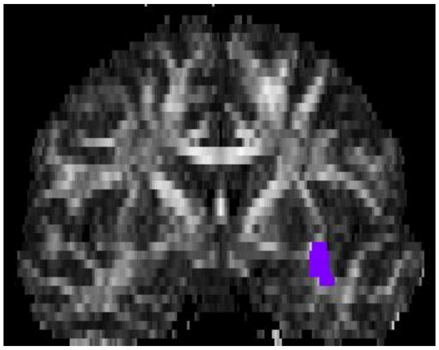


Fig. 15. Example of region of interest (ROI) for the left uncinate fasciculus (UF).

5.6 Parietal Regions of Interest

The left hemisphere parietal ROIs were traced following the procedure outlined in Gold et al. (2007), “from the slice in which the lateral ventricles were first visible until the anterior and posterior horns of the lateral ventricles were clearly separated (due to the appearance of the thalamus)” (p2441) (Fig. 16). According to Gold et al. (2007), the manually traced ROIs “may have included small portions of [white matter] associated with the superior temporal region” (p2441).

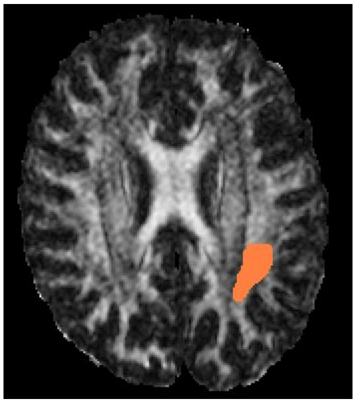


Fig. 16. Example of the left parietal region of interest (ROI).

5.7 Reliability of Region of Interest Analysis

Seven participants were randomly selected from the pool of participants and ROI analysis was performed again to check the intra-rater reliability. For most of the regions of interest, it was found that the FA value obtained from the second ROI analysis correlated strongly with the FA value from the first ROI analysis: IFOF ($r(5) = 0.949$, $p = 0.001$, two-tailed), AF ($r(5) = 0.917$, $p=0.004$, two-tailed), PLIC ($r(5) = 0.831$, $p = 0.021$, two-tailed) and parietal region ($r(5) = 0.756$, $p = 0.049$, two-tailed). However, no correlation was found between the first ROI analysis and the second ROI analysis for the regions of interest associated with the ILF ($r(5) = 0.672$, $p = 0.098$, two-tailed) and the UF ($r(5) = 0.485$, $p =0.270$, two-tailed). A paired-samples t-test was conducted to evaluate whether the mean difference between the two sets of analyses were significantly different from zero. It was found that there was no significant difference between the FA value obtained from the first ROI analysis and the FA value obtained from the second ROI analysis: ILF ($t(6) = -0.444$, $p =0.673$, two-tailed), IFOF ($t(6) = -1.867$, $p = 0.111$, two-tailed), UF ($t(6) = -2.029$, $p = 0.089$, two-tailed), AF ($t(6) = 0.679$, $p = 0.522$, two-tailed), PLIC ($t(6) = -1.263$, $p = 0.253$, two-tailed), and parietal region. ($t(6) = -1.486$, $p = 0.118$, two-tailed).

6. Hybrid of Tract-Based Spatial Statistics and Voxel Based Analysis of FA and Reaction Time Correlation

Imaging data was corrected for eddy currents and effects of head movement. The image values were then scaled and aligned to the target template from FSL FMRIB58. The data was then transformed to Montreal Neurological Institute (MNI152) space, and the normalized FA maps were smoothed using a 4-mm smoothing kernel. Only voxels with a threshold FA of 0.2 or greater were used for further analysis. Voxel-based correlation of FA with reaction times to reading different word types was performed using SPM8.

Monte Carlo simulations were conducted to determine the appropriate cluster size that corresponds to an overall alpha value of 0.05 when corrected for multiple comparisons. These simulations showed that a cluster size of 77 corresponded to a p-value of 0.046. Therefore this cluster size was used to determine clusters with significant correlations between FA values and reaction time for reading. Clusters were identified using a human white matter atlas (Oishi et al., 2011).

7. Results

This study sought to determine whether or not there is a relationship between the reaction time (RT) for naming stimuli that typically activate the ventral stream (i.e., exception words and regular words) and the structural integrity (i.e., FA) of the underlying white matter tracts in the ventral region (i.e., IFOF, ILF, UF). The study also sought to determine whether or not there is a relationship between the RT for naming stimuli that typically activate the dorsal stream (i.e., regular words, pseudohomophones and non-words) and the structural integrity of the underlying white matter tracts in the dorsal region (i.e., PLIC, AF).

7.1 Tractography Results

Mean FA values for each of the reconstructed tracts are presented in Table 3. A correlation between FA and age was run to rule out age as a confounding factor. The correlations were not significant for any of the stimulus types (see Table 4).

	Mean	SD	Range
Left AF	0.55	0.02	0.08
Left PLIC	0.58	0.02	0.06
Left IFOF	0.56	0.02	0.09
Left ILF	0.53	0.02	0.08
Left UF	0.49	0.02	0.09

Table 3. Mean, standard deviation (SD), and range of fractional anisotropy (FA) values for the left hemisphere arcuate fasciculus (AF), posterior limb of the internal capsule (PLIC), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus (UF) obtained through tractography analysis.

	Age	p-value
Left AF	-0.198	0.284
Left PLIC	-0.146	0.433
Left IFOF	0.198	0.285
Left ILF	0.049	0.792
Left UF	-0.08	0.686

Table 4. Pearson's correlation coefficients of age with the fractional anisotropy (FA) of the left hemisphere white matter tracts arcuate fasciculus (AF), posterior limb of the internal capsule (PLIC)), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF) obtained through tractography.

7.1.1 Tractography Analysis: Dorsal White Matter Tracts

Correlational analyses found no significant relationship between the mean FA derived from tractography of white matter tracts in the left hemisphere of the brain thought to underlie the dorsal processing stream and RT for reading regular words, pseudohomophones, and non-words (see Table 5; Figures 17-22).

	REG	PH	NW
Left AF	-0.169	-0.032	0.081
Left PLIC	-0.017	-0.067	0.077

Table 5. Pearson's correlation coefficients of the fractional anisotropy (FA) of the left hemisphere dorsal white matter tracts (arcuate fasciculus (AF) and posterior limb of the internal capsule (PLIC)) derived from tractography and mean reaction times for regular words (REG), pseudohomophones (PH), and non-words (NW).

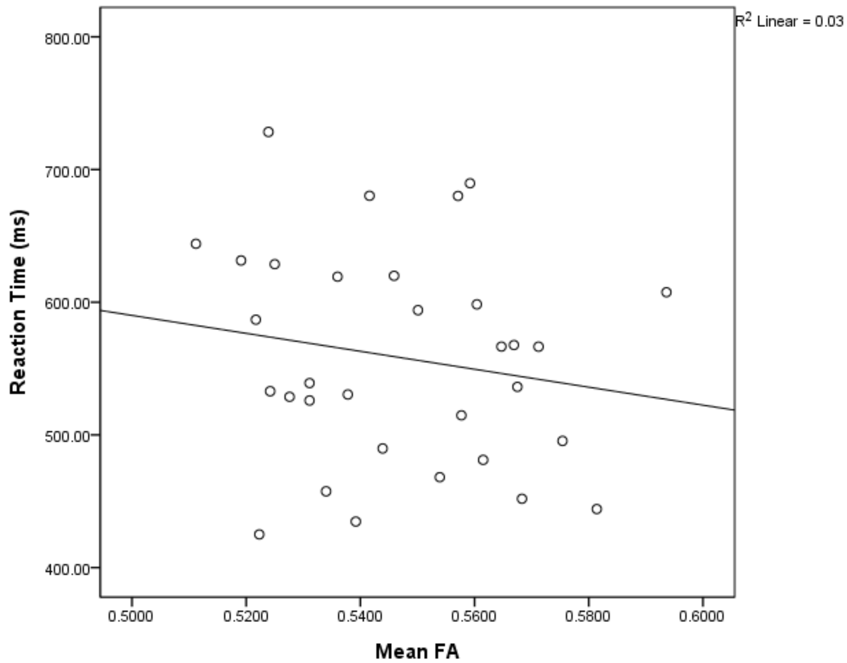


Figure 17. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from tractography and the mean reaction time (RT) for regular words (REG).

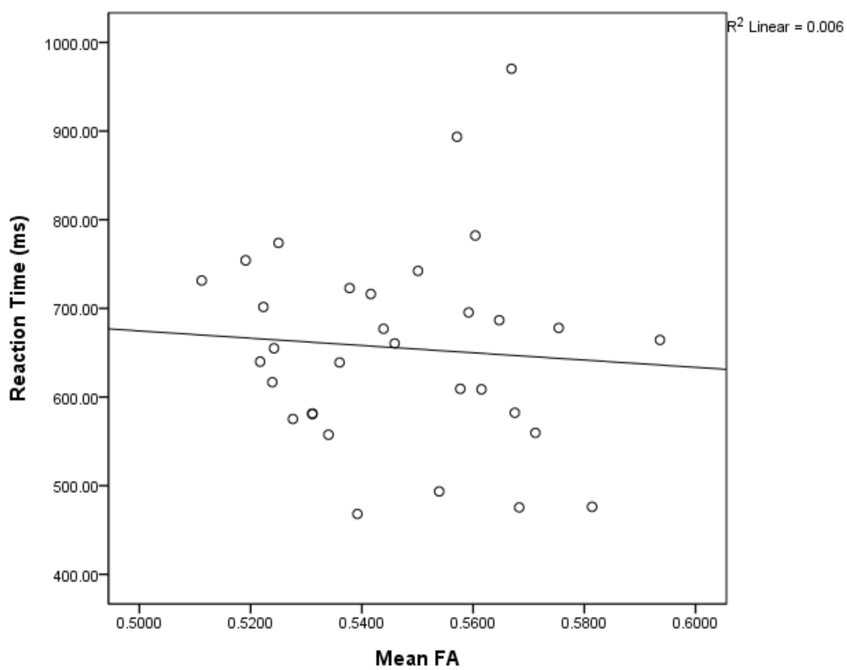


Figure 18. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from tractography and the mean reaction time (RT) for pseudohomophones (PH).

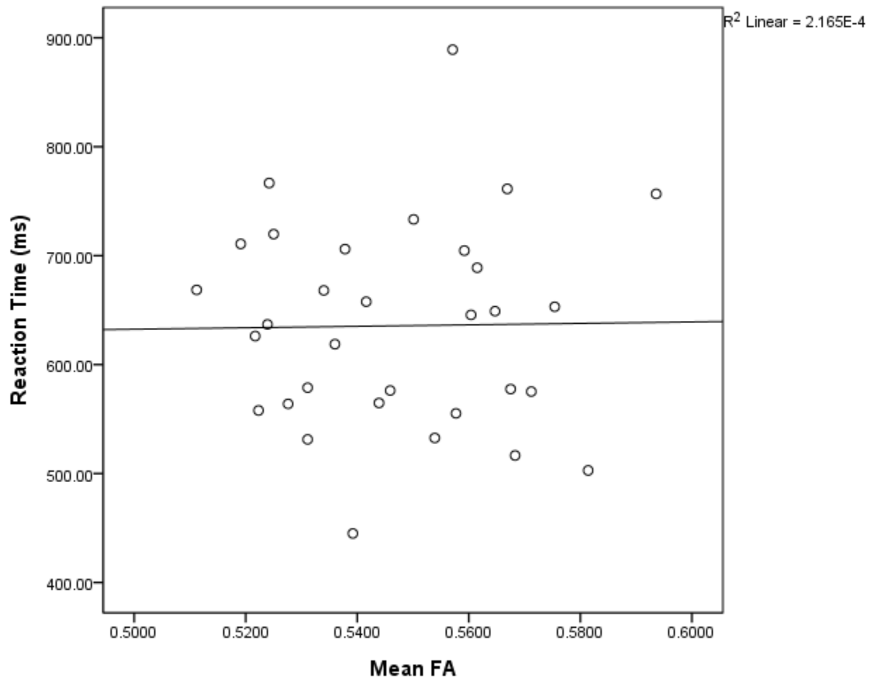


Figure 19. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from tractography and the mean reaction time (RT) for non-words (NW).

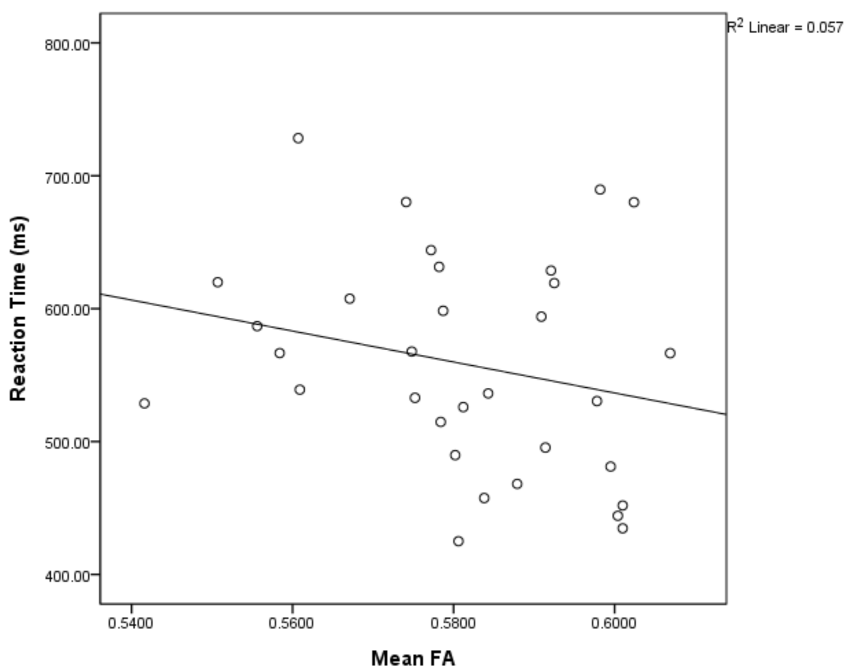


Figure 20. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from tractography and the mean reaction time (RT) for regular words (REG).

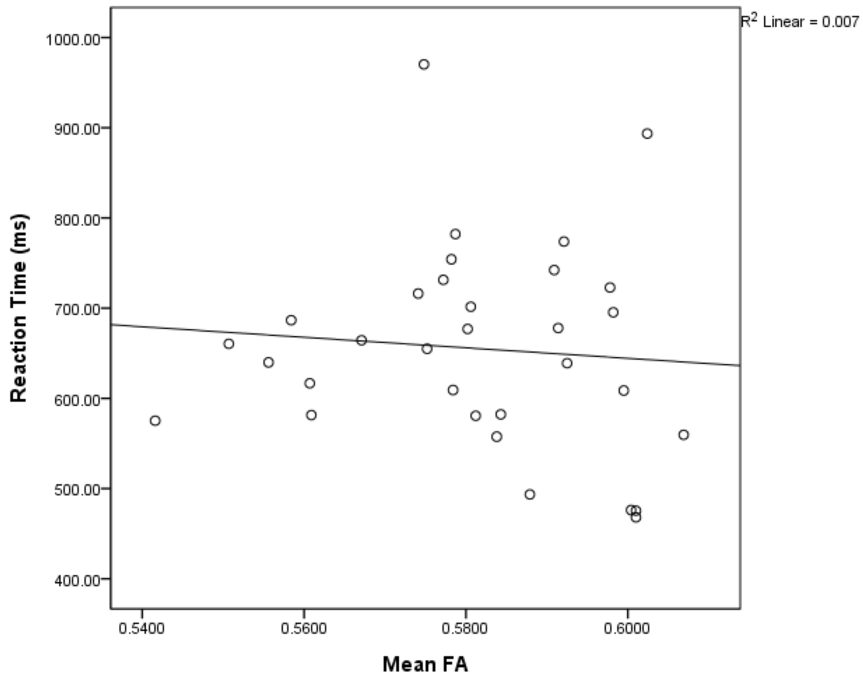


Figure 21. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from tractography and the mean reaction time (RT) for pseudohomophones (PH).

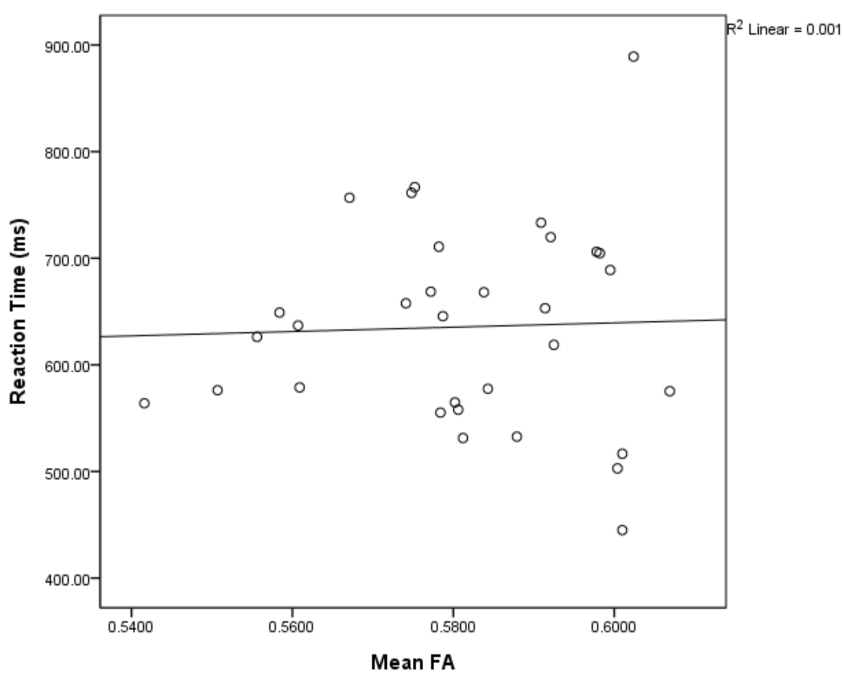


Figure 22. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from tractography and the mean reaction time (RT) for non-words (NW).

7.1.2 Tractography Analysis: Ventral White Matter Tracts

Correlational analyses found no relationship between the mean FA obtained from tractography of two of the three white matter tracts in the left hemisphere of the brain thought to underlie the ventral processing stream and RT for reading exception and regular words (see Table 6; Figures 23-28). The only significant relationship found was between FA of the UF and the RT for overt naming of exception words (see Figure 27) and regular words (see Figure 28 and Table 6).

	EXC	REG
Left ILF	-0.068	-0.083
Left IFOF	-0.198	-0.215
Left UF	-0.405*	-0.354*

Table 6. Pearson's correlation coefficients of the fractional anisotropy (FA) of the left hemisphere ventral white matter tracts (inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus (UF)) derived from tractography and mean reaction times for exception words (EXC) and regular words (REG).
*Significant correlation, $p < 0.05$, two-tailed.

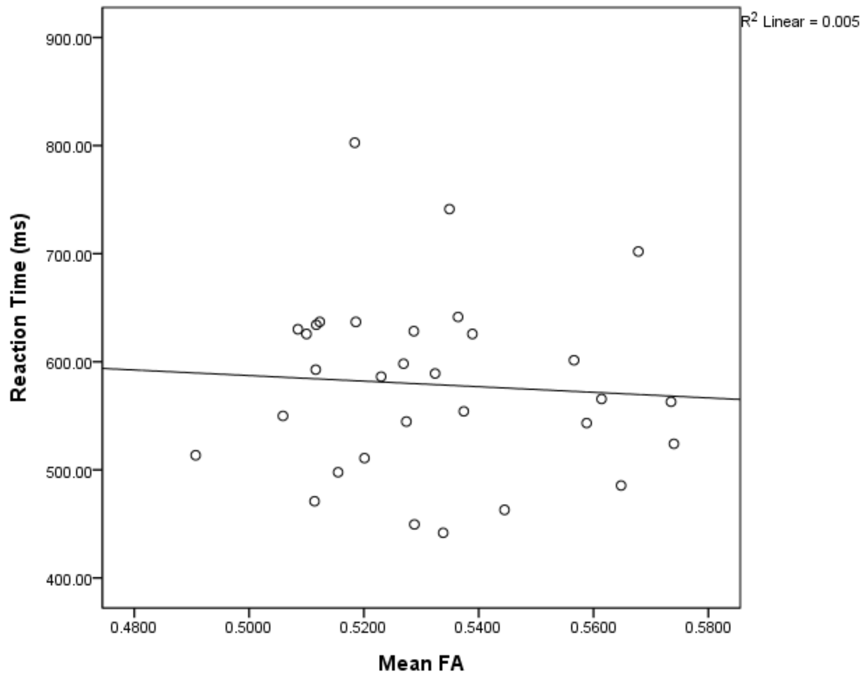


Figure 23. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior longitudinal fasciculus (ILF) derived from tractography and the mean reaction time (RT) for exception words (EXC).

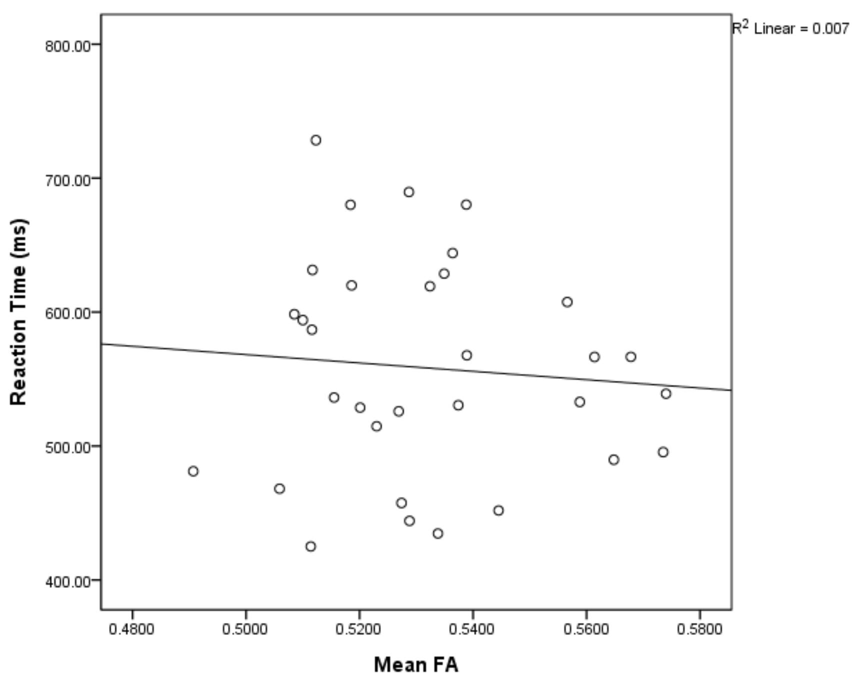


Figure 24. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior longitudinal fasciculus (ILF) derived from tractography and the mean reaction time (RT) for regular words (REG).

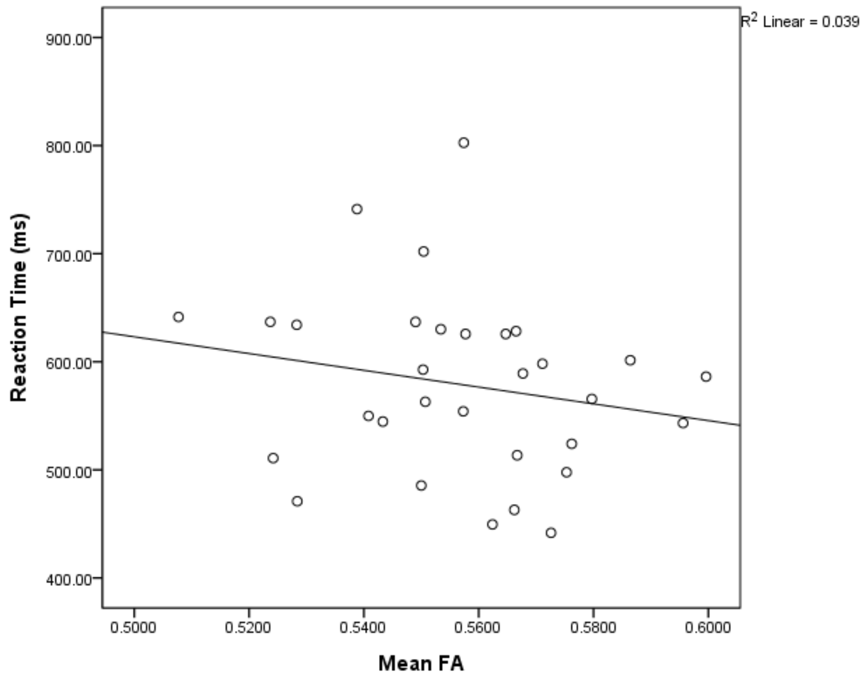


Figure 25. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior fronto-occipital fasciculus (IFOF) derived from tractography and the mean reaction time (RT) for exception words (EXC).

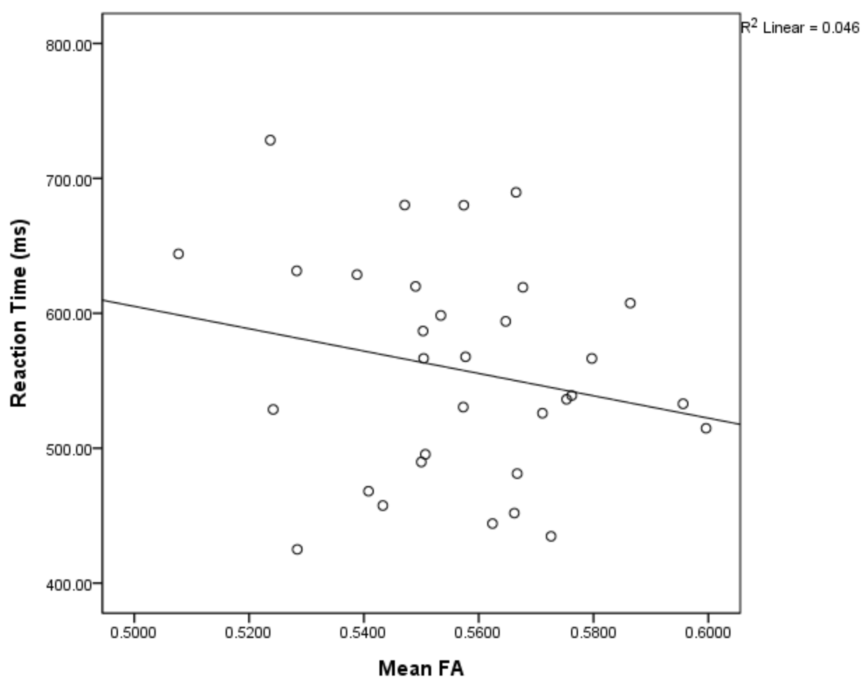


Figure 26. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior fronto-occipital fasciculus (IFOF) derived from tractography and the mean reaction time (RT) for regular words (REG).

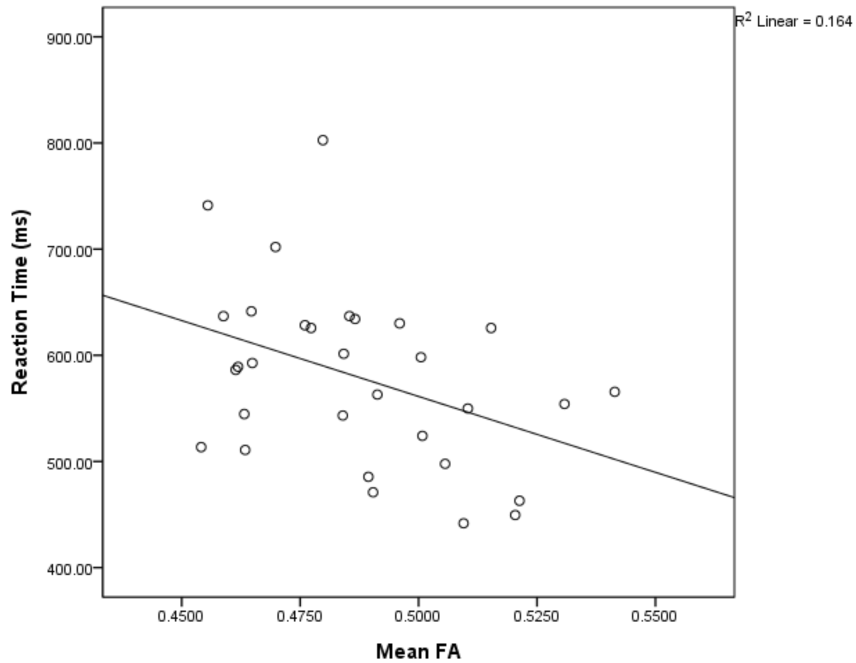


Figure 27. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left uncinate fasciculus (UF) derived from tractography and the mean reaction time (RT) for exception words (EXC).

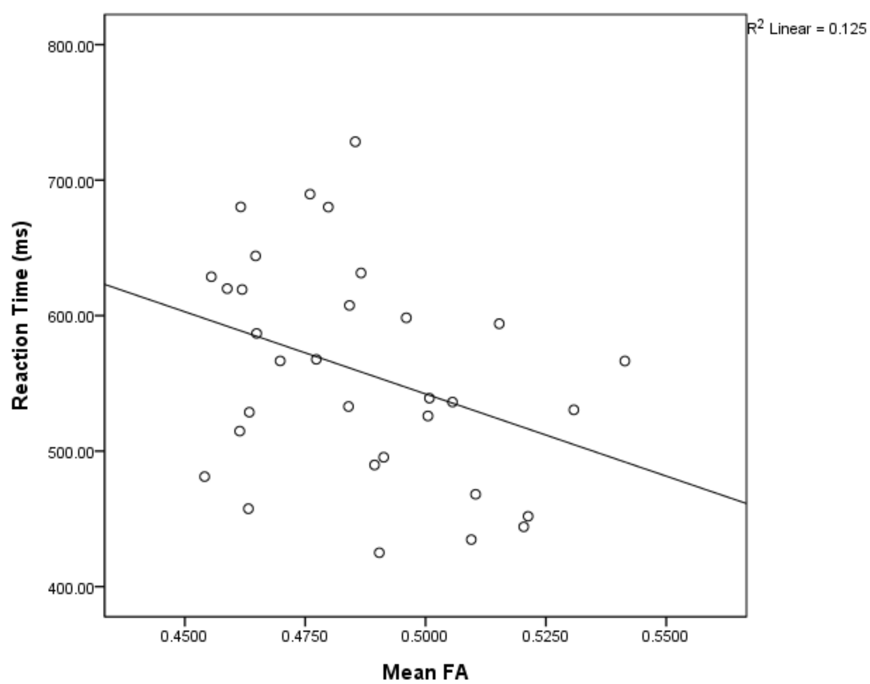


Figure 28. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left uncinate fasciculus (UF) derived from tractography and the mean reaction time (RT) for regular words (REG).

7.2 Region of Interest Results

Mean FA values for each tract are presented in Table 7. A correlation between FA and age was run to rule out age as a confounding factor. The correlations were not significant for any of the stimulus types (see Table 8).

	Mean	SD	Range
Left AF	0.51	0.03	0.15
Left PLIC	0.64	0.02	0.08
Left IFOF	0.49	0.03	0.11
Left ILF	0.47	0.03	0.14
Left UF	0.46	0.04	0.24
Left Parietal	0.48	0.03	0.13

Table 7. Mean, standard deviation (SD), and range of fractional anisotropy (FA) values for the left hemisphere arcuate fasciculus (AF), posterior limb of the internal capsule (PLIC), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF) and parietal region of interest (ROI) obtained through ROI analysis.

	Age	p-value
Left AF	-0.119	0.522
Left PLIC	-0.215	0.246
Left IFOF	0.034	0.856
Left ILF	-0.002	0.990
Left UF	0.105	0.573
Left Parietal	-0.339	-0.062

Table 8. Pearson's correlation coefficients of age with the fractional anisotropy (FA) of the left hemisphere white matter tracts arcuate fasciculus (AF), posterior limb of the internal capsule (PLIC)), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF) and the parietal region of interest (ROI) obtained through ROI analysis.

7.2.1 Region of Interest Analysis: Dorsal White Matter Tracts

Correlational analyses found no significant relationship between the mean FA derived from ROI analysis of white matter tracts in the left hemisphere of the brain thought to underlie the dorsal processing stream and RT for reading regular words, pseudohomophones, and non-words (see Table 9; Figures 29-34).

	REG	PH	NW
Left AF	-0.169	-0.032	0.081
Left PLIC	-0.017	-0.067	0.077

Table 9. Pearson's correlation coefficients of the fractional anisotropy (FA) of the dorsal white matter tracts (arcuate fasciculus (AF) and posterior limb of the internal capsule (PLIC)) derived from region of interest (ROI) analysis and mean reaction times for regular words (REG), pseudohomophones (PH), and non-words (NW).

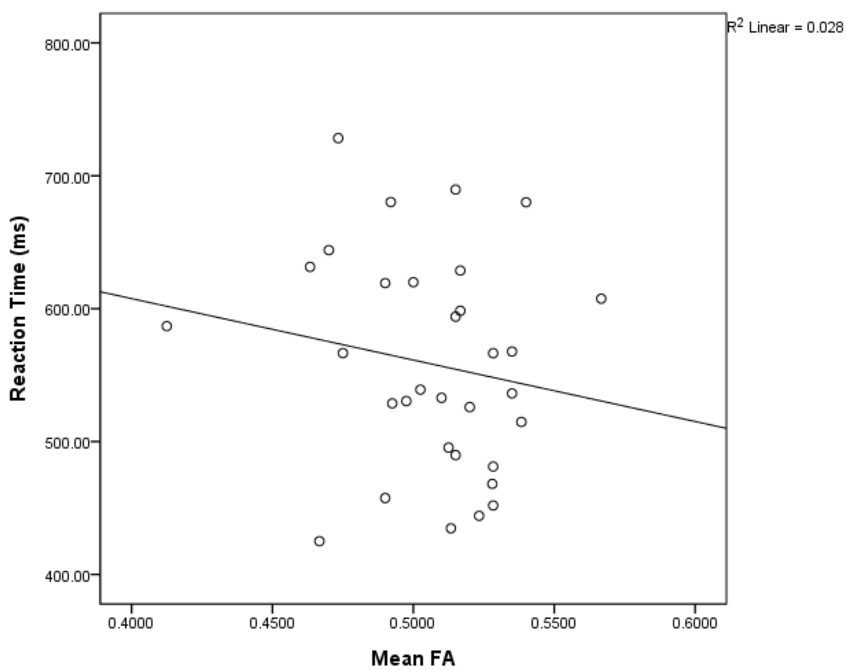


Figure 29. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

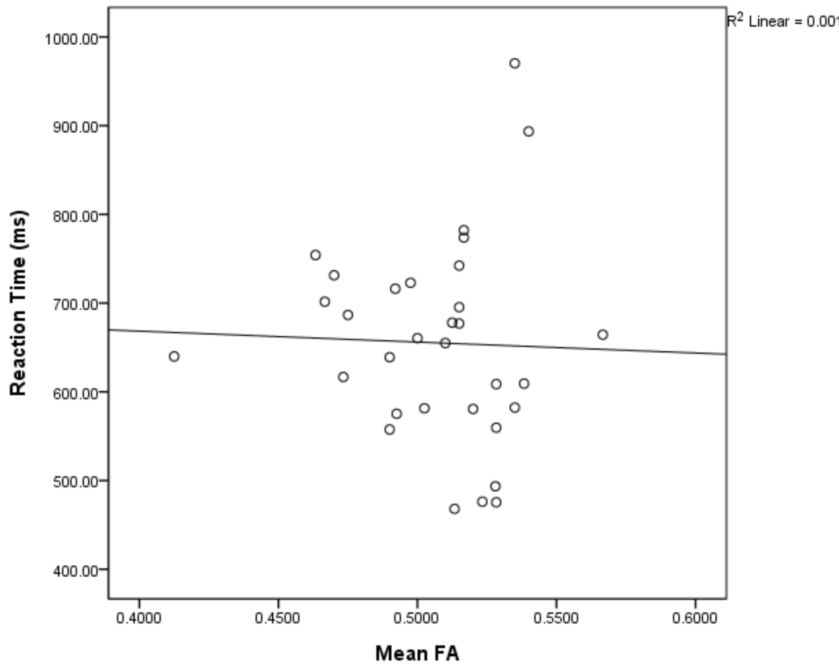


Figure 30. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from ROI analysis and the mean reaction time (RT) for pseudohomophones (PH).

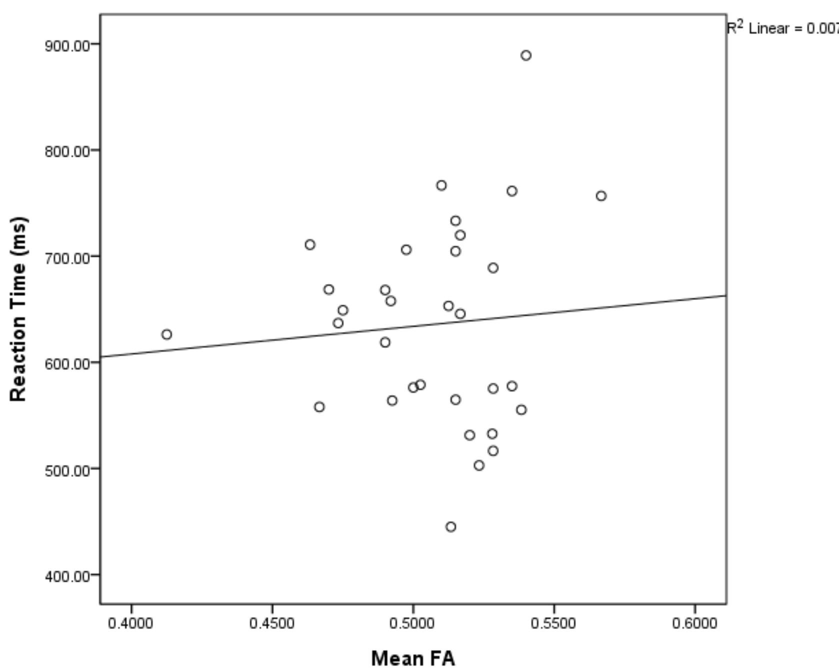


Figure 31. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left arcuate fasciculus (AF) derived from ROI analysis and the mean reaction time (RT) for non-words (NW).

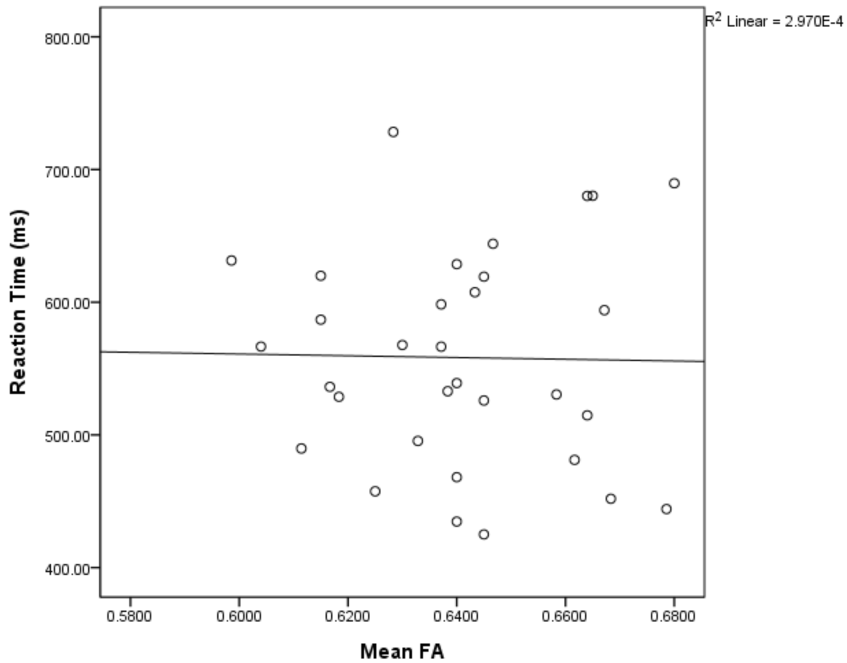


Figure 32. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

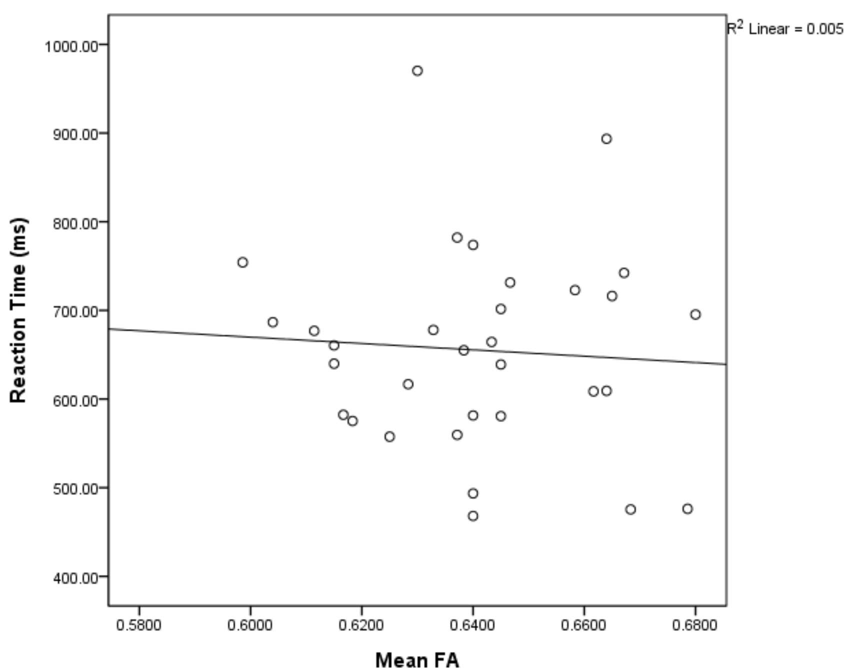


Figure 33. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from ROI analysis and the mean reaction time (RT) for pseudohomophones (PH).

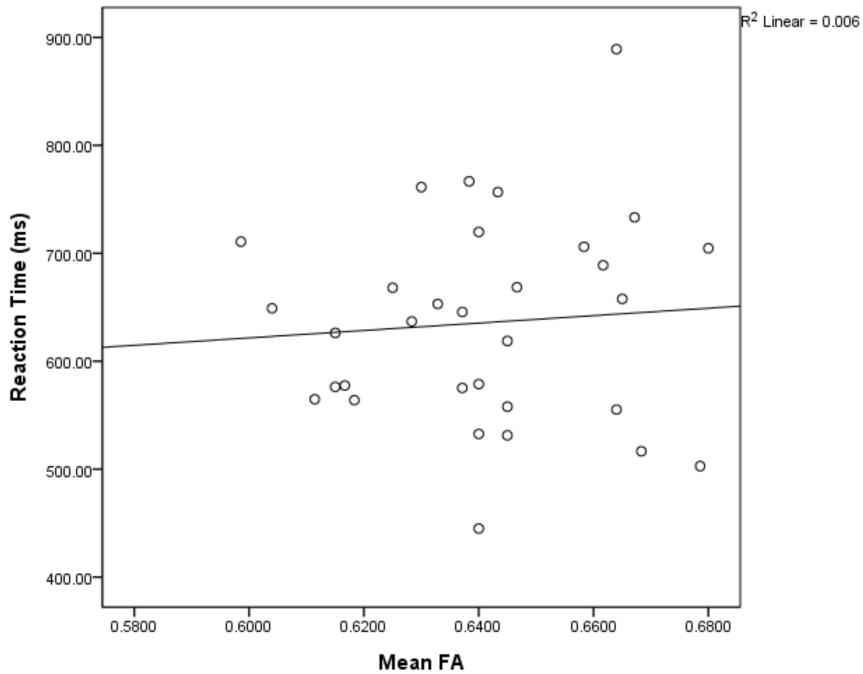


Figure 34. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left posterior limb of the internal capsule (PLIC) derived from ROI analysis and the mean reaction time (RT) for non-words (NW).

7.2.2 Region of Interest Analysis: Ventral White Matter Tracts

Correlational analyses found no significant relationship between the mean FA derived from tractography of white matter tracts in the left hemisphere of the brain thought to underlie the ventral processing stream and RT for reading exception and regular words (see Table 10; Figures 35-40). These results do not correspond with the results from analyses using mean FA derived from tractography.

	EXC	REG
Left ILF	-0.276	-0.214
Left IFOF	-0.190	-0.305
Left UF	-0.238	-0.191

Table 10. Pearson's correlation coefficients of the fractional anisotropy (FA) of the ventral white matter tracts (inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus (UF)) derived from region of interest (ROI) analysis and mean reaction times for exception words (EXC) and regular words (REG).

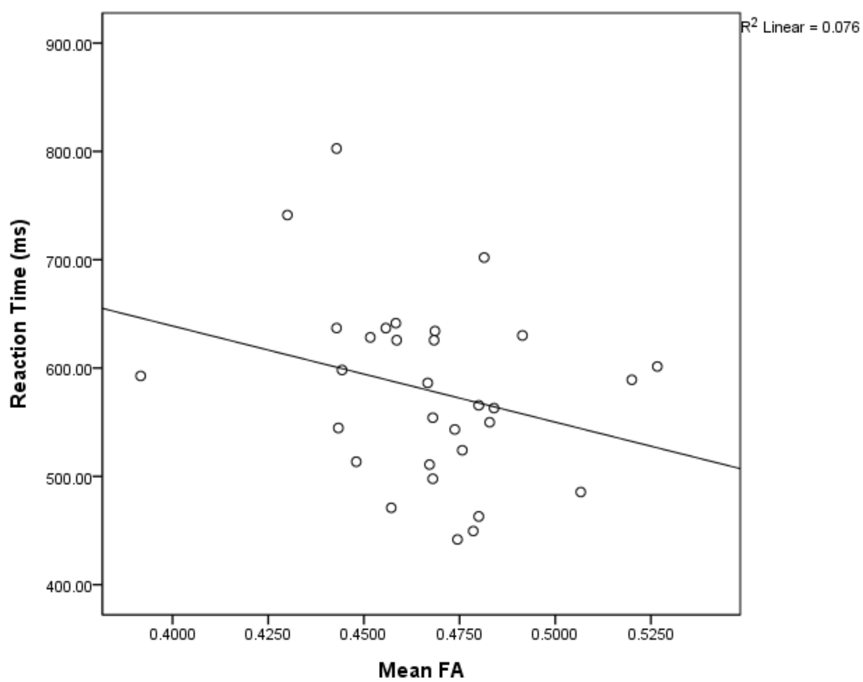


Figure 35. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior longitudinal fasciculus (ILF) derived from ROI analysis and the mean reaction time (RT) for exception words (EXC).

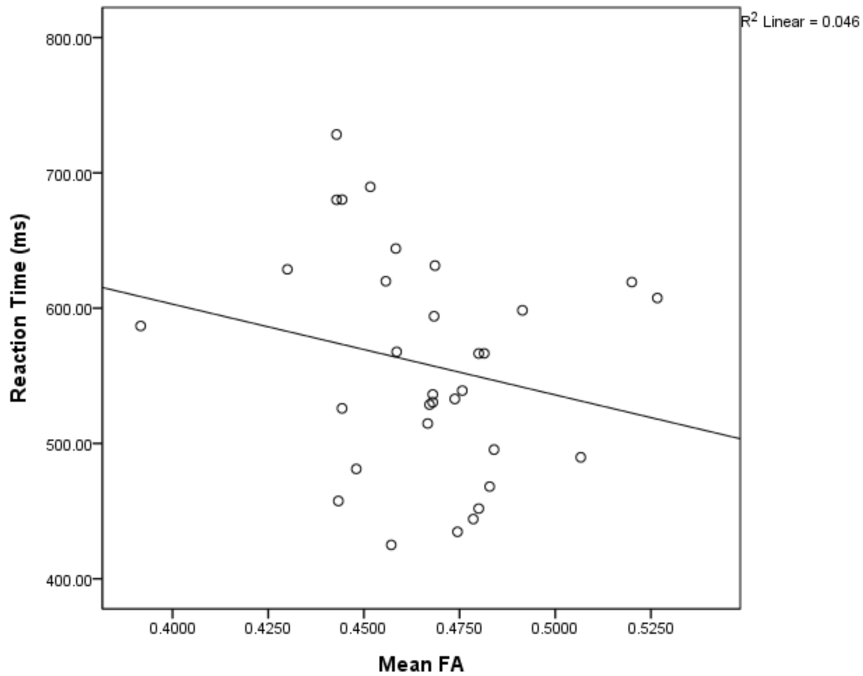


Figure 36. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior longitudinal fasciculus (ILF) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

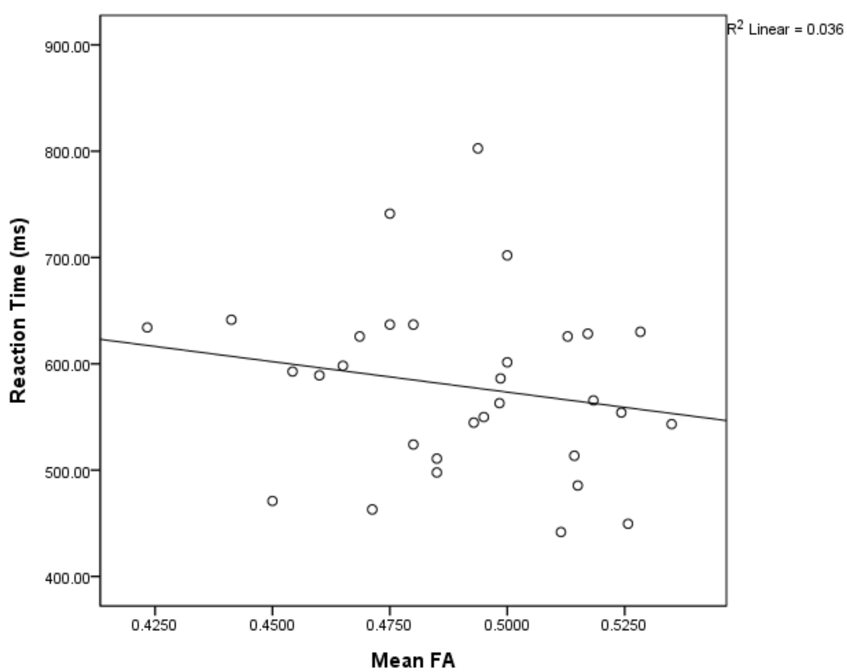


Figure 37. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior fronto-occipital fasciculus (IFOF) derived from ROI analysis and the mean reaction time (RT) for exception words (EXC).

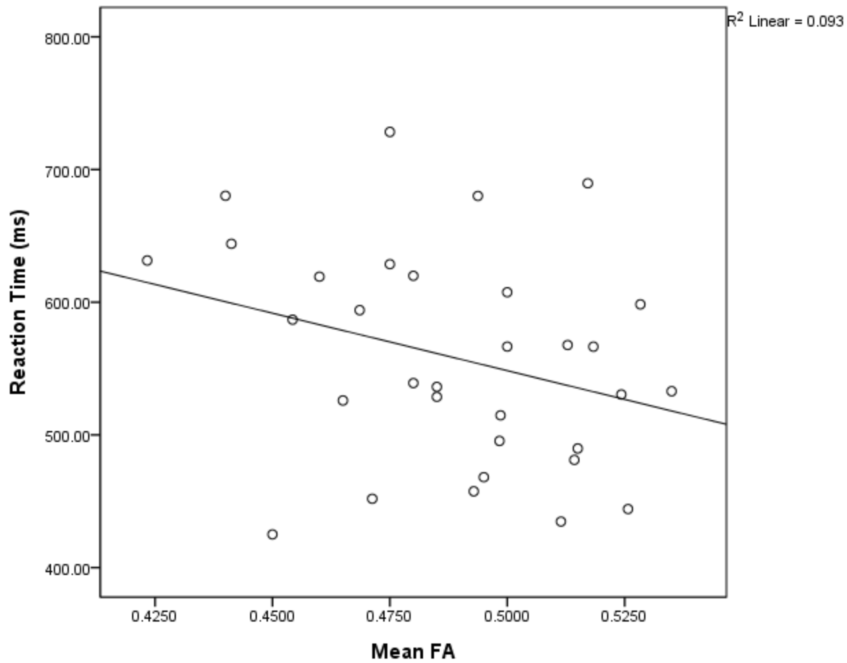


Figure 38. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left inferior fronto-occipital fasciculus (IFOF) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

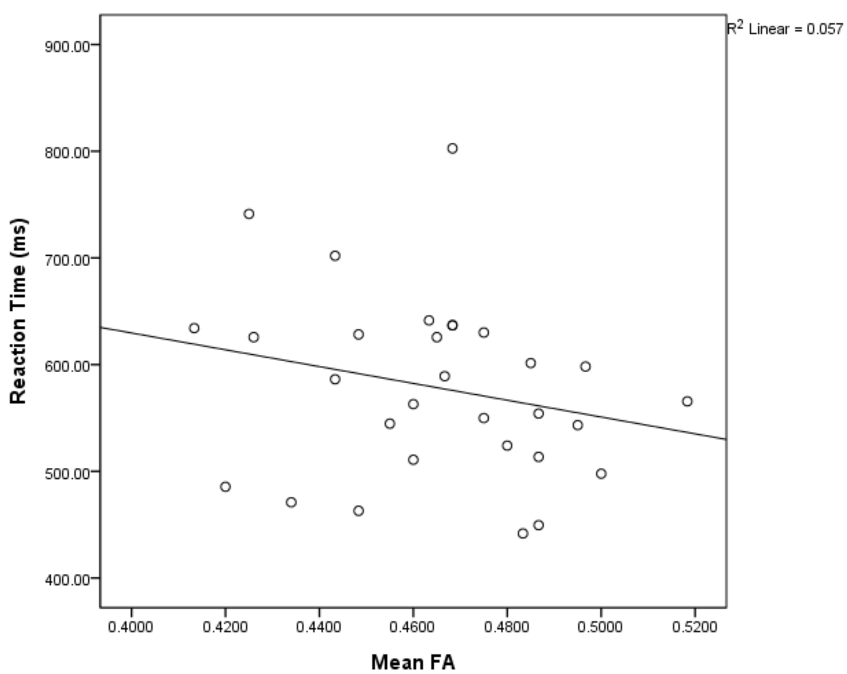


Figure 39. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left uncinate fasciculus (UF) derived from ROI analysis and the mean reaction time (RT) for exception words (EXC).

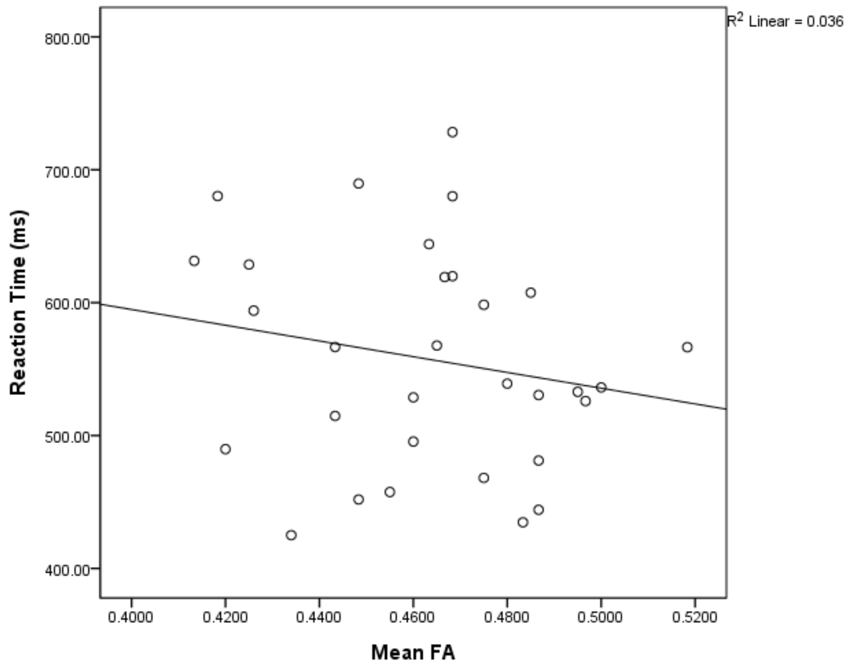


Figure 40. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left uncinate fasciculus (UF) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

7.2.3 Region of Interest Analysis: Parietal ROI

This study also examined the correlation between the mean FA of the parietal ROI defined by Gold et al. (2007) and mean RT for overt naming of exception words, regular words, pseudohomophones, and non-words. No correlational relationships were observed between the mean FA obtained from the parietal ROI and the RT for overt naming of the different word types (see Table 11; Figures 41-44).

	EXC	REG	PH	NW
Left Parietal	-0.159	-0.224	-0.254	-0.229

Table 11. Pearson’s correlation coefficients of the fractional anisotropy (FA) of the left parietal region of interest (ROI) and mean reaction times for exception words (EXC), regular words (REG), pseudohomophones (PH), and non-words (NW).

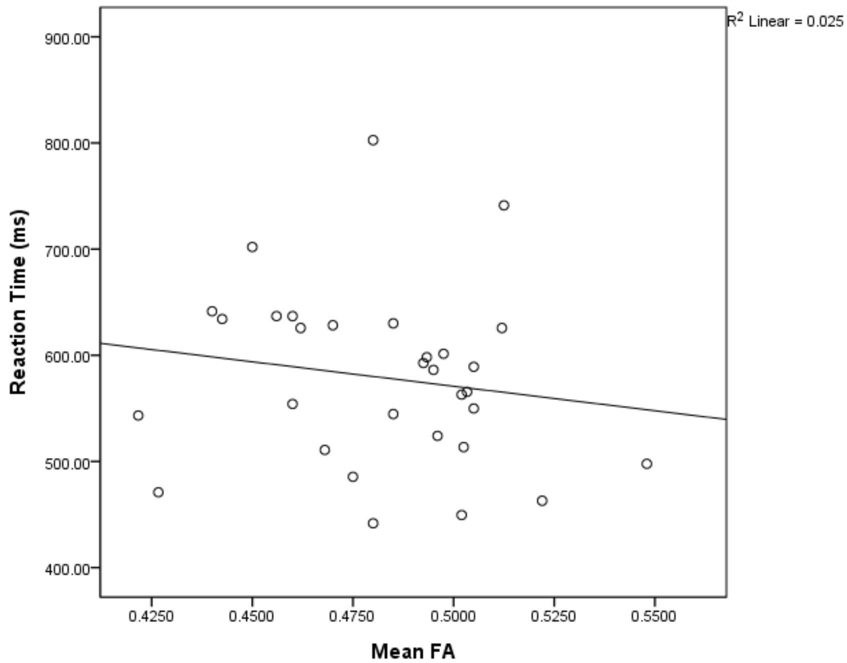


Figure 41. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left parietal region of interest (ROI) derived from ROI analysis and the mean reaction time (RT) for exception words (EXC).

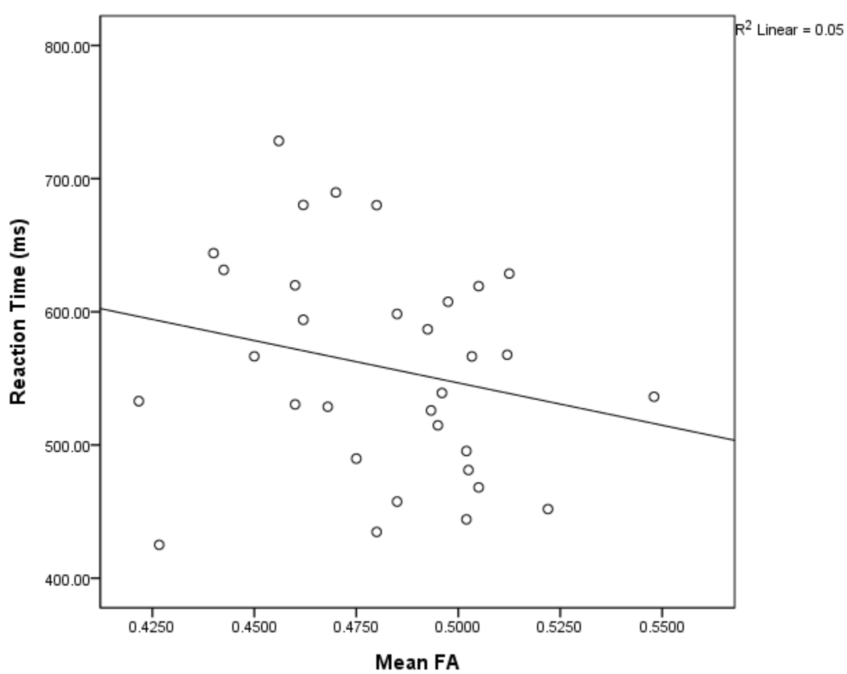


Figure 42. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left parietal region of interest (ROI) derived from ROI analysis and the mean reaction time (RT) for regular words (REG).

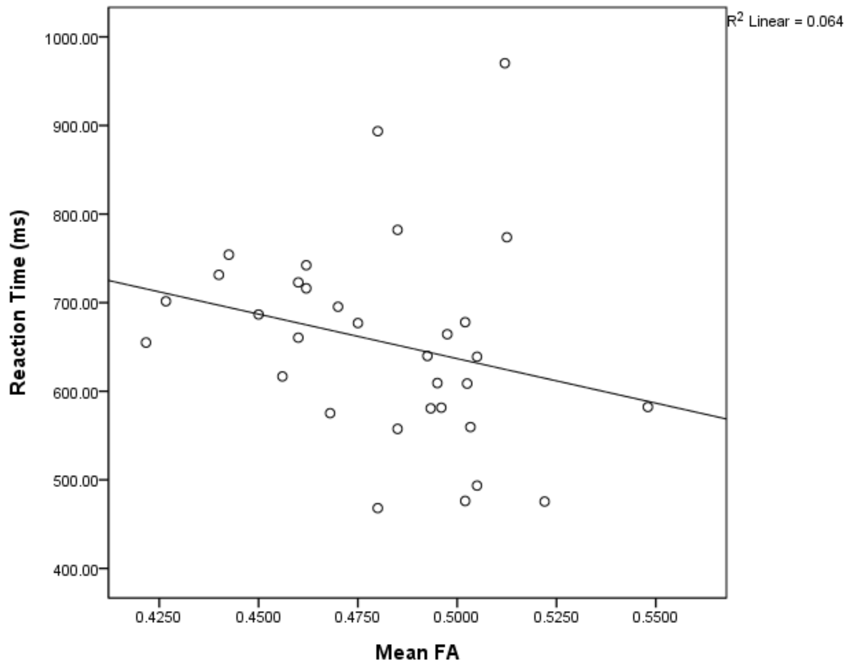


Figure 43. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left parietal region of interest (ROI) derived from ROI analysis and the mean reaction time (RT) for pseudohomophones (PH).

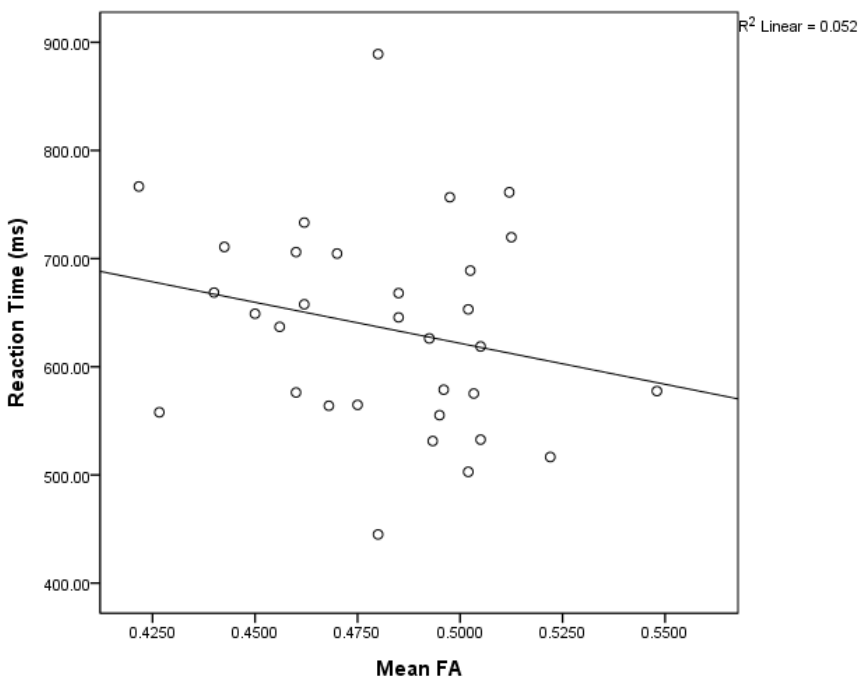


Figure 44. Scatter plot of the correlational relationship between the mean fractional anisotropy (FA) of the left parietal region of interest (ROI) derived from ROI analysis and the mean reaction time (RT) for non-words (NW).

7.3.1 Hybrid of TBSS and VBA: Exception Words

The exploratory hybrid analysis combining Tract-Based Spatial Statistics (TBSS) and voxel based analysis (VBA) revealed 2 clusters with significant correlations between FA and the RT for overt naming of exception words (see Table 12; Figure 45). These were located in the inferior portion of the right frontal lobe (in the region consistent with projections of the right IFOF) and the left parietal lobe (in a region consistent with the left PLIC or the left superior longitudinal fasciculus (SLF)).

Cluster size (# of voxels)	MNI coordinates of most correlated voxel	Anatomical location	t-value	p-value
244	19, 12, -7	Right frontal lobe	5.22	<0.001
125	-29, -25, 36	Left parietal lobe	4.28	<0.001

Table 12. Location and MNI coordinates of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of exception words.

a) Right frontal lobe b) Left parietal lobe

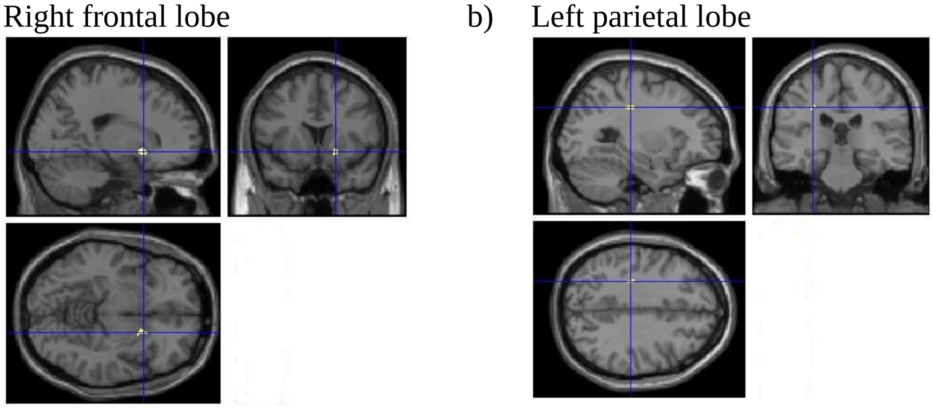


Figure 45. Location of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of exception words, a) in the right frontal lobe, b) left parietal lobe.

7.3.2 Hybrid of TBSS and VBA: Regular Words

The exploratory hybrid analysis combining Tract-Based Spatial Statistics (TBSS) and voxel based analysis (VBA) revealed 3 clusters with significant correlations between FA and the RT for overt naming of regular words (see Table 13; Figure 46). These were located in the left medial temporal lobe (in the region of the hippocampal white matter) and the superior portion of the right frontal lobe (in regions consistent with the centrum semiovale (CS)).

Cluster size (# of voxels)	MNI coordinates of most correlated voxel	Anatomical location	t-value	p-value
175	-27, -32, -7	Left temporal lobe	5.52	<0.001
107	6, 9, 53	Right frontal lobe	4.67	<0.001
90	42, -11, 46	Right frontal lobe	4.27	<0.001

Table 13. Location and MNI coordinates of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of regular words.

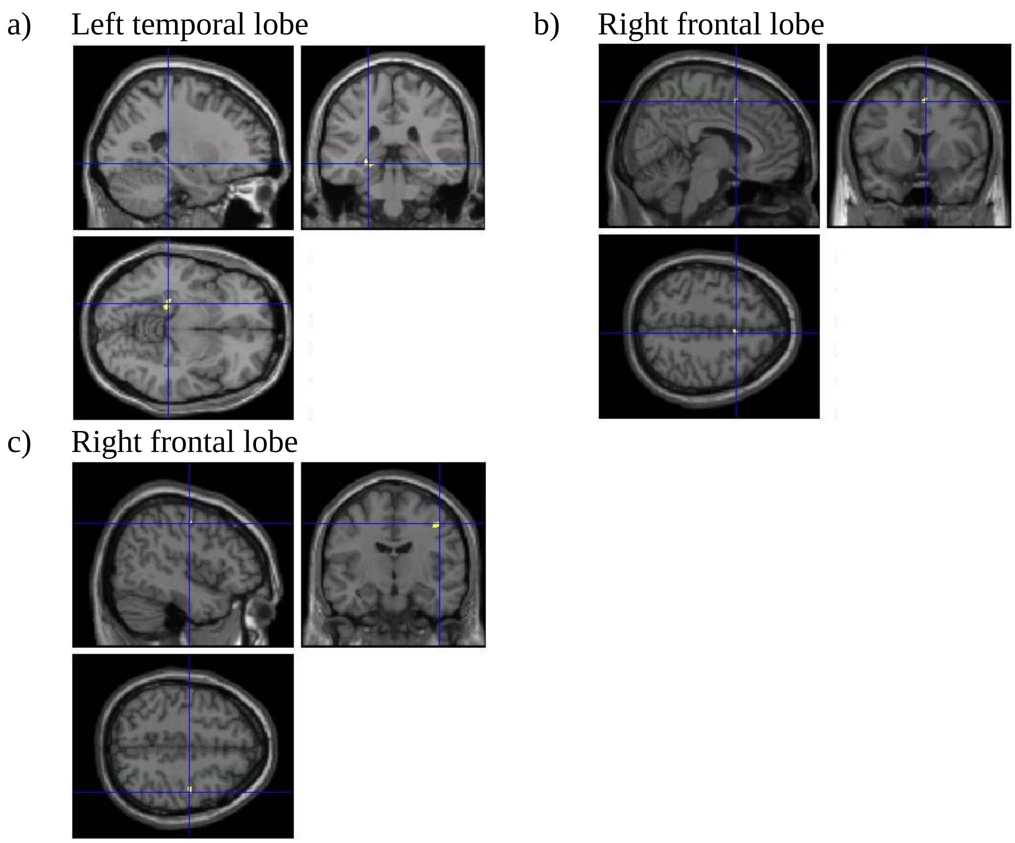


Figure 46. Location of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of regular words in the a) left temporal lobe, b) right frontal lobe, c) right frontal lobe

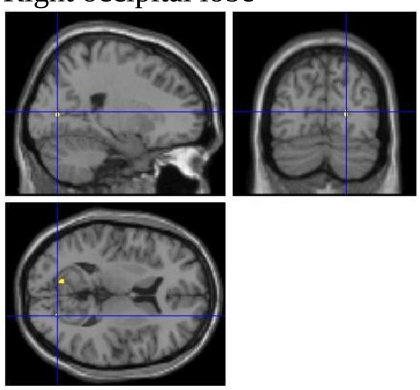
7.3.3 Hybrid of TBSS and VBA: Pseudohomophones

The exploratory hybrid analysis combining Tract-Based Spatial Statistics (TBSS) and voxel based analysis (VBA) revealed 3 clusters with significant correlations between FA and the RT for overt naming of pseudohomophones (see Table 14; Figure 47). One was located in the medial portion of the left inferior frontal lobe (in a region consistent with projections of the UF). The remaining two clusters were located in the white matter of the cuneus/lingual gyrus of the left and right occipital lobes (in regions that could be consistent with the white matter projections of the IFOF or the ILF).

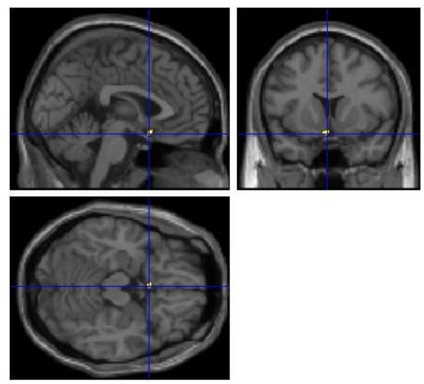
Cluster size (# of voxels)	MNI coordinates of most correlated voxel	Anatomical location	t-value	p-value
84	21, -76, 8	Right occipital lobe	6.05	<0.001
104	-2, 13, -16	Left frontal lobe	5.01	<0.001
101	-12, -71, 11	Left occipital lobe	4.37	<0.001

Table 14. Location and MNI coordinates of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of pseudohomophones.

a) Right occipital lobe



b) Left frontal lobe



c) Left occipital lobe

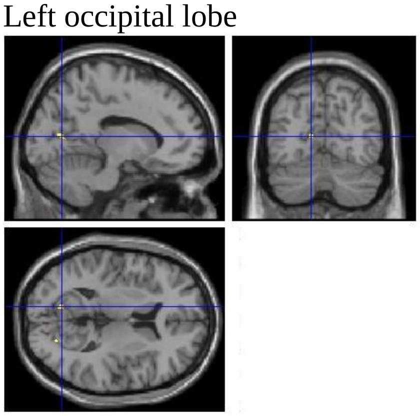


Figure 47. Location of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of pseudohomophones in the a) right occipital lobe, b) left frontal lobe, c) left occipital lobe.

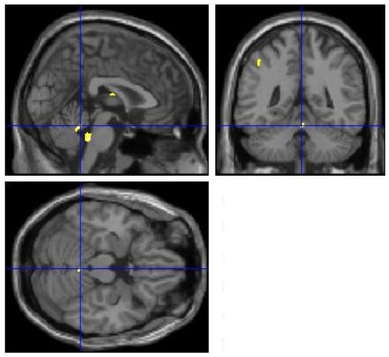
7.3.4 Hybrid of TBSS and VBA: Non-Words

The exploratory hybrid analysis combining Tract-Based Spatial Statistics (TBSS) and voxel based analysis (VBA) revealed 9 clusters with significant correlations between FA and the RT for overt naming of non-words (see Table 15; Figure 48). The clusters were located in regions consistent with the left and right anterior corona radiata (ACR), the left and right thalamus, the left and right cerebral peduncles, the left PLIC, and the superior cerebellar peduncle.

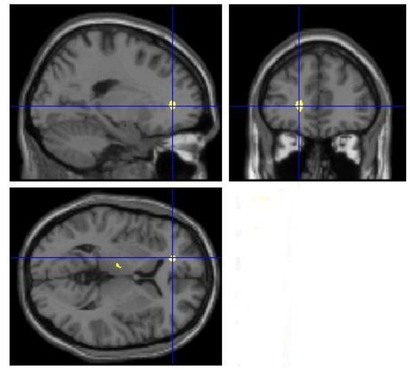
Cluster size (# of voxels)	MNI coordinates of most correlated voxel	Anatomical location	t-value	p-value
95	3, -48, -22	Cerebellum	5.33	<0.001
328	-18, 40, 5	Left frontal lobe	5.13	<0.001
243	-10, -26, -11	Left diencephalon	5.00	<0.001
150	16, -17, -14	Right midbrain	4.88	<0.001
183	-15, 30, 22	Left frontal lobe	4.68	<0.001
164	-8, -6, -10	Left midbrain	4.56	<0.001
81	-43, -44, 50	Left parietal lobe	4.34	<0.001
84	1, -11, 13	Right diencephalon	4.16	<0.001
85	20, 29, 27	Right frontal lobe	4.09	<0.001

Table 15. Location and MNI coordinates of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of non-words.

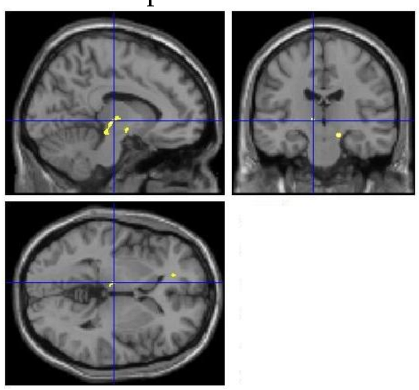
a) Cerebellum



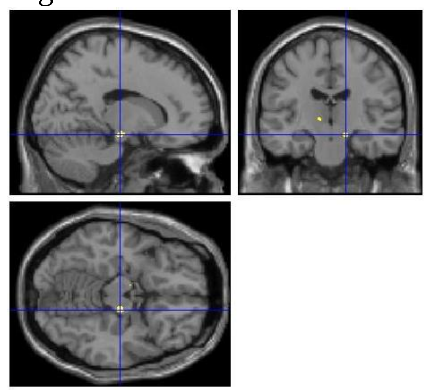
b) Left frontal lobe



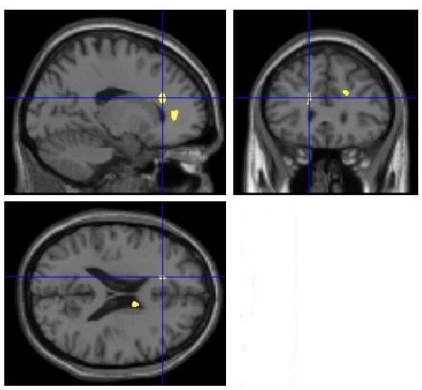
c) Left diencephalon



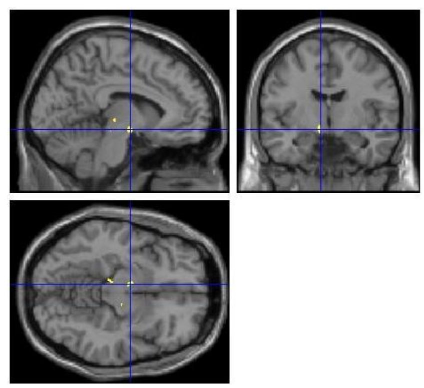
d) Right midbrain



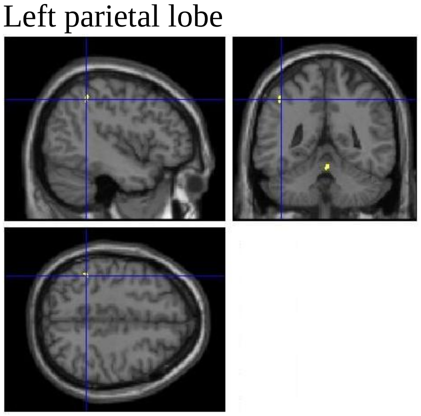
e) Left frontal lobe



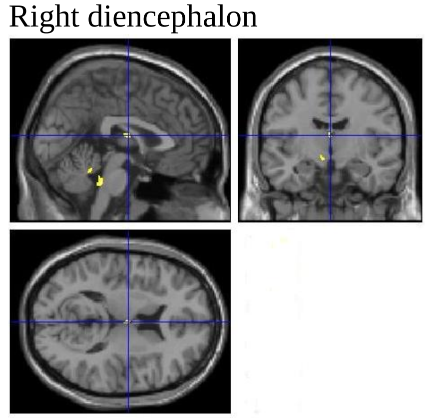
f) Left midbrain



g) Left parietal lobe



h) Right diencephalon



i) Right frontal lobe

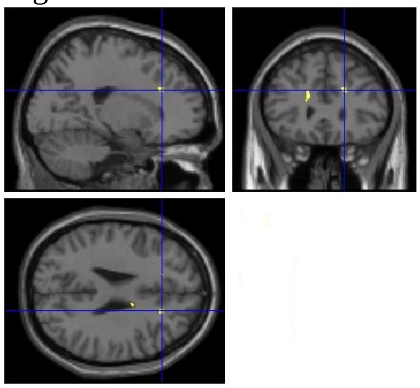


Figure 48. Location of clusters with significant correlation between fractional anisotropy (FA) and reaction time (RT) for overt naming of non-words in the a) cerebellum, b) left frontal lobe, c) left diencephalon, d) right midbrain, e) left frontal lobe, f) left midbrain, g) left parietal lobe, h) right diencephalon, i) right frontal lobe.

8. Discussion

Overall, the results of this study provide mixed support for current theories which suggest that stimuli processed in the cortical regions of the ventral and dorsal processing stream (e.g., exception words and pseudohomophones, respectively) are associated with the underlying white matter tracts in the corresponding ventral (i.e., IFOF, ILF, and UF) and dorsal regions (i.e., AF and PLIC), respectively. Whereas tractography analysis found that RTs for naming of exception and regular words were correlated with the FA of left UF, supporting the theories that the left hemisphere UF plays a role in the ventral processing stream, the results of ROI analysis and the hybrid approach did not support such findings. In addition, while the hybrid approach found that RTs for reading non-words were correlated with a region of white matter consistent with the left PLIC, the findings were not supported by ROI and tractography analysis.

8.1 Tractography Analysis

Tractography analysis found a significant, negative correlation between the naming of exception and regular words with the mean FA of the left hemisphere UF, a ventral white matter tract. These results partially support the hypothesis that there was a relationship between stimuli that typically activate the ventral stream and the underlying white matter, specifically the UF. These results also support the theory from previous research that the UF may be potentially important for basic language processes (Papagno et al., 2011; Duffau et al., 2009). However, the current results do not support the hypothesis that there was a relationship between stimuli that typically activate the ventral stream and the IFOF and ILF, nor was there a relationship between stimuli that typically activate the dorsal stream and the left AF and PLIC. The current results do not support previous research that the IFOF, ILF, AF and PLIC may be important for reading.

Although tractography had been used extensively to discover the origin, pathway, and termination of specific white matter tracts (Turken & Dronkers, 2011; Bernal & Altman, 2009; Yeatman et al., 2012) and to map tracts passing through specific ROIs (Beaulieu et al., 2005; Niogi & McCandliss 2006; Colnat-Coulbois et al., 2010), studies that have directly used tractography to examine the relationship between white matter integrity and reading processes are limited (Yeatman et al., 2011; Vandermosten et al., 2012). It is possible that tractography may not be the most effective method for uncovering relationships between white matter integrity and behavioural data. Previous studies using VBA analysis have found that FA derived from only portions of white matter tracts in the left temporo-parietal and fronto-temporal regions correlated with reading ability (Klingberg et al., 2000; Deutsch et al., 2005; Steinbrink et al., 2008; Beaulieu et al., 2005). In the current study, tractography analysis derived the mean FA from the entire reconstructed tract. Considering the fact that the IFOF, ILF, AF and PLIC are all large white matter tracts, it is possible that by examining the entire tract, any correlations with small portions of white matter within the reconstructed tracts are obscured. Although some studies have found a relationship between the FA of the left AF and phonological processing (Yeatman et al., 2011; Vandermosten et al., 2012) and a relationship between the FA of the left IFOF and orthographic processing (Vandermosten et al., 2012), the present study was not able to corroborate those findings. This may be due to several factors such as data processing, differences in participant population, and perhaps most importantly, differences in the nature of the behavioural measures. To illustrate, Vandermosten et al., (2012) used two separate tasks to assess phoneme awareness: a phoneme deletion task and a spoonerism task. Both tasks involved auditory presentation of the stimuli, therefore these tasks also involve other processes such as auditory processing, attention, and working memory in addition to phonological processing. These processes are different from that used during overt reading and may have made a difference in detecting a correlation between reading processes and FA.

8.2 Region of Interest Analysis

Contrary to the hypothesis, the results of ROI analysis did not detect a relationship between exceptions and regular words and the underlying white matter such as the left IFOF, ILF and the UF, nor did the current results detect a relationship between pseudohomophones, non-words and regular words and the underlying white matter such as the left AF and the PLIC. The results from this type of analysis were not able to corroborate previous research that the UF, IFOF, ILF, AF and PLIC may be related to reading.

Some possibilities that might account for the discrepancy between the results from this study and previous research are the differences in methodology for tracing the ROI. In the present study, ROI was manually traced on multiple slices on FA maps by referencing a white matter atlas and the FA was averaged. It is possible that the ROIs may not have included the portions of white matter that correlate with reading; conversely the ROIs may have been too large and thus obscured any correlation between white matter microstructure and reading. Furthermore, this method of ROI selection may not be the most reliably reproducible considering the fact that the intra-rater statics were not significant for two of the tracts, the ILF and UF. In contrast, prior research had used different methods to select ROIs, such as using Reproducible Objective Quantification Scheme (a semi-automated process based on user-selected seed pixels) (Niogi & McCandliss, 2006), using software written in Interactive Data Language (Niogi & McCandliss, 2006), and taking the average of three attempts at a manually drawn ROI on colour maps (Rollins et al., 2009).

In addition, the type of correlational analysis used may have affected the outcome of this study. The present study used the parametric test of correlation (i.e., Pearson's r) when performing statistical analysis on FA values derived from ROI analysis. In contrast, a few studies used the non-parametric Spearman's rank correlation when performing analysis on FA values derived from ROI analysis (Gold et al., 2007; Niogi & McCandliss, 2006). Gold et al. (2007) suggested that non-parametric tests of correlation, such as Spearman rank correlation might be preferable to Pearson correlation due to the possibility that the FA distribution across individuals may not follow a normal distribution. Differences in the type of correlational analysis used would likely influence the degree to which the results of the present study correspond with that of previous studies.

The present study also attempted to investigate whether a correlation existed between the FA of the parietal ROI outlined by Gold et al. (2007) and RT for naming of different word types. The parietal ROI was of interest due to the fact that Gold et al. (2007) found a negative correlation between lexical decision RT and the mean FA of a parietal ROI. However, the results from the current study failed to detect a correlation between the mean FA of the parietal ROI and the RTs for overt naming of exception words, regular words, pseudohomophones, or non-words. A potential explanation for the difference between the results obtained by Gold et al. (2007) and the current study is the use of different statistical tests (see Appendix A) Another possible explanation for the difference in results is that the findings by Gold et al. (2007) were task dependent. In the study by Gold et al. (2007), participants were requested to make a lexical decision (i.e., whether a presented letter string is a word or non-word using a button press); as such the results may not be generalizable to reading tasks involving phonological processing. In contrast, the present study asked participants to perform overt naming of the letter-strings presented; the stimuli included pseudohomophones, which is a phonologically demanding task.

8.3 Hybrid Analysis Combining TBSS and VBA

Using the hybrid approach, correlations were found between RTs for overt naming of different word types and the structural data of white matter tracts in the brain. The RTs for overt naming of exception words were found to be correlated with 2 clusters, one located in an area consistent with the right IFOF, and the other in an area consistent with the left PLIC or the left superior longitudinal fasciculus (SLF). The correlation found between the white matter of the right inferior frontal lobe and RT for exception words appears to suggest a potential role for the right frontal lobe white matter in reading processes. The location of the right frontal lobe cluster is in the proximity of a cluster associated with reading performance that was reported by Rimrodt et al. (2010). The idea that right frontal lobe may be involved in reading processes is also consistent with existing fMRI evidence that have found right frontal lobe activation during reading and decoding of exception words (Binder et al., 2005; Senaha et al., 2005; Levy et al., 2008; De Diego Balaguer et al., 2006; Osipowicz et al., 2011). The left parietal lobe cluster that also correlated with exception word RT, was located in the proximity of the white matter in the left temporo-parietal region that have been reported to correlate with reading ability (Klingberg et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005; Niogi & McCandliss 2006). Taken together these findings support theories that suggest the left temporo-parietal white matter may play an important role in reading.

The RTs for overt naming of regular words were found to correlate with 3 clusters, one located in the left hippocampus and the remaining two located in the right centrum semiovale (CS) in the fronto-parietal region. The correlation found between the white matter of the left hippocampus and regular word RT suggests a potential role for the hippocampal white matter in the ventral stream. Previous research on tractography of the hippocampus, has reported connections from the occipital regions to the hippocampus, from the hippocampus to the amygdala, which in turn is connected to the orbitofrontal cortex via the uncinate fasciculus (Colnat-Coulbois et al., 2010). This observation may indicate a potential alternative to the white matter tracts that were hypothesized to underlie the ventral processing stream. Furthermore, the fibres of the ILF have also been found to extend medially into regions close to the hippocampus and amygdala (Catani et al., 2003). It is therefore possible that there exist connections between the hippocampal white matter and the ILF, which might explain the correlation with regular word RT. An alternative but less likely explanation is that the correlation between the left hippocampal white matter and regular word RT may indicate a role for the hippocampus in reading processes. Previous studies investigating the role of hippocampus in language processes have reported mixed results. Hippocampal involvement have been reported during naming (Howell et al., 1994), word retrieval (De Diego balaguer et al., 2006), fluency (Gleissner & Elger, 2001; Pihlajamaki et al., 2000), and comprehension (Bartha et al., 2004; 2005; Friederici, 2002). However, no activation of the hippocampus was observed during covert non-lexical or lexical decoding of single words (Osipowicz et al., 2011). The correlation between the right centrum semioval (CS) and regular word RT suggest a potential role for the right hemisphere dorsal white matter in reading. This corroborates the results of other studies that have also found a correlation between reading ability and the integrity of the right dorsal white matter (Klingberg et al., 2000; Deutch et al., 2005; Beaulieu et al., 2005; Niogi & McCandliss, 2006; Richards et al., 2008; Odegard et al., 2009; Rimrodt et al., 2010).

RTs for naming of pseudohomophones were correlated with 3 clusters. One was located in the left UF, and the remaining two were located in bilateral occipital regions consistent with the left and right IFOF or ILF. The left UF have long been suspected to play a role in language processing, especially in lexical retrieval, semantic associations, and naming (Grossman et al., 2004; Lu et al., 2002). Nevertheless, the finding of a correlation relationship between pseudohomophone RT and the left UF was unexpected given that the UF was not hypothesized to play a role in phonological processing. In previous DTI studies, performance on reading of pseudowords (e.g., Woodcock-Johnson Word Attack Subtest) have been correlated with FA in the left temporoparietal region (Deutsch et al., 2005; Klingberg et al., 2000; Odegard et al., 2009; Steinbrink et al., 2008) rather than with the left UF. This result does not support the hypothesis that there is a relationship between stimuli that typically activate the dorsal stream and the underlying white matter in the dorsal region. However, neuroimaging studies have reported activation in the left inferior frontal gyrus during tasks that require heavy phonological processing (Salmelin et al., 1996; Rumsey et al., 1997; Shaywitz et al., 1998; Richards et al., 1998; Brunswick et al., 1999; Levy et al., 2008). Considering the fact the UF underlies this region, it is conceivable that the left UF is involved in phonological processing. Another explanation for this finding is the possibility that the UF is playing a role in phonological-lexical processing, which is activated when a letter string sounds like a real word. The insular cortex has been reported as being sensitive to phonological-lexical processing (Borowsky et al., 2006; Cummine et al., 2012) and it is located just medial to the inferior frontal gyrus. Correlation of pseudohomophone RT with the FA of white matter in the left and right occipital lobe in the region of the cuneus/lingual gyrus suggest involvement of the left and right hemisphere IFOF and ILF in reading processes. These two occipital clusters were located in the proximity of clusters reported by a prior DTI study to be correlated with reading ability (Richards et al., 2008). Furthermore, fMRI studies have reported bilateral occipital lobe activation during reading tasks; Levy et al. (2008) concluded that bilateral involvement of the occipital lobes in reading tasks was due to visual processing. Thus, it is possible that the regions in the bilateral occipital lobes that demonstrated correlation with pseudohomophone RT may be more indicative of the white matter tracts that underlie visual processing than phonological processing.

The RTs for naming of non-words were correlated with 9 clusters. Clusters were located in the left anterior corona radiata (ACR), the right ACR, bilateral thalami, both of the cerebral peduncles, the cerebellar peduncle, and the left PLIC. The correlation found between the left and right ACR and non-word RT suggest a potential role for the ACR in reading processes. The left ACR has been reported to correlate with reading ability in both English (Beaulieu et al., 2005) and Chinese (Qiu et al., 2008). The FA values in bilateral ACR have also been found to correlate with working memory (Nagy et al., 2004; Olesen et al., 2003) and digit recall (Niogi & McCandliss, 2006). In addition, fMRI studies have found activation of the bilateral middle frontal gyri during word and pseudo-word reading (Levy et al., 2008). Greater grey matter volume in bilateral medial frontal regions has been associated with better non-word reading (Pernet et al., 2009). Considering that the ACR is the white matter that underlies the middle frontal gyrus, it may have a role in reading processes. Alternatively, the correlation between bilateral ACR and non-word RT may be due to the ACR's involvement with working memory rather than reading. The correlation found between the white matter of both thalami and non-word RT suggested a potential role for thalamic connections in reading processes. The thalamus has connections with a number of cortical and subcortical regions (Stein et al., 2000). Furthermore, bilateral activation of the thalamus has been seen in a variety of language tasks such as lexical decision, reading and working memory (for a review, see Llano, 2012). In the current study, the correlation between non-word RT and the white matter of both cerebral peduncles and the left PLIC suggested the involvement of the left and right dorsal white matter in reading processes, as the white matter fibres running through the cerebral peduncles extends superiorly through the internal capsule, to the corona radiata and then to the centrum semiovale. The cerebral peduncles also projects to the thalamus and thus the correlation between the cerebral peduncles and non-word RT may be related to the correlation found between the thalamus and non-word RT. Finally, the correlation found between the superior cerebellar peduncle and non-word RT suggested a role for the cerebellar white matter in reading. The superior cerebellar peduncle contains fibres passing from the cerebellum to the midbrain, including the thalamus. Furthermore, fMRI studies have found cerebellar activation during reading of words and non-words (Fullbright et al., 1999; Senaha et al., 2005), which supports the involvement of the cerebellum and by extension, the cerebellar white matter in reading. Additionally, structural differences in the cerebellum between dyslexic readers and typically readers are some of the most consistent findings in neuroimaging studies (Eckert et al., 2003), for instance increased gray matter volume in the cerebellum has been associated with faster word reading (Kronbichler et al., 2008).

Overall, the hybrid approach provided no evidence to support the hypothesis that there is a relationship between stimuli that typically activate the ventral stream and the underlying white matter in the ventral region. To illustrate, none of the clusters that correlated with exception word RT were located in regions that are associated with the left IFOF, ILF, and UF. This finding is consistent with results from ROI analysis in which no correlational relationship was detected between FA of left hemisphere white matter and RTs for exception words. However, this result contradicted the current finding from tractography analysis indicating a negative correlation between exception word RT and the left UF. Investigation of the clusters that correlated with regular word RT showed that none of them were located in regions associated with the left IFOF, ILF, and UF, nor were they located in regions associated with the left hemisphere dorsal white matter (AF, and PLIC). This does not support the hypothesis that the left ILF, UF, and IFOF underlie the ventral processing stream, nor does it provide support for the hypothesis that the left AF and PLIC underlie the dorsal processing stream. This result was consistent with the findings from the ROI analysis that there is no correlational relationship between RT for naming of regular words and left hemisphere ventral and dorsal white matter. However, it contradicted the finding from tractography analysis of a negative correlation between RT for naming of regular words and the left UF.

The hybrid analysis provided mixed support for the hypothesis that there is a relationship between stimuli that typically activate the dorsal stream and the underlying white matter in the dorsal region. The results for the pseudohomophones did not support the hypothesis due to the fact that none of the clusters were located in the left AF or PLIC. This was consistent with findings from the ROI and tractography analyses, which had found no correlation between RT for pseudohomophones and the FA of left hemisphere dorsal tracts. In contrast the results for the non-words did provide some evidence to support the hypothesis. The RTs for overt naming of non-words were found to correlate with a cluster that was consistent with projections of the left PLIC. This result was inconsistent with the findings from the ROI and tractography analyses, which found no correlation between RT for non-words and the FA of left hemisphere dorsal white matter.

8.4 Summary

In this study, it was hypothesized that there is a relationship between stimuli that typically activated the ventral stream and the underlying white matter tracts in the ventral region and that there is a relationship between stimuli that typically activate the dorsal stream and the underlying white matter tracts in the dorsal region. This hypothesis was formed based on existing understanding of the dual route model of reading and on previous research examining the connection between structural integrity of the left hemisphere white matter and reading. Three different methods of DTI analysis were employed to test the hypothesis and examine the relationship between reading and white matter structural integrity: tractography, ROI analysis, and an exploratory approach combining TBSS with VBA. Unexpectedly, there was little agreement in results between the three different methods. The tractography analysis provided support to suggest that the left UF played a role in ventral stream. In conjunction with the TBSS analysis, it appears that the UF is more explicitly involved in phonological-lexical processing. The ROI analysis proved to be fairly variable and provided little to no support for the hypotheses. Finally the TBSS analysis provided some support to suggest that the left PLIC is related to the dorsal stream. Although the results of this study cannot fully support the hypothesis, it does indicate that the relationship between reading processes and the underlying white matter tracts is highly complex and may involve far more than the five tracts measured in the current study.

The results of this study provided more information to aid our understanding of the relationship between white matter and reading and expands upon previous DTI research examining the relationship between the FA of white matter tracts and reading (Klingberg et al., 2000; Deutsch et al., 2005; Beaulieu et al., 2005; Niogi & McCandliss, 2006; Gold et al., 2007; Richards et al., 2008; Qiu et al., 2008; Steinbrink et al., 2008; Odegard et al., 2009; Rollins et al., 2009; Carter et al., 2009; Palmer et al., 2010; Rimrodt et al., 2010; Yeatman et al., 2011; Vandermosten et al., 2012). Much of the previous research focused on reading ability and used scores from standardized tests such as the Woodcook Reading Mastery Test (Klingberg et al., 2000; Beaulieu et al., 2005; Niogi & McCandliss, 2006;), the Woodcook Johnson Tests of Academic Achievement (Palmer et al., 2010), or a battery of standardized reading measures (Steinbrink et al., 2008; Carter et al., 2009; Odegarde et al., 2009; Rollins et al., 2009; Deutsch et al., 2005; Yeatman et al., 2011). In contrast, the present study used reaction time from overt naming tasks as measure of reading. It is likely that the reaction time for overt naming captures different aspects of the reading process than the standardized measures previously used and is a likely reason we find varying results to those previously reported.

Furthermore, as we already mentioned, a majority of previous studies examining the relationship between reading and the structural integrity of white matter tracts compared the reading ability of participants with dyslexia and normal participants (see: Klingberg et al., 2000; Deutsch et al., 2005; Niogi & McCandliss, 2006; Steinbrink et al., 2008; Odegard et al., 2009; Rollins et al., 2009; Carter et al., 2009; Vandermosten et al., 2012). Correlational analysis using two distinct groups of participants could be affected by the differences between the two groups. It is possible that the previously reported relationships may have been driven by between-group differences and the inclusion of two groups of participants in a single analysis. The current study attempted to determine whether those previously reported findings could be isolated using only healthy adult participants. While using a single group of participants removed the potentially confounding factor of between group differences, it resulted in reduced variability. Thus, it is possible that the reduced variability in reaction times for overt reading of word types among healthy adult participants may not be robust enough to be revealed in FA differences. Given that the results of the current study does not fully support a relationship between basic reading processes and the white matter tracts believed to underlie the dorsal and ventral processing streams, it is currently uncertain whether some of the previously reported findings are in fact tenable or whether they are an artefact of the inclusion of two groups. In addition, some of the other studies that examined white matter connectivity and reading used participants with brain tumour (see: Palmer et al., 2010; Mandonnet et al., 2007; Duffau et al., 2009; Epelbaum et al., 2008; Papagno et al., 2011) who may already have neuroplastic changes and possibly reorganization of function as a result of the tumour. The results from these studies may not be generalizable to healthy adult participants.

9. Conclusion

Overall, the findings of this study have important implications for our understanding of the relationship between data on white matter microstructure and reading processes. Two main findings are presented in this study. Firstly, that there is limited detection of a relationship between stimuli that activate the ventral and dorsal processing streams and the underlying white matter tracts of the respective regions when examining the RTs for overt naming of different word types of healthy adults. Secondly, this study also provided some insights on the different types of DTI analyses. The use of the three different methods and their differing results suggest that the method of analysis used for DTI imaging data is very important to the kind of conclusions that can be drawn.

This study had some notable limitations. Due to the fact that the data was pre-processed for the hybrid analysis and not processed for tractography or ROI analysis, it is unknown what effects this may have had on the final results and whether and to what extent the results of the hybrid analysis are comparable with that of tractography and ROI analysis. Replication of this study is necessary to eliminate the potential confound presented by selectively pre-processing the DTI data for certain analyses but not others. Another limitation of this study was the fact that tractography and ROI analysis were only performed on the left hemisphere white matter. The hybrid analysis of the DTI data suggested that the relationship between white matter and reading is highly complex and may involve much more than the five left hemisphere tracts that was examined. Replicating the study will allow us to examine additional white matter tracts, such as the right hemisphere tracts, using ROI analysis and tractography. It is also important to note that the hybrid analysis is an exploratory method that combined both TBSS and VBA analysis, thus the results for the hybrid analysis are preliminary and further work is needed to ensure the validity of this methodology. In addition, this study only examined one aspect of white matter microstructure, the FA. It may be necessary to examine other white matter microstructure indices (e.g., axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (D_{av}) and macrostructure (e.g., white matter volume) to fully understand the role played by white matter in the reading network. It may also be important to combine a variety of neuroimaging techniques to identify the processes and pathways associated with reading. For example, fMRI or PET could be used to delineate functional connectivity between brain regions while DTI could be utilized within the same study to examine anatomical connectivity between those regions. With consideration to the potential effects of low variability within the participant sample, future studies should also include a greater range of participants, from poor readers to great readers. Finally, future research should incorporate additional behavioural measures that examine performance on phonological and orthographic processing tasks as these tasks may help to further elucidate the role of specific white matter tracts in the dorsal and ventral processing streams.

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Appendix A

When we followed Gold et al. (2007)'s procedure of using Spearman's rho for correlational analysis, we did find a significant correlation between the parietal ROI and RT for naming pseudohomophones (rho = -0.344, p = 0.027, one-tailed). Gold et al. (2007) suggested that non-parametric tests of correlation, such as Spearman rank correlation may be preferable to Pearson correlation due to the possibility that FA across individuals may not follow a normal distribution. However, we examined the histogram of the mean FA derived from the parietal ROI and found that it did follow a normal distribution, which suggests that a parametric test of correlation may be a better choice.