Evidence for the functional and structural differentiation of the inferior fronto-occipital fasciculus using DTI tractography

by

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ABSTRACT

The inferior fronto-occipital fasciculus (IFOF), a major ventral white matter pathway, has been shown to be a crucial component of semantic (Moritz-Gasser, Herbet & Duffau, 2013) and lexical/orthographic (Vandermosten, Boets, Polemans, Sunaert, Wouters & Ghesquière, 2012) processing. However, recent anatomical studies of the brain have revealed at least two differentiable components of the IFOF: a dorsal component projecting from the frontal lobe to the superior parietal lobule, and a ventral component connecting the frontal lobe with the inferior occipital gyrus and posterior temporal lobe (Martino, Brogna, Robles, Vergani & Duffau, 2010). We have replicated this anatomical division using a new deterministic tractography protocol in DTI Studio, and found this protocol to have high inter-rater reliability (ICC > 0.9). Furthermore, we provided the first evidence of a functional distinction between these two components. We compared diffusion measures (e.g., fractional anisotropy [FA], an indirect measure of white matter microstructural integrity) with reaction times on five different reading tasks: basic naming of pure exception words, regular words, and mixed exception/regular words, and go/no-go tasks involving either pseudohomophone or nonword foils. We found a clear functional divide in the left IFOF, whereby dorsal FA was specifically correlated with performance on tasks that required higher levels of visual attention and response selection (go/no-go and mixed naming tasks), while ventral FA was more broadly correlated with naming performance. This demonstrates that the anatomical distinction described by Martino et al. (2010) is indeed mirrored by a functional distinction, and suggests that future investigations of neuroanatomical models of reading and speech production should consider the dorsal and ventral IFOF as separate entities.

PREFACE

This thesis is an original work by Claire Rollans. No part of this thesis has been previously published. However, the behavioural and structural imaging data referred to in Chapter 2 was collected prior to the start of this project by Dr. Jacqueline Cummine, as part of a larger study on reading that included functional imaging. Ethics approval was given for the original study by the University of Alberta Heath Research Ethics Board (Pro00008951) and the appropriate updates were made prior to the start of this project. I was responsible for the formulation of new hypotheses specific to this project, as well as data analysis and manuscript composition. Additional tractography was performed by Alesha Reed as part of the reliability analysis of the tractography procedure.

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LIST OF ABBREVIATIONS

DTI: Diffusion Tensor Imaging

IFOF: Inferior Fronto-Occipital Fasciculus

FA: Fractional Anisotropy

MD: Mean Diffusivity

RD: Radial Diffusivity

AD: Axial Diffusivity

IT: Inferior Temporal (Cortex)

SPL: Superior Parietal Lobule

AF: Arcuate Fasciculus

HARDI: High-Angular Resolution Diffusion Imaging

VWFA: Visual Word-Form Area

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1. Introduction

1.1 Anatomy of the IFOF

Prior to the advent of diffusion tensor imaging (DTI), which allows for in vivo tracking of white matter in the brain, the anatomy of the IFOF was known exclusively through post-mortem studies. Dejerine (1895) was the first to suggest a ventral tract distinct from the inferior longitudinal fasciculus, running from occipital to frontal areas. However, Trolard (1906) revised Dejerine's description and provided a characterization of the tract that is more in line with current descriptions. For example, while Dejerine (1895) described the central portion of the IFOF as running above the caudate nucleus, Trolard (1906) suggested a more inferior course, just above the middle portion of the claustrum. Since then, multiple post-mortem studies have been able to clearly delineate this fascicle, which directly connects occipito-temporal (and parietal) areas to the frontal lobe through the external/extreme capsule region (Curran, 1909; Davis, 1921; Hultkrantz, 1929; Crosby et al., 1962; Ebeling & von Cramon, 1992; Kier et al., 2004).

Catani et al. (2002) performed the first comprehensive in vivo study of human white matter tracts, comparing to previous post-mortem results. They were able to clearly delineate the IFOF, projecting from the inferior-lateral and dorsal-lateral frontal cortex to the posterior temporal cortex and the occipital lobe. Again, these results have been replicated in vivo, showing very similar anterior and posterior terminations (Lawes et al., 2008; Wakana et al., 2004; Catani et al., 2008; Mori et al., 2002). Interestingly, several of these studies show IFOF parietal projections in their figures, but fail to discuss these superiorly-projecting fibers (Catani et al., 2002; Wakana et al., 2004). More recent anatomical studies have demonstrated, not only diverse connectivity in the IFOF, but also several discernable components (Martino et al., 2010; Sarubbo et al., 2013; Caverzasi et al., 2014), which have raised questions about the separability of the IFOF into multiple sections.

Martino et al., (2010) were the first to suggest a differentiation between a dorsal and ventral IFOF. In their post-mortem study, they discovered that the IFOF could be separated into two easily distinguishable components at the ventral portion of the external capsule. The dorsal (superficial) component projected from the frontal operculum to the superior parietal lobule and superior/middle occipital gyri, while the ventral (deep) component projected to the posterior/basal temporal region (inferior temporal gyrus, temporal-occipital sulcus) and the inferior occipital gyrus. In light of these findings, Sarubbo et al. (2013) also did a careful post-mortem study of the IFOF, and additionally attempted to reproduce the dorsal/ventral distinction in vivo using diffusion-weighted imaging (DTI) of a single subject. They replicated the findings of Martino et al. (2010) in that they found a superficial and deep layer of the IFOF. However, they further divided the deep layer into three different subcomponents (anterior/middle/posterior) based on their frontal connections.

Most recently, Caverzasi et al. (2014) have conducted a much larger-scale in vivo study using Q-ball reconstruction of High-Angular Resolution Diffusion Imaging (HARDI), which allows for high resolution of white matter, particularly in regions of crossing fibers. Not only did they reveal much more complex anterior connectivity than had previously been described, but they found that a dorsal component of the IFOF did appear to project into the superior parietal lobule in all participants. This provides strong evidence for the validity of the findings in Martino et al. (2010), and demonstrates the feasibility of delineating a dorsal and ventral IFOF in vivo.

Such detailed parsing of white matter tracts is becoming more common. Indeed, the arcuate fasciculus (AF) is now frequently characterized as consisting of at least three major sub-components (Catani & De Schotten, 2008, Catani, Jones, & Ffytche, 2005; Makris et al., 2005). This distinction has proved fruitful, as recent studies have found different components to be associated with separate behavioural functions (Makris et al., 2005; Vandermosten et al., 2012). This indicates that distinguishing between a dorsal and ventral IFOF may not just be feasible, but may similarly allow for greater functional specificity in studies of white matter and language.

1.2 IFOF and Language

Current neurophysiological models of language distinguish between a dorsal (occipital-parietal-frontal) pathway and a ventral (occipital-temporal) pathway (Cohen et al., 2008; Hickock & Poeppel, 2004; Indefrey & Levelt, 2004; Saur et al., 2008). It is hypothesized that the dorsal pathway is invoked during tasks that include processing of unfamiliar stimuli (e.g., rotated words; Cohen et al., 2008), and/or tasks that are highly reliant on phonological decoding/sequencing (e.g., overt pronunciation of nonwords [letter strings that do not spell or sound like a real word]; Jobard et al., 2003). In contrast, the ventral pathway is thought to be involved when individuals are processing highly familiar stimuli, for example, high frequency words (Cohen et al., 2008; Jobard et al., 2003) or completing tasks that require semantic information, for example, text comprehension (e.g., Saur et al., 2008; see also Dick & Trembley, 2012).

To date, the IFOF has been generally thought to be the major direct pathway underlying the ventral stream described above. In line with this hypothesis, dysfunction in this region can have a significant negative effect on reading and semantic processes. For example, electrostimulation of this tract causes severe semantic paraphasias (Mandonnet et al., 2007;

Duffau et al. 2005; 2008; Gil-Robles et al., 2013) as well as impairments in semantic tasks, such as picture naming (Mortiz-Gasser et al., 2013). Lesions to this region similarly cause impairments in both semantic fluency (Almairac et al., 2014) and object naming/association tasks (Han et al., 2013). Furthermore, recent studies have indicated a potential IFOF dysfunction in subjects with dyslexia. Steinbrink et al. (2008) found decreased FA (fractional anisotropy - an indirect measure of white matter microstructural integrity; Deutsch et al., 2005) in the IFOF for adults with a history of developmental dyslexia when compared to controls. Vandermosten et al., (2012) also report a positive relationship between FA and behavioural measures across subjects with and without dyslexia, with improved performance on orthographic processing being associated with higher FA in the left IFOF. Lebel et al. (2013) supported this evidence, by demonstrating that reading ability (based on scores from the Woodcock-Johnson test) was positively correlated with FA values in the IFOF. Importantly, these previous examinations of the IFOF's role in lexico-semantic/reading tasks characterize the tract as a single functional pathway. However, the posterior cortical areas to which the IFOF projects are anything but homogenous. To illustrate, let us examine some of the functional roles of two of the more novel extra-striatal grey matter regions associated with the IFOF: the inferior temporal cortex (inferior temporal gyrus/fusiform gyrus) and the superior parietal lobule.

1.2.1 Ventral IFOF projections to inferior temporal cortex. The inferior temporal (IT) cortex is a crucial component of downstream visual processes. Multiple studies have shown the primate IT region to be involved in shape recognition (Schwartz et al., 1983; Logothetis et al., 1995; Lafer-Sousa & Conway, 2013) and invariant object recognition (Goodale et al., 1982; Lueschow et al., 1994; Haxby et al., 2001; Hung et al., 2005; Lafer-Sousa & Conway, 2013). This object recognition is also commonly shown to be category-specific, with distinctive patterns of activity in response to faces, man-made objects, etc., (Haxby et al., 2001; Lafer-Sousa & Conway, 2013; Emadi & Etesky, 2013). Relevant to the current work, the IT cortex has also been shown to play a role in language processes, such as visual word recognition. Particularly critical to this aspect of reading is a portion of the left fusiform gyrus, often referred to as the visual word form area (VWFA; McCandliss et al., 2003). This part of the ventral visual system seems to be particularly tuned to letter strings, supporting the process of combining multiple letters into a perceptual unit (Nobre et al., 1994; Gaillard et al., 2006; Glezer et al., 2009; Pegado et al., 2011). Not only that, but this region seems largely insensitive to variations like case and font (Dehaene et al., 2004; Qiao et al., 2010). Damage to this region reliably causes pure alexia, an acquired reading impairment that results in letter-by-letter reading (Miozzo & Caramazza, 1998; Leff et al., 2001; Gaillard et al., 2006), further demonstrating the IT cortex's critical involvement in reading processes (although see McCandliss et al., 2003 and Dehaene & Cohen, 2011 for discussions on IT generality).

1.2.2 Dorsal IFOF projections to the superior parietal lobule. The superior parietal lobule (SPL), on the other hand, is a more general, integrative region that serves several functions. For example, it is crucial for visual-motor transformations, such as grasping, pointing, and reaching behaviours (Simon et al., 2002). Another central function seems to be orienting visual attention. The SPL becomes active during both covert and overt shifts of visual spatial attention (Corbetta et al., 1995; Vandenberghe et al., 2001; Simon et al., 2002). Specifically, the SPL may be responsible for goal-oriented attentional shifting, exerting a top-down influence on the rest of the visual system (Corbetta & Shulman, 2002). Lesions to this region disrupt even covert disengagement from an attentional target (Posner et al., 1984). However, the SPL's role in attentional processes is not limited to the visual domain, as tasks involving both kineasthetic attention and auditory attention modulate SPL activity (Stoeckel et al., 2003; Shomstein & Yantis, 2006). This attentional role also appears to mediate language-related functions of the SPL. For example, dyslexic children with significant visual attention span deficits fail to activate this region during visual attention tasks (Peyrin et al., 2011), as well as during manipulation of verbal material (Vasic et al., 2008). Adding to this, activation of the SPL demonstrates a significant length effect during reading/naming of pseudowords (Juphard et al., 2004; Valdois et al., 2006). These findings indicate that the SPL may be involved in the attentional demands of decoding unfamiliar letter strings.

1.3 Summary

Overall, evidence has been provided for an anatomical distinction between ventral and dorsal components of the IFOF. Given the terminating projections of the ventral and dorsal IFOF into semantic/orthographic and novel/attentional regions, respectively, an inquiry into the functional separability of the IFOF into multiple segments is warranted. Considering the diverse connectivity of the IFOF, it seems likely that individual components may underlie divergent language functions. Despite this fact, no study has yet examined the possible functional distinctiveness of the IFOF's different components. To fully evaluate the practicality of individually isolating the dorsal and ventral IFOF in vivo, we need to determine whether this anatomical separation is functionally relevant (i.e., sensitive to tasks [Go/No-Go vs. basic naming] and items [exception vs. regular spelling-to-sound correspondance] that vary in their attentional and lexico-semantic requirements). This tract is perhaps the most significant white matter bundle underlying the ventral language stream. Therefore, a more detailed understanding of the functional role of the IFOF's various projections will help, not only in refining language models, but also in gaining a better understanding of the neuroanatomical correlates of language disorders such as dyslexia and aphasia. The more we understand about the underlying anatomy of these disorders, the better we can make predictive models of language disability, as well as more effective learning and rehabilitative tools.

1.4 Research Questions and Hypotheses

In this study, we wish to address three major questions: 1) Can the inferior fronto-occipital fasciculus of typical-reading adults be accurately separated into a dorsal and ventral component using standard DT-MRI deterministic tractography, based on the anatomical data in Martino et al., (2010) and Caverzasi et al., (2014)? 2) Is the tractography procedure for isolating the dorsal and ventral IFOF reliable, whereby there is over 90% absolute agreement (ICC ≥ 0.9) between raters for the computed fractional anisotropy of each component? And 3) In typical-reading adults, are diffusion measures (e.g., fractional anisotropy) in the dorsal vs. ventral inferior fronto-occipital fasciculus predictive of performance on different tasks that vary in their semantic and attentional requirements (basic naming, Go/No-Go)?

In general, we anticipate that fractional anisotropy (FA) will negatively correlate with reaction time, but positively correlate with accuracy, when there is a relationship between the microstructural integrity of the tract and task performance. A negative relationship between FA and reaction time indicates that better tract integrity and organization (higher FA) is associated with faster performance (shorter reaction times). Conversely, we expect improved accuracy to be related to higher FA. Based on the above literature, we further predict that basic naming tasks, which rely primarily upon automatized word recognition processes, will be correlated with FA in the ventral IFOF, while Go/No-Go tasks, requiring greater attention and response inhibition, will be specifically correlated with FA in the dorsal IFOF. A summary of the hypotheses is provided in Table 1. It should be noted that because the literature primarily concerns the left hemisphere, these hypotheses are intended for the left IFOF. Right hemisphere analysis should be considered exploratory.

Table 1: Summary of Hypotheses by Task

	Basic Naming: Regular	**Basic Naming: Exception**	**Basic Naming: Mixed**	**Go/No-Go: Pseudohom.**	**Go/No-Go: Non-word**
Dorsal IFOF (FA)	RT: (n) Acc: (n)	RT: (n) Acc: (n)	RT: (n) Acc: (n)	RT: (-) Acc: (+)	RT: (-) Acc: (+)
Ventral IFOF (FA)	RT: (-) Acc: (+)	RT: (-) Acc: (+)	RT: (-) Acc: (+)	RT: (n) Acc: (n)	RT: (n) Acc: (n)

RT = Reaction time, Acc = Accuracy
(+) = Anticipated positive relationship, (-) = Anticipated negative relationship, (n) = Anticipated null relationship

2. Materials and Methods[1]

2.1 Participants

A convenience sampling of 12 typical-reading adults (7 female, 5 male) was taken from the population at the University of Alberta. Participants were between the ages of 18 and 22 years (Mean = 19.83; SD = ± 1.46), and 10 were right-handed. However, one subject was removed from the analysis (except for the reliability analysis) due to a synchronization error in the collection of their behavioural data. Subjects were included if they were generally healthy and over the age of 18, with English as their primary language. Participants were excluded if they had any non-corrected vision problems, head injuries, or reading/learning disabilities that might interfere with the behavioural tasks. Participants were also excluded if they had any conditions that did not comply with the safety regulations of the MRI facility (e.g., if they had any metallic surgical implants).

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[1] Please note that the data presented here was collected as part of a larger reading study, and is being re-analyzed for this project. All data collection occurred prior to the development of this study. The hypotheses of the current study are in line with the goal of the larger reading study, which is to understanding the relationship between behavioural reading measures and neuroanatomical measures. As such, ethics related to a secondary analysis was not sought.

2.2 Data Collection

2.2.1 DTI Data Collection. Diffusion tensor imaging (DTI) uses indirect measures of water diffusion brain tissues to provide structural and directional information about white matter structures in the brain (Le Bihan et al., 2001). DTI is a powerful tool for white matter analysis, because unlike simple structural MRI, it can discriminate between white matter regions, and provide information on fiber orientation, axon integrity, myelination, and fiber coherence (Mukherjee et al., 2008).

Diffusion-weighted brain images were acquired on a 1.5T Siemens Sonata scanner in the Peter S. Allen MR Research Centre at the University of Alberta. Images were collected by a trained MRI technician, and were positioned along the anterior- posterior-commissure line. Anatomical scans included a high-resolution axial T1 MPRAGE sequence with the following parameters: TR = 2000ms, TE = 4.38ms, number of slices = 144, base resolution 256 x 256, voxel size 1x1x1mm, scan time 4:48 minutes. DTI data was collected with a 1.5 T Seimens Sonata MRI scanner, using a dual-spin-echo single-shot echo-planar imaging sequence. Thirty non-collinear directions of diffusion-sensitizing gradients were acquired, with a b-value = 1,000 s/mm^2, repetition time = 6,900 ms, and echo time = 100 ms. Forty contiguous axial slices (slice thickness = 3 mm, voxel size = 2 x 2 x 4 mm) were obtained with an image matrix of 128 x 128 and 75% phase partial Fourier zero-filled to 256 x 256. Raw images were visually inspected for motion artifacts, and none were found. DTI image acquisition took approximately 8 minutes.

2.2.2 Reliability Data Collection. To ensure the reliability of the tractography procedure, an independent tractographer experienced with DTIStudio software (see Jiang et al., 2006 for specifics on this software program) reproduced the tractography procedure described below for all 12 participants. Both the principle investigator and the independent tractographer analyzed every subject. The FA data was then extracted within DTIStudio. For the reliability analysis, we were only interested in the primary outcome (FA) for three reasons: 1) FA is the most robust measure of white matter integrity, 2) FA is co-related with all secondary diffusion measures, and 3) FA is the most commonly reported dependent measure in DTI studies.

2.2.3 Behavioural Data Collection. The behavioural data was collected in-scanner as part of a larger study that included functional magnetic resonance imaging (fMRI) scans. Stimuli were presented using E-Prime 2.0 professional software (Psychology Software Tools, Pittsburgh, PA) and administered by the supervising professor. Response time was collected via an MRI safe microphone (Audio-Technica, Model AT 803b) that was attached to the headcoil. The microphone was connected to a computer in the MRI suite, and voice onsets and offsets were recorded on TF32 software (Milenkovic, 2005) at a sampling frequency of 44,100 Hz. Only correct responses were used for the calculation of reaction times. There were two main task types: basic naming, Go/No-Go naming. The order of tasks was randomized for each participant within E-Prime.

In the basic naming tasks, subjects were asked to name aloud all letter strings from lists that were either 50 pure regular words (i.e., highly familiar letters strings with a typical spelling-to-sound correspondence, for example, *hint*), 50 pure exception words (i.e., highly familiar words with atypical spelling-to-sound correspondence, for example, *pint*), or 100 mixed regular words and exception words (half regular, half exception). Because these words are all highly familiar, they should rely on highly automatized basic word recognition processes, including orthographic, phonological and articulatory processes. Basic naming has been shown to be a valid measure for predicting aspects of reading ability (Katz et al., 2012), and has reliable reaction times within participants (Yap et al., 2012).

In the Go/No-Go naming tasks, participants were asked to only name aloud the letter strings that *spelled* a real word. One participant's Go/No-Go behavioural data could not be used, as they responded to all letter strings, despite these instructions. The Go/No-Go word lists consisted of 50 regular words and 50 exception words that were either mixed with 50 pseudohomophones (i.e., unfamiliar letter strings that sound like a word when sounded out, for example, *toest*) or mixed with 50 non-words (i.e., unfamiliar letter strings that do not sound like a word when sounded out, for example, *tuest*). This task has higher attentional demands, including, but not limited to, additional phonological sequencing of unfamiliar letter strings, monitoring, and response inhibition (Rubia et al., 2001). The Go/No-Go task has shown good validity in studies of attentional processes in reading and action inhibition, particularly in terms of attention deficit disorders (Trommer et al., 1988; Yong-Liang et al., 2000). Furthermore, this task has been shown to have good test-retest reliability (Epstein et al., 2011), and patterns of brain activation are consistent across versions of the Go/No-Go task (Rubia et al., 2001).

Stimuli across the basic naming and Go/No-Go naming tasks were matched for onset phoneme, length, bigram sum, frequency, phonological neighbourhood, and orthographic neighbourhood using the MRC Psycholinguistic Database (Wilson, 1988) (see Appendix 1 for an example of words used in the five tasks).

2.3 Analysis

2.3.1 DTI Analysis. Diffusion tensor imaging (DTI) scans were analyzed using the deterministic tractography method of Fiber Assignment by Continuous Tracking (FACT) and brute-force fiber searching approach (Jiang et al., 2006) in order to replicate the anatomical distinction described by Martino (2010) and Caverzazi (2014). Deterministic tractography is a method of tract reconstruction that traces white matter pathways from a specified seed region, following the primary direction of diffusion voxel-by-voxel (Li et al., 2013). Raw images were pre-processed using the Automatic Image Registration (AIR) function in DTIStudio, which realigns images and minimizes misregistration due to subject motion (Jiang et al., 2006). Tractography analysis was performed by the principle investigator using a multiple-ROI approach of three-dimensional tract reconstruction within DTIStudio. (see Jiang et al., 2006 for specifics on this software program). DTIStudio is an efficient and user-friendly tractography program that has been shown to provide reliable results when compared to other DTI analysis software (Zakaria et al., 2014). Furthermore, the multiple-ROI approach has been shown to have greater validity in tract reconstruction than a single-ROI approach (Huang et al., 2004). Tracking was regulated using a minimum FA threshold of 0.2 and a maximum turning angle of 60º. This follows the parameters of Caverzasi (2014), although we have used a slightly less permissive minimum FA threshold, as we are not attempting such a detailed resolution of frontal projections. The principal investigator was blind to the behavioural results and order of stimulus conditions until after all results from the tractography analysis had been obtained.

The inferior fronto-occipital fasciculus was first isolated in its entirety based on the multiple-ROI tractography procedures outlined in Wakana et al. (2007). In this procedure, ROI 1 is placed on the coronal plane at the level of the posterior commissure, selecting all fibres in the specified hemisphere using the OR function. ROI 2 is then placed on the coronal plane at the level of the anterior commissure, selecting the easily differentiable bundle of fibres that pass through the extreme/external capsule region using the AND function (see Figure 1). Fibres that clearly did not belong to the tract, such as those crossing into the other hemisphere, were removed using the NOT function.

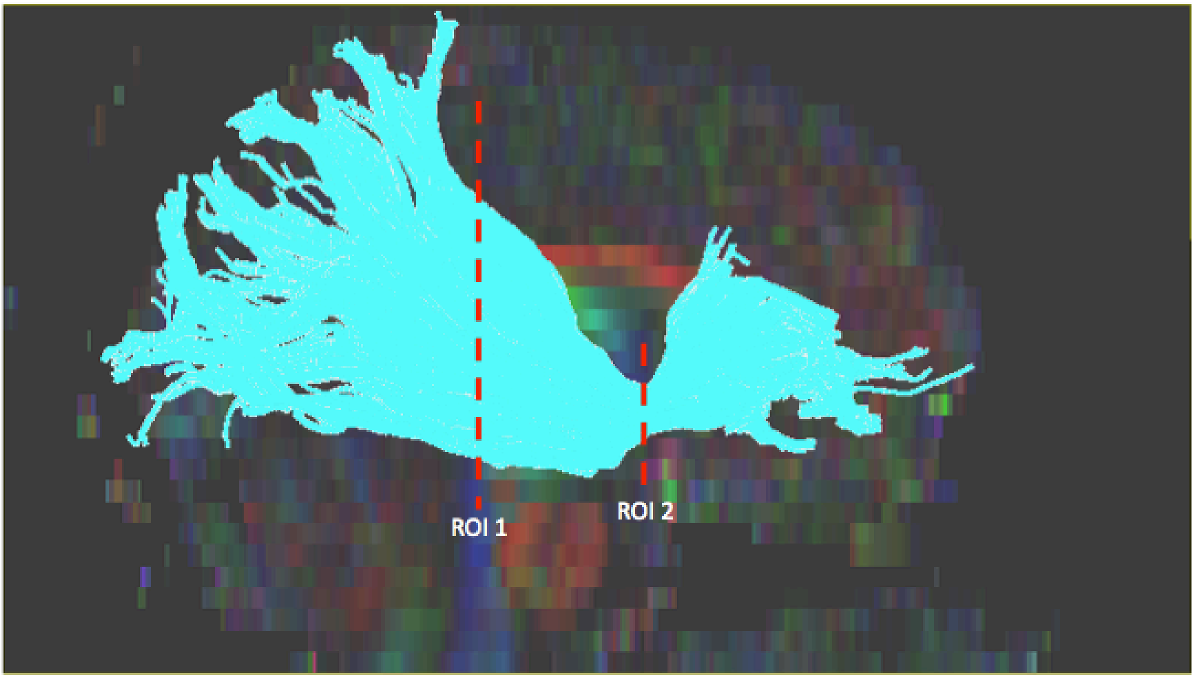

Figure 1. Placement of ROIs for isolation of the complete IFOF

The dorsal and ventral segments of the IFOF were then separated on the coronal plane at the anterior edge of the splenium of the corpus callosum, using a tractography protocol developed specifically for this study. The dorsal segment was defined as the portion of the tract projecting into the superior parietal lobule (Martino et al., 2010, Caverzasi et al., 2014), while the ventral segment was defined as the portion of the tract projecting into areas including the inferior temporal gyrus, lingual gyrus, cuneus, lateral occipital lobe, and fusiform gyrus (Martino et al. 2010, Caverzasi et al., 2014). This separation was made approximately in line with the ventral edge of the atrium as seen in the coronal plane, using the AND function to select the appropriate fibres (see Figure 2). Fibres that clearly did not belong to these segments were removed using the NOT function.

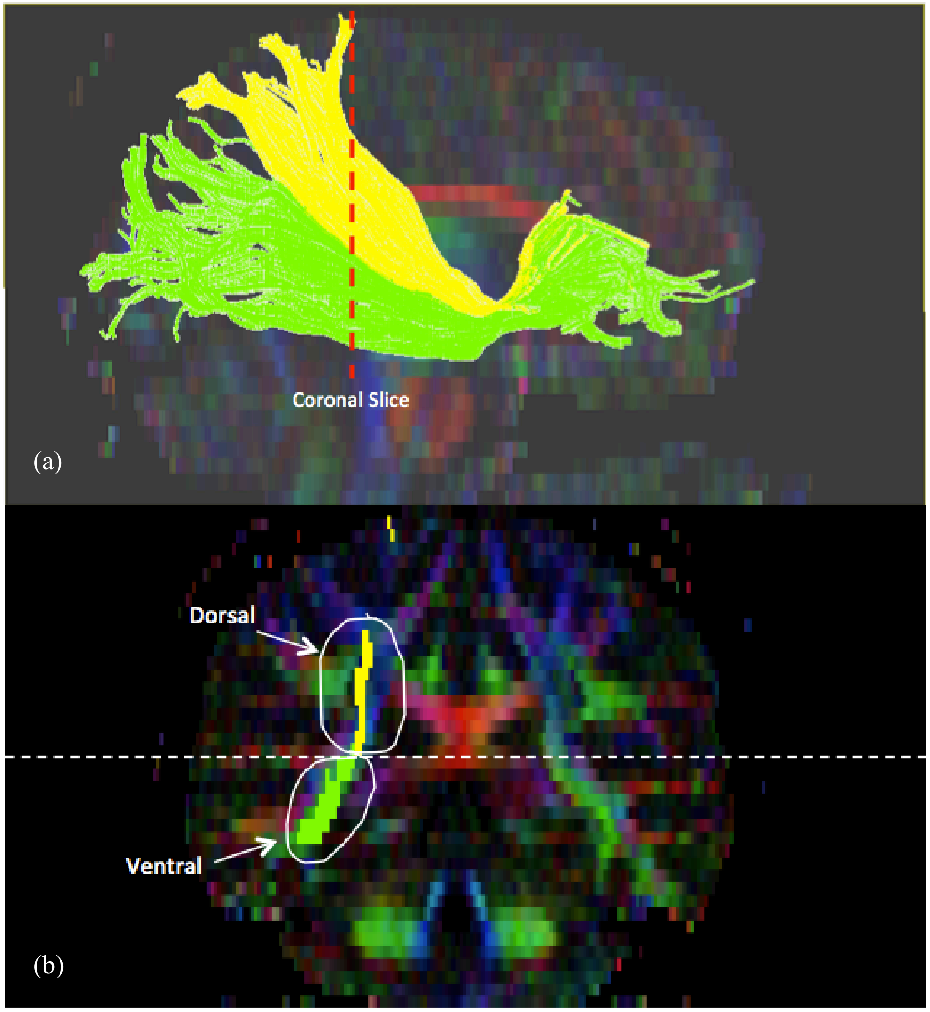

Figure 2. Tractography protocol for the isolation of the dorsal/ventral IFOF: a) Placement of the coronal slice for separation of dorsal and ventral IFOF b) Separation was made at the level of the ventral edge of the lateral atrium

Diffusion measures (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD]), reflecting the microstructural integrity of the white matter (Deutsch et al., 2005; Clark et al., 2011; Song et al., 2002), were calculated for the bilaterally isolated tracts within DTIStudio. FA is the most common measure used in DTI research, and is an index of the amount of anisotropic diffusion (i.e. diffusion parallel to the tract). High FA values suggest highly organized axon bundles, with water diffusing along a single principle axis (Deutsch et al., 2005). This measure has shown good construct validity in studies of language and reading disability. For example, FA levels in language-related tracts consistently correlate with performance on reading tasks (Deutsch et al., 2005; Niogi & McCandliss, 2006). FA is also very responsive to microstructural changes in white matter, and is therefore often used as an indicator of axon integrity (Klingberg et al., 2000; Deutsch et al., 2005; Niogi & McCandliss, 2006; Vandermosten et al., 2012). However, although it is a sensitive measure, it is also relatively non-specific, and is therefore frequently combined with other measures of axon microstructure. Mean diffusivity (MD) is the average of the three principle eigenvalues ($MD = [\lambda_1 + \lambda_2 + \lambda_3]/3$), and represents the average non-directional magnitude of diffusion within a particular brain region. Differences in this value could reflect variations in intra-/extracellular space, neuropil, and/or cerebrospinal fluid (Clark et al., 2011). For example, an increase in MD could be the result of increased tissue water or inflammation, reduced fiber organization, or even increased axon size (Frye et al., 2011). Other measures can give more specific information about axon microstructure. Radial diffusivity ($RD = [\lambda_2 + \lambda_3]/2$) appears to be modulated by myelination, while axial diffusivity ($AD = \lambda_1$) is connected to axon degeneration (Song et al., 2002). An increase in RD combined with a decrease in FA would indicate reduced myelination (Alexander et al. 2007), but may also be the result of reduced organization or increased axonal size when combined with a significant MD increase (Frye et al., 2011). AD tends to decrease when axons are of poorer quality, but will also decrease when there is greater fiber complexity (Frye et al., 2011). It should be noted, that while these measures are frequently used, there have been some questions about their validity, particularly in areas of crossing fibers (Wheeler-Kingshott et al., 2009). However, they have been shown to have predictive power. For example, increased RD has been consistently shown to be predictive of demyelination in patients with multiple sclerosis (Kim et al., 2006; Roosendaal et al., 2009; Klawiter et al., 2011). Therefore, the relationships among these white matter variables should give a clearer picture of the microstructural factors affecting white matter as it relates to naming.

2.3.2 Statistical Analysis: Reliability. The FA data collected by both the primary investigator and the independent tractographer were compared using Intraclass Correlational (ICC[2,1]) analysis in SPSS (go to <http://www-01.ibm.com/software/analytics/spss/products/statistics/> for product details) for the entire IFOF, as well as dorsal and ventral components, bilaterally. In total, there were 72 pairs of FA data points for the ICC analysis. As we generally only have one assessor performing tractography analysis, we have used a $k = 1$ for this analysis, to determine the reliability for a single rater. The tractography procedure was deemed to have a sufficient level of reliability if there was a minimum single-measure ICC of 0.9, indicating a very high level of absolute agreement between raters.

2.3.3 Statistical Analysis: Behavioural and DTI Analysis. Descriptive statistics, including mean values and standard deviations, were calculated in SPSS for reaction times, accuracy, and all four diffusion measures (FA, MD, AD, RD). Two-tailed paired samples *t*-tests ($\alpha < 0.05$) were conducted to compare reaction time and accuracy levels across the two main task-types outlined in our methods: naming and Go/No-Go. Furthermore, two-tailed Pearson correlational analysis was performed to determine whether there was a significant relationship ($\alpha < 0.05$) between FA and the other three diffusion measures (MD, AD, RD) in each of the tracts.

2.3.3 Statistical Analysis: Correlation Between Diffusion Measures and Behavioural Measures. The FA data collected through the tractography procedure was compared with reaction time data from basic reading (of exception and regular words) and Go/No-Go (mixed with pseudohomophone or non-word foils) tasks. Directional (i.e., one-tailed) Pearson correlational analyses were performed in SPSS to determine whether there were any significant relationships between the response time collected for each of the reading tasks and the diffusion parameters from the two tracts. Given that this is the first study to attempt to establish a functional distinction between the dorsal and ventral IFOF, an uncorrected $\alpha < 0.05$ was utilized. A directional analysis was selected due to the predicted negative relationship between diffusion measures such as FA and reaction times on reading tasks. This directional FA-behavioural relationship has been consistently observed in studies of white matter and reading, whereby faster reaction times were correlated with higher FA values (e.g., Gold et al., 2007; Vandermosten et al., 2012). Positive relationships between reaction time and FA are much more difficult to interpret, and were not of interest to the current research.

3. Results

3.1 Reliability

The two-way random effects model comparing the FA results from both the principle investigator and the independent tractographer yielded a single-measures *ICC* = .938. This indicates a very high level of absolute agreement between the two raters, and suggests that this tractography procedure has good inter-rater reliability.

3.2 Behavioural Tasks

Accuracy was very high across all tasks, with a minimum accuracy of 95% on all naming tasks and 90% on all Go/No-Go tasks. The only exception was participant 14, who had particularly low accuracy across all tasks, with accuracy as low as 90% for pure exception words and 89% for Go/No-Go with pseudohomophones (see Table 2 for a summary). A two-tailed paired samples *t*-test confirmed that participants were significantly less accurate on Go/No-Go tasks than they were on naming tasks (mean difference = .026%, *t* (10) = 5.298, *p* = .0005).

In terms of reaction times (RTs), people were fastest on the pure naming tasks, with average RTs close to 600 ms. The next fastest tasks were mixed naming and Go/No-Go with nonwords at mean RT = 723 ms and mean RT = 771 ms, respectively. Participants were slowest on the Go/No-Go task with pseudohomophones, with a mean RT = 924 ms (see Table 2 for a summary). A two-tailed paired samples *t*-test showed that participants were significantly faster on naming tasks than on Go/No-Go tasks (mean difference = -182 ms, *t* (10) = -.3649, *p* = .005).

Table 2: Behavioural descriptives

	Pure Exception Naming	Pure Regular Naming	Mixed Naming	GNG: Nonwords	GNG: Pseudohomophones
Reaction Time (ms) (SD)	599 (191)	602 (191)	723 (113)	710 (93)	924 (249)
Accuracy (SD)	.982 (.032)	.988 (.017)	.981 (.026)	.954 (.027)	.962 (.034)

3.3 DTI Data

Mean diffusion measures (FA, MD, AD, RD) are reported for the bilateral IFOF total, dorsal and ventral segments in Table 3. Although the mean FA is somewhat greater for the left IFOF as compared to the right IFOF, this difference is not significant (mean difference = .00414, *t* (10) = 1.039, *p* = .323). The dorsal component reliably had the smallest FA, while the ventral component had the largest FA. Using a Pearson's correlation test, the FA for each tract was consistently found to be significantly (*p* < .05) negatively correlated to RD. AD and MD were not significantly correlated with FA. This indicates that lower FA values may be primarily the result of reduced myelination, as opposed to fibre organization, coherence, or extracellular fluid.

Table 3: Diffusion Measure Descriptives (N=11)

	FA (SD)	MD (SD)	AD (SD)	RD (SD)
Right IFOF total	.5297 (.0153)	7.773 x 10^{-4} (2.56 x 10^{-5})	1.290 x 10^{-3} (4.25 x 10^{-5})	5.213 x 10^{-4} (2.16 x 10^{-5})
Right IFOF dorsal	.4744 (.0266)	7.744 x 10^{-4} (2.74 x 10^{-5})	1.162 x 10^{-3} (5.52 x 10^{-5})	5.347 x 10^{-4} (2.50 x 10^{-5})
Right IFOF ventral	.5484 (.0154)	7.913 x 10^{-4} (2.65 x 10^{-5})	1.333x 10^{-3} (4.51 x 10^{-5})	5.201 x 10^{-4} (2.49 x 10^{-5})
Left IFOF total	.5338 (.0150)	7.870 x 10^{-4} (2.35 x 10^{-5})	1.315 x 10^{-3} (4.23 x 10^{-5})	5.229 x 10^{-4} (1.91 x 10^{-5})
Left IFOF dorsal	.4647 (.0231)	7.510 x 10^{-4} (3.07 x 10^{-5})	1.165 x 10^{-3} (6.22 x 10^{-5})	5.441 x 10^{-4} (2.44 x 10^{-5})
Left IFOF ventral	.5528 (.0160)	7.974 x 10^{-4} (2.28 x 10^{-5})	1.358 x 10^{-3} (4.07 x 10^{-5})	5.171 x 10^{-4} (2.03 x 10^{-5})

3.3 Correlations Between Diffusion Measures and Behavioural Tasks

3.3.1 Accuracy. Accuracy was only found to be significantly correlated with FA for the pure exception word reading task in the right ($r = .682$, $p = .015$) and left ($r = .638$, $p = .024$) ventral IFOF. This was a positive relationship, whereby greater levels of accuracy were related to higher FA in the ventral IFOF. No other tasks showed a significant FA-accuracy relationship with any of the examined tracts.

3.3.2 Reaction Time. Several significant relationships between FA and reaction time (RT) were found in the right hemisphere. RT for pure exception naming was significantly correlated with FA in the right IFOF total ($r = -.626$, $p = .020$), as well as the right ventral IFOF ($r = -.781$, $p = .002$). In contrast, the right dorsal IFOF was significantly correlated with both pure regular naming ($r = -.701$, $p = .008$) and Go/No-Go with nonwords ($r = -.691$, $p = .013$). There were no significant relationships for either mixed naming or Go/No-Go with pseudohomophones.

The only FA-reaction time relationship in the left hemisphere was between the left dorsal IFOF and Go/No-Go with pseudohomophones ($r = -.570$, $p = .043$) (See Table 3 for a summary).

Table 4: FA-Reaction Time Relationships For Individual Tasks

	Pure Exception Naming (*p*)	Pure Regular Naming (*p*)	Mixed Naming (*p*)	GNG: Nonwords (*p*)	GNG: Pseudohomophones (*p*)
Right IFOF total	-.626 (.020)*	-.347 (.148)	.192 (.714)	-.034 (.463)	.732 (.992)
Right IFOF dorsal	-.515 (.052)	-.701 (.008)**	.062 (.572)	-.691 (.013)*	.105 (.614)
Right IFOF ventral	-.781 (.002)**	-.517 (.052)	.193 (.715)	-.440 (.101)	.404 (.876)
Left IFOF total	.074 (.586)	-.313 (.174)	-.354 (.142)	.267 (.772)	.491 (.925)
Left IFOF dorsal	.148 (.668)	.046 (.554)	-.491 (.062)	-.415 (.116)	-.570 (.043)*
Left IFOF ventral	-.271 (.210)	-.339 (.154)	-.389 (.118)	-.359 (.154)	-.196 (.294)

* $p < .05$; ** $p < .01$ (one-tailed)

3.3.3 Follow-up Analysis. Based off of our hypotheses and observed correlational trends between FA and RT in the individual tasks, we averaged RT data across broader task categories to determine whether we could get a clearer picture of the role of the dorsal and ventral IFOF in various reading conditions. Pure naming and Go/No-Go tasks were easily separable. However, mixed naming showed a pattern of relationships that made it difficult to group with either task type. Therefore, several different task combinations are shown in Table 4. The first two are the pure naming and Go/No-Go tasks without the mixed condition. Then each of these broad task categories is combined with the mixed condition. Finally, each participant was given an overall reading score, which is the reaction time averaged across all task types.

In the right hemisphere, all three tracts showed a very similar pattern of results. The right total, dorsal, and ventral IFOF were all significantly correlated with pure naming tasks ([*r* = -.593, *p* = .027], [*r* = -.741, *p* = .005], and [*r* = -.792, *p* = .002], respectively), and the right dorsal and ventral IFOF were additionally correlated with naming tasks that included the mixed condition ([*r* = -.781, *p* = .002] and [*r* = -.731, *p* = .005], respectively). These tracts were not significantly correlated with the Go/No-Go tasks or overall reading scores.

The left hemisphere displayed much greater task separation. The left dorsal IFOF was significantly related to Go/No-Go tasks, both alone (*r* = -.610, *p* = .031) and when combined with the mixed task (*r* = -.717, *p* = .010). The left ventral IFOF, on the other hand, was significantly related to naming tasks that included the mixed condition (*r* = -.734, *p* = .005). In contrast, FA in the left dorsal IFOF was not at all related to pure naming reaction times (*r* = .119, *p* = .636), and FA in the left ventral IFOF was not related to Go/No-Go reaction times (*r* = -.277, *p* = .219) (see Figure 3). The total IFOF did not show any significant relationships. It is also interesting to note, that only left hemisphere tracts, specifically the dorsal and ventral IFOF, were significantly related to the overall reading score ([*r* = -.573, *p* = .033] and [*r* = -.575, *p* = .032], respectively).

Table 5: FA-Reaction Time Relationships for Combined Tasks

	Pure naming (*p*)	GNG (*p*)	Naming (pure + mixed) (*p*)	GNG + mixed (*p*)	Overall Reading (*p*)
Right IFOF total	-.593 (.027)*	.605 (.968)	-.509 (.055)	.589 (.963)	.333 (.841)
Right IFOF dorsal	-.741 (.005)**	-.129 (.361)	-.781 (.002)**	-.086 (.406)	-.427 (.095)
Right IFOF ventral	-.792 (.002)**	.201 (.711)	-.731 (.005)**	.226 (.735)	-.040 (.454)
Left IFOF total	-.146 (.335)	.497 (.928)	-.452 (.082)	.336 (.829)	.062 (.572)
Left IFOF dorsal	.119 (.636)	-.610 (.031)*	-.267 (.214)	-.717 (.010)**	-.573 (.033)*
Left IFOF ventral	-.372 (.130)	-.277 (.219)	-.734 (.005)**	-.369 (.147)	-.575 (.032)*

* $p < .05$; ** $p < .01$ (one-tailed)

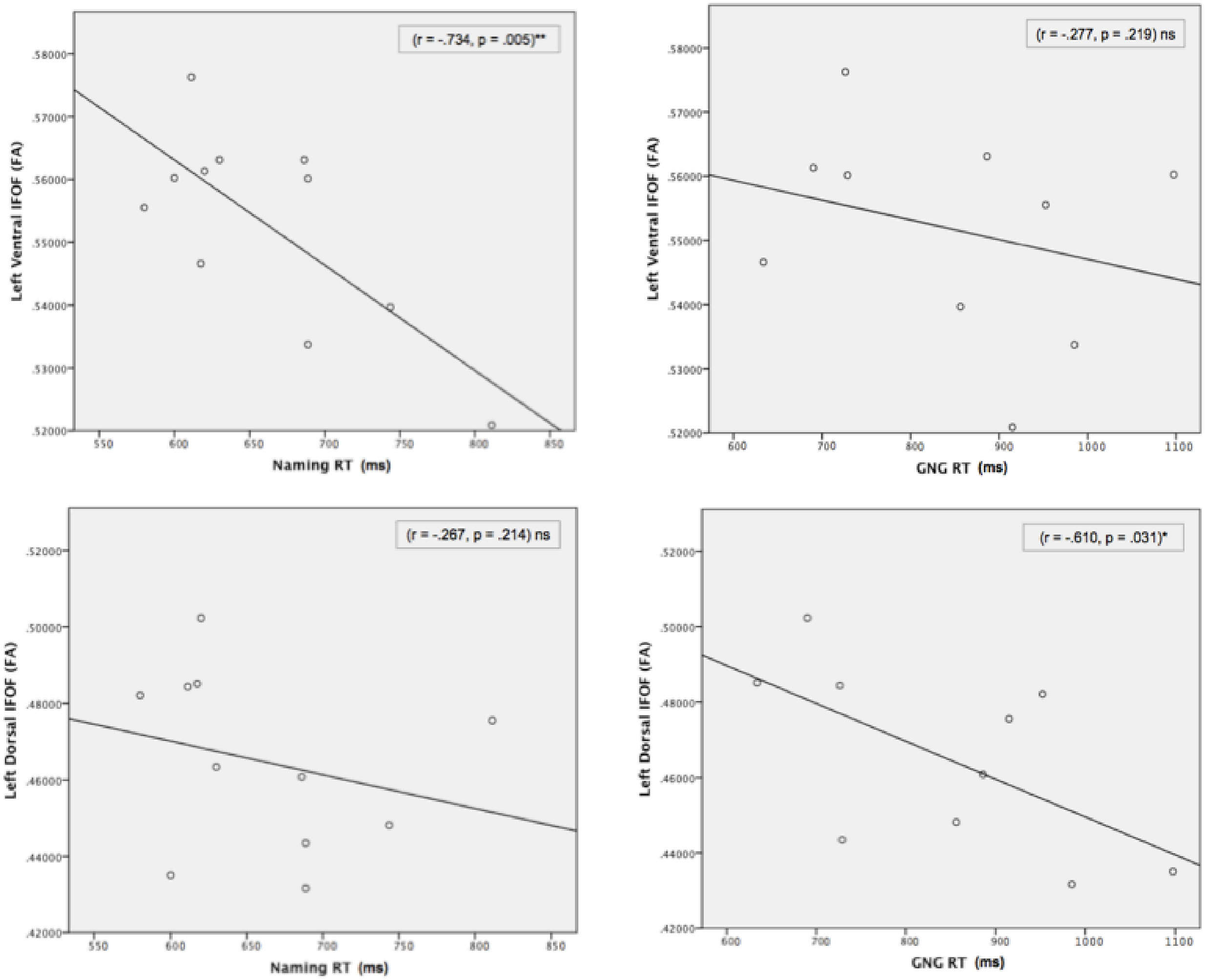

Figure 3: Scatterplots depicting the functional dissociation of the left dorsal and ventral IFOF: a) Correlation between ventral IFOF and naming, b) Correlation between ventral IFOF and go/no-go, c) Correlation between dorsal IFOF and naming, d) Correlation between dorsal IFOF and go/no-go

4. Discussion

In general, the results of this study confirm our hypotheses. We were able to consistently isolate both a dorsal and ventral IFOF with a high level of reliability. Furthermore, we found a probable functional dissociation between the dorsal and ventral components in the left hemisphere, with the dorsal IFOF correlating more strongly with Go/No-Go tasks, and the ventral IFOF correlating more broadly to simple naming tasks. We will explore the implications of these findings, as well as limitations and future directions, in the following discussion.

4.1 Reliability of New Tractography Procedure

The tractography procedure used in this study to isolate, and then segment, the bilateral IFOF into dorsal and ventral components was found to have a high level of inter-rater reliability. This indicates that the anatomical separation described by Martino et al. (2010) and Caverzasi et al. (2014) can be reliably replicated, even with lower-resolution 1.5T scans and simple deterministic tractography software. This makes it a feasible protocol for use by a wide variety of researchers studying neuroanatomical models of language.

In the current work, both a dorsal and ventral component could be isolated bilaterally in every subject. However, the dorsal component was more difficult to isolate consistently across participants than the ventral component, which tended to be robust and easy to distinguish. In five of the twelve participants, at least one of the dorsal IFOF components was smaller than usual or did not appear to project all the way into the frontal lobe, ending abruptly in the extreme/external capsule region. This could have several explanations. First, the maximum turning angle for fibres was capped at 60º. Because the dorsal component turns much more sharply to project up into superior parietal areas, some of these fibres may have been excluded from analysis. Furthermore, one major downside to using a lower-resolution scanning protocol is that frontal fibres are very difficult to resolve. A higher proportion of crossing fibers in this region means that multiple fiber directions may be averaged across a single voxel, artificially lowering the FA (Oouchi et al., 2007). If this has a sufficiently large effect, fibers may not even appear during tractography as they fall below the 0.2 FA threshold for fibre reconstruction. Caverzasi et al. (2014) used a lower minimum FA threshold of 0.15 specifically for this reason.

As these dorsal components would stop abruptly in the extreme/external capsule region, rather than the normal branching ends you would expect to see at a tract terminus, it is most likely a problem with the tract reconstruction, rather than the tract itself. Ultimately, a study that manipulates both the maximum turning angle and the minimum diffusion threshold during tractography is needed to fully test this claim. Furthermore, a comparative study of FA values obtained using high- vs. low-resolution scanning procedures would help clarify what effect these crossing fibre regions have on whole-tract FA values.

However, even within this handful of unusual dorsal IFOF components, it was possible to distinguish a dorsal component that passed through the critical extreme/external capsule area, and then projected to the superior parietal lobule and/or superior occipital areas. Furthermore, the other seven participants had easily distinguishable dorsal components with full frontal projections, indicating that this is not a universal issue. The overall high level of reliability demonstrates that the tractography procedure held up for even the more challenging cases, providing further evidence for its general applicability.

4.2 The Left Dorsal IFOF: Response Inhibition

In line with our hypothesis, FA in the left dorsal IFOF was significantly correlated with reaction time performance on Go/No-Go tasks, such that as FA values went up response times went down. Go/No-Go tasks are a unique kind of reading task, because they rely, not only on accurate, efficient reading, but also on appropriate response selection (i.e. the execution or inhibition of a response based on the stimulus type). Several studies have found that frontoparietal areas, primarily including the left inferior frontal lobe and superior parietal lobule, are consistently activated across a range of Go/No-Go tasks (Garavan et al., 1999; Rubia et al., 2001).

The left inferior frontal lobe, along with its contralateral counterpart, has been shown to be critical for response inhibition, a key aspect of the Go/No-Go paradigm (Hampshire et al., 2010; Swick et al., 2008). Although the superior parietal lobule has not been shown to be specifically related to response inhibition, it may have a different role in Go/No-Go tasks. The superior parietal lobule is known to be involved in visuo-motor transformations (Simon et al., 2002), attention (Corbetta et al., 1993), and even manipulating information in working memory (Koenigs et al., 2009). Therefore, this region may be required to handle the increased attentional and visuo-motor load needed for correct response selection and execution in Go/No-Go tasks. A related explanation is that the superior parietal lobule forms part of the error signal system that activates when a response has not been correctly inhibited (Menon et al., 2001). Therefore, a more efficient connection between the error system and the response inhibition system would help prevent further errors, and improve performance and efficiency in Go/No-Go tasks. Furthermore, Cobetta & Shulman (2002) argue that superior parietal areas are involved in top-down stimulus and response selection by linking sensory representations to the appropriate motor response. As the dorsal IFOF forms a direct connection between inferior frontal and the superior parietal lobule, it seems possible that this tract may form part of this frontoparietal network underlying aspects of response selection. This role in response selection may additionally contribute to semantic processing in the IFOF, by helping to sort through the competing semantic concepts that are activated during comprehension (Jung-Beeman, 2005). Further testing of the role of this tract in overt articulatory response selection, semantic selection, and non-linguistic response selection is needed to clarify these relationships.

As anticipated, the left dorsal IFOF was not at all correlated with pure naming tasks. What was surprising was the apparent involvement of the left dorsal IFOF in mixed naming. FA in this tract was almost as strongly correlated to reaction time in the mixed naming condition as it was in the Go/No-Go tasks. We believe this finding stems from competing phonological information that is present during mixed naming. More specifically, mixed naming does not only involve simple word retrieval as in the pure naming condition, but also attentional control, as participants must monitor information being produced from spelling-to-sound correspondences, which would be accurate for regular words but inaccurate for exception words (i.e., see the literature on frequency and regularity effects in basic visual word recognition; Coltheart et al., 2001). This explanation is also extended to reading strategies, for example, Zevin et al. (2000) showed that participants can adjust the relative contributions of sublexical (phonological) and lexical (orthographic) reading strategies based on the presented words using attentional control processes. As the superior parietal lobule is critically involved in attentional shifting (Corbetta et al., 2000; Thut et al., 2005), it may be necessary for shifting visual attention between different word segments (ex. whole word vs. individual letters or groups of letters) as the reader monitors their reading performance in the mixed reading condition.

4.3 The Left Ventral IFOF: Word Recognition and Naming

We saw strong negative correlations between basic naming and FA in the left ventral IFOF when reaction times were averaged across all naming tasks, including the mixed condition. This fits with our hypothesis that FA in the ventral IFOF would show negative correlations across the three naming tasks. The left ventral IFOF projects into areas of the inferior temporal lobe, which is known to be important for word recognition (McCandliss et al., 2003), orthographic decoding (Binder et al., 2006) and semantic processing (Vandenberghe et al., 1996). The left temporal lobe is known to not only be critical for word recognition in reading, but also for word retrieval in naming output (Miozzo et al., 1994; Sakurai et al., 1994). However, the ventral IFOF was not significantly correlated with any of the Go/No-Go tasks, which suggests that this tract is not necessarily involved in general naming processes. The ventral IFOF was much more strongly related to tasks that relied on more straightforward word recognition and naming than those that relied on response selection/inhibition. Ultimately, studies of the ventral IFOF that specifically contrast word retrieval and/or semantic processing (ex. object naming) with naming tasks that explicitly require phonological decoding (ex. naming longer pseudowords/nonwords) are needed to support this claim.

4.4 A Print-to-Speech Model

Recent fMRI work (Cummine et al., 2015) has provided evidence that reading is built upon the framework of speech production (e.g., the Directions into Velocities of Articulators, DIVA; Guenther, 2006; Tourville & Guenther, 2011). The structural findings in the current work provide additional support for this notion. More specifically, the ventral IFOF provides a direct connection between occipital and VWFA regions and the inferior frontal/premotor cortex. This frontal region acts as the “speech sound map” and is the first node in the feedforward loop of the DIVA model, storing frequently encountered speech sounds. When activated, in this case by a visual input, it sends feedforward motor commands to the motor cortex to produce a particular set of articulatory gestures. We propose that this pathway is activated in all visually guided naming tasks, which explains the broad correlations seen in the ventral IFOF. In addition, this may be especially true for more straightforward, basic naming tasks.

The DIVA model also describes a feedback loop, which helps track and correct speech production errors and aids in speech development (Guenther, 2006; Tourville & Guenther, 2011). The speech sound map in the inferior frontal gyrus projects to auditory and somatosensory target maps in the superior temporal and ventral parietal cortices, respectively. The expected sensory inputs are checked with the speech sound map, and inhibitory signals are sent to the appropriate regions of the auditory/somatosensory error maps. At the same time, these error maps receive input about the current sensory states. In this way, the error maps are able to process discrepancies between the expected and real sensory states generated by the articulatory response. This error signal can then be fed back into the motor cortex to correct the articulatory output. Although the dorsal IFOF does not terminate in ventral parietal and/or superior temporal areas, it does pass through these regions as it projects to the inferior frontal lobe. Therefore, it may play some part in the articulatory feedback loop, where in this case the error is caused by an incorrect Go/No-Go response (i.e. improper inhibition/execution of articulation). A more simplistic explanation would be that the dorsal IFOF plays a role in a separate, yet analogous, feedback system that is more generally involved in error detection for response selection tasks. Either way, the functional separability of the dorsal and ventral IFOF in naming tasks suggests that further work should be done to explore the possible relationships between these white matter systems and the print-to-speech model for reading.

4.5 The Right Dorsal/Ventral IFOF

It was somewhat surprising to see such strong correlations between reaction time and FA in the right hemisphere, as the left hemisphere is generally agreed to be language-dominant in most cases. However, in contrast with the left hemisphere, there was much greater task overlap between the right dorsal and ventral IFOF. For example, the total, dorsal, and ventral right IFOF all showed strong correlations across pure naming tasks. There were some slight differences when looking at the individual task correlations. While the ventral IFOF was strongly correlated with pure exception word naming, the dorsal IFOF was most strongly correlated with pure regular naming and Go/No-Go with nonwords. Therefore, it’s possible that reading-related functional differences also exist for the dorsal and ventral IFOF in the right hemisphere, but this is not yet clear. After all, the task relationships were always in the same direction for both of these components, and were generally moderate-to-strong if not significant (ex. the FA of the dorsal component has a correlation of $r = -.515$, $p = .052$ with reaction time in pure exception word naming). Furthermore, when looking at overall trends, all three tracts were only significantly correlated with naming tasks, and pure naming in particular. This indicates that while there may be some functional differences between the dorsal and ventral IFOF in the right hemisphere, these differences are either not as dramatic, or not well elucidated by these reading tasks.

But why would performance on pure naming tasks be related to IFOF FA in the right hemisphere? As we have seen, the left inferior temporal lobe is critical for naming. However, there have been cases where damage to right temporal areas has similarly caused naming deficits, even in right handed patients (Tyrrell et al., 1990). Furthermore, right temporal lobe damage can cause deficits in visual identification of complex stimuli (Kimura, 1963; Milner, 1968; Evans et al., 1995), and more general right hemisphere lesions can cause language disturbances as well as visuospatial and perceptual disturbances (Rivers & Love, 1980). Studies of split-brain patients also suggest that while the right hemisphere cannot effectively perform grapheme-to-phoneme translation, it can recognize whole words and connect them to semantic concepts (Zaidel & Peters, 1981). Therefore, the right hemisphere may have some role in whole-word reading and semantically based word recognition. What is critical to note is that the right hemisphere does play some supportive role in visual word recognition and basic naming tasks that needs to be considered in future studies.

Still, in line with previous language models, while the left hemisphere tracts were predictive of overall reading scores, the right hemisphere tracts were not. In other words, despite the fact that FA in the right hemisphere tracts was related to certain naming measures, this was not generalizable. Clearly, the structural integrity of the right hemisphere tracts was not as critical to the overall reading performance.

4.6 Additional Findings

4.6.1 Accuracy. Accuracy on the pure exception word naming task was significantly related to FA in the bilateral ventral IFOF. This is consistent with our finding that performance on naming tasks is related to white matter microstructural integrity in both the right and left ventral IFOF. It is interesting that we only see this significant relationship for pure exception naming. However, because exception words do not have good spelling-to-sound correspondence, naming these words relies heavily on feedforward, semantic, orthographic, ventral word recognition processes. Therefore, this task may also depend more upon the ventral IFOF pathway, which connects areas such as the VWFA to the inferior frontal lobe. But apart from exception word naming, accuracy scores did not closely match patterns of reaction time across the tasks. Accuracy levels in these tasks tend to be quite high with low variability, and therefore may not be as sensitive a measure as reaction time for capturing task performance.

4.6.2 Relationship between FA and RD. FA scores were correlated with other diffusion measures, to investigate the potential cause of FA differences. Although AD was somewhat related to the differences in FA scores, RD was the only diffusion measure significantly related to FA. Therefore, we propose that the degree of myelination may be driving these FA differences, and that greater myelination of the dorsal/ventral IFOF leads to increased conduction speed and improved reaction times for reading tasks.

4.7 Limitations and Future Directions

One of the major limitations of this study is the relatively small sample size. Although DTI studies often have somewhat smaller sample sizes due to the cost and complex nature of data collection and analysis (see Barnea-Goraly et al., 2004; Caverzasi et al., 2014), having only eleven subjects does limit the statistical power. Additionally, we chose to use an uncorrected *p*-value given that this is the first study to explore the functional attributes of the dorsal and ventral IFOF. Still, even with this smaller sample, we were able to see some clear trends emerging, with the dorsal IFOF being specifically related to tasks involving higher attentional demands and response inhibition and the ventral IFOF being more broadly related to naming processes. Future studies should consider performing a similar separation with a larger sample size and more stringent controls on Type I error to both confirm and more clearly elucidate these trends.

Tractography is also a somewhat subjective process, and the results can be shaped by several factors. For example, changing the maximum turning angle or minimum FA threshold settings will necessarily give you somewhat different results. Furthermore, the protocol calls for the tractographer to manually draw ROI in specific locations based on visible landmarks. This is due to the fact that individual brains can display a lot of variability in terms of size, shape, etc., while retaining reliable structures that can be used as reference points. However, the manual draw technique, while allowing for more flexibility, also makes perfect replication impossible. You cannot reliably draw an ROI that is the exact same size, location, and shape every time, and different tractographers will obtain slightly different results. This is evidenced by the fact that we were not able to obtain a perfect ICC. However, we have tried to mitigate these issues by using similar threshold levels to Caverzasi et al. (2014) and by including a reliability measure in our design. Researchers are encouraged to further validate and refine these tractography procedures.

As mentioned previously in section 4.2, one of the drawbacks to using a lower-resolution scan and simple FACT-based reconstruction, is that there can be problems in resolving individual tracts in areas with a large amount of crossing fibres. However, this is somewhat by design. Caverzasi et al. (2014) attempted to overcome some of these challenges by using High Angular Resolution Diffusion Imaging (HARDI) and q-ball reconstruction, which is much more effective at resolving crossing fibres. At the same time, HARDI currently requires very long scan times, which are not practical for most non-anatomical studies. Therefore, one of the goals of this study was to see whether this finer anatomical distinction could be replicated with the kinds of tools commonly used by language researchers (for examples see McDonald et al., 2008; Gopal et al., 2012; Kim et al., 2011). As improvements are made to HARDI to improve practicality and reduce scan times (Cho et al., 2009), perhaps this will become a more feasible and standard scanning procedure at some point in the near future. Therefore, an investigation of the functional correlates of the ventral and dorsal IFOF using high-resolution imaging is warranted.

Finally, this study only used a small subset of possible reading measures. It would be interesting to see if there is functional distinctiveness in the IFOF for tasks such as naming non-linguistic items (ex. objects), semantic associations, verbal and non-verbal working memory, emotional processing of language, visual attention span, and phonological processing. For example, since a few studies have indicated a role for the SPL in the decoding of unfamiliar letter strings (Tagamets et al., 2000; Valdois et al., 2006), it may be possible to find a specific role for the dorsal IFOF in tasks such as naming of pseudohomophones and/or nonwords. Not only that, but this anatomical model has yet to be tested on clinical populations, including those with specific core deficits in dyslexia, such as phonological processing, rapid naming, or visual attention span disorders. More research is needed to explore the full range of functional roles for these two white matter components, in order to further refine language models of the brain.

5. Conclusion

We have shown, not only that it is possible to reliably isolate the dorsal and ventral IFOF using simple deterministic tractography procedures, but that this distinction has meaningful functional implications for brain-based reading models. The FA in the left dorsal IFOF was found to be specifically related to tasks, such as Go/No-Go and mixed naming, that require response selection, attention switching, and/or higher visual attentional demands. In contrast, FA in the left ventral IFOF was more broadly related to naming and word recognition processes. This is the first evidence of a functional distinction between the dorsal and ventral IFOF, and demonstrates the importance of characterizing these tract components as separate entities in future white matter studies of language. Not only will this improve the specificity of neurolinguistic models, but it may also give further insight into the relationships between white matter and language disorders, and help inform the development of future language interventions.

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Appendix 1: Example of Words Used in Behavioural Tasks

Pure exception	Pure regular	Mixed naming	GNG with nonwords	GNG with pseudohomophones
ground	black	stroke	trial	fule
stood	shout	are	bright	worm
said	proud	apt	yeast	shreik
heart	fence	earn	coush	tuf
where	punch	boss	seg	pause
pour	dial	cause	grew	yor
month	sweet	prove	crow	aunt
threat	craft	crawl	norve	doun
floor	brain	hearth	glove	done
joust	too	ninth	gross	gone
calf	torn	song	threet	flute
bomb	stitch	poll	breek	steel
give	mug	tread	soize	graph
mourn	surf	throne	shoa	mouth
mange	air	broad	sense	wel
leapt	saw	mauve	won	pohr
full	food	frame	swoap	yearn
breath	hear	sole	pusk	musst
suite	feel	ton	woald	blow
taunt	strike	breach	charm	will
source	well	grove	brief	whood
round	cruise	bulk	swear	stawck
would	snatch	stop	view	tun
soot	win	bought	cliff	court
climb	nine	pare	stock	suede
pouch	speech	great	besh	lawss
both	hoarse	fool	mind	nyne
sew	drill	steal	threab	hahnd
grow	carve	gauge	truth	crepe
dread	freeze	mould	whoce	ghoul
troll	days	veil	land	glyde
love	skate	soul	stern	flame
break	forge	merge	brodge	one
dough	steep	home	meent	breaf
come	pray	hour	height	twice
once	blade	year	short	ease
tour	swell	seize	says	sweat
noun	did	blood	sour	siv
clause	stage	step	launch	gaze

red = exception word

black = regular word

green = nonword

blue = pseudohomophone

wood
pear
hound
worse
chief
waste
put
two
grey
couch
herb

brown
pine
vale
mince
ledge
aid
gland
perm
guess
scream
crime

pierce
cloth
arch
croup
nurse
bear
munch
pleat
ditch
does
realm
starch
hoop
own
flour
coil
cringe
surge
juice
wear
flair
learn
quart
wealth
suave
slave
whose
scribe
flood
fruit
tooth
thread
hint
world
girl
grief
goes
youth
swerve
sauce
dance
proof
shoe

steam
welf
storm
down
whom
creek
flash
sainf
thrust
caste
wape
plague
frant
foot
cime
crook
dole
steak
brair
wipe
grev
sparse
cost
brooch
door
doce
vose
whole
pem
cust
hold
guide
swathe
toin
breit
binch
while
with
breest
front
sheb
seb
dearth

hite
lunch
same
vogue
death
staff
style
bound
monk
sweep
pohrk
thret
hence
ledj
shed
tin
scarce
stead
buhlk
duz
mintz
sware
cross
breth
plaid
had
some
wage
leave
pope
tryal
soup
hoal
stick
gihv
tue
touch
frea
broach
most
crowd
risk
mow

loss
prey
dodge
draw
bush
blind
hand
cough
bribe
bread
role
much
have
swoop
drop
chunk
scroll
sponge

darf
olf
throat
ranch
tomb
fraud
scale
board
shove
lose
saint
triat
mov
trap
tronce
glide
savs
soite
whece
yoarn
pork
push
post
bridge
mulch
blink
drawer
sare
spread
claim
truce
tough
must
youn
path
wisp
heard
heat
trance
flane
barb
pint
meant

breatch
saynt
host
off
dost
fleet
toast
dress
hood
ern
gess
pyne
wool
freak
heet
bath
bull
glahnd
trough
showt
grouch
whyle
jaunt
heer
bawss
plain
wich
prime
pull
hooht
haunt
south
sez
dawdge
vase
bunch
wunce
breast
prufe
tree
dohr
couch
four

do
flow
house
which
toask
move
mist
swean
grov
moive
sieve
stroll
hoot
priest
count
glow
snow
earth
tov
none
per
free
grind
easc
range

burp
faith
doh
dark
stow
work
green
psalm
scent
hook
mount
comb
roll
clash
match
bowl
lahnd
chart
taste
head
nerve
sag
womb
bare
stack