Is language laterality related to language abilities?

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Abstract

It is well known that language processing depends on specialized areas in the left side of the brain in the majority of the population. A popular view is that developmental language disorders result from a poorly lateralized brain, but evidence in support of this has been weak and inconsistent.

In this thesis, I investigated language-related asymmetries in brain structure and function, and their behavioural relevance in both individuals with specific language impairment (SLI) and typically developing adults. Combining different brain imaging techniques, I looked at group-level as well as individual estimates of language laterality and its relationship to language abilities.

The aim of my first two studies was to investigate the neural underpinnings of SLI in terms of white matter microstructure and functional organization associated with auditory processing. For this, diffusion and functional MRI data was obtained in a small number of families with a history of SLI and in control families. Compared with neurotypical controls, children with SLI had lower white matter integrity in the corpus callosum, and in white matter areas corresponding to the dorsal and ventral language pathways. The expected functional lateralization for auditory processing was not observed in either group.

In the second half of my thesis, I assessed language laterality in 215 neurotypical adults. I demonstrated that functional transcranial Doppler (FTCD) ultrasonography could reliably assess functional lateralization across different language processes. From this large group, I identified 16 individuals with atypical language lateralization and compared them to a group of 16 typically lateralized individuals using a combination of FTCD, MRI and behavioural measures of language laterality and language abilities. The two groups differed significantly in terms of lateralization assessed by functional MRI and diffusion imaging. The atypical group had lower left and greater right hemisphere activation compared with the typical group, and lacked the leftwards asymmetry in the ventral language tract seen in the typical group. The groups did not differ in terms of cognitive measures. Different functional laterality assessments were concordant in the typically lateralized individuals but were inconsistent in the individuals assessed as atypical by FTCD.

In brief, my findings suggest that for some individuals language lateralization may be unstable and varies depending on task or other factors. Even so, such differences do not appear to have consequences for language or other cognitive development.

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Für Ida.

Ich wünsche dass dir, wenn du das Sprechen erst einmal gemeistert hast,
nie die ‘richtigen Worte’ fehlen.

Acknowledgments

Thank you, diolch, grazie, gracias, terima kasih, obrigado, köszönöm, or danke - in any language it fails to convey my deep gratitude and respect for all the people who inspired and supported me during my exciting, sometimes bumpy PhD journey.

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Preface

The data presented in Chapters 2 and 3 of the thesis was inherited from an investigation led by Professor Kate Watkins and Professor Dorothy Bishop at the University of Oxford. Other data obtained in some of these participants was previously reported by Badcock et al. (2012), who documented abnormalities in brain structure and function in the language-impaired children using a different task. The analysis of the functional and diffusion magnetic resonance imaging data, was my original work.

I collected and analysed all data presented in the remained chapters, which focused on neurotypical adults.

Abstract

It is well known that language processing depends on specialized areas in the left side of the brain in the majority of the population. A popular view is that developmental language disorders result from a poorly lateralized brain, but evidence in support of this has been weak and inconsistent.

In this thesis, I investigated language-related asymmetries in brain structure and function, and their behavioural relevance in both individuals with specific language impairment (SLI) and typically developing adults. Combining different brain imaging techniques, I looked at group-level as well as individual estimates of language laterality and its relationship to language abilities.

The aim of my first two studies was to investigate the neural underpinnings of SLI in terms of white matter microstructure and functional organization associated with auditory processing. For this, diffusion and functional MRI data was obtained in a small number of families with a history of SLI and in control families. Compared with neurotypical controls, children with SLI had lower white matter integrity in the corpus callosum, and in white matter areas corresponding to the dorsal and ventral language pathways. The expected functional lateralization for auditory processing was not observed in either group.

In the second half of my thesis, I assessed language laterality in 215 neurotypical adults. I demonstrated that functional transcranial Doppler (FTCD) ultrasonography could reliably assess functional lateralization across different language processes. From this large group, I identified 16 individuals with atypical language lateralization and compared them to a group of 16 typically lateralized individuals using a combination of FTCD, MRI and behavioural measures of language laterality and language abilities. The two groups differed significantly in terms of lateralization assessed by functional MRI and diffusion imaging. The atypical group had lower left and greater right hemisphere activation compared with the typical group, and lacked the leftwards asymmetry in the ventral language tract seen in the typical group. The groups did not differ in terms of cognitive measures. Different functional laterality assessments were concordant in the typically lateralized individuals but were inconsistent in the individuals assessed as atypical by FTCD.

In brief, my findings suggest that for some individuals language lateralization may be unstable and varies depending on task or other factors. Even so, such differences do not appear to have consequences for language or other cognitive development

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Introduction

Language is the bridge that connects each of us with the world. It is central to how we make sense of things and fundamental to how we communicate and share our experience. It is the essence of interpersonal connection in the present, and cultural connection – in the form of stories and histories – to the past and future. Language is, to many, what makes us human. So it's no surprise that a large number of psychologists, linguists, and neuroscientists are fascinated by how the brain processes "words and the methods of combining them for the expression of thought" (The Oxford English Dictionary, Language 1933, p. 57). A PubMed search with the keywords "brain" and "language" found 1523 articles that were published just this year (January to September 2016). A hundred of those papers focussed on hemispheric specialization for language including structural brain asymmetries (44) and functional lateralization (56).

What is brain lateralization? The longitudinal fissure separates the human brain into a left and right hemisphere, which are connected by the corpus callosum. At a first glance the two cerebral hemispheres seem to be identical, but it is well known that the left and right sides of the brain are not entirely symmetrical - neither in structure nor in function. The term 'lateralization' refers to the extent to which a particular cognitive function is localized primarily in one half of the brain. In most people, speech and language abilities are predominantly mediated by the left hemisphere.

Advances in neuroimaging have offered significant insight into the structural and functional organization of the neural language network. Differences in image acquisition parameters and image analysis techniques between studies, however, have led to many inconsistencies in the literature. The extent to which results and methods are comparable and reliable is not well established. It is crucial to determine statistically valid, powerful, and reliable methods, which can be used in combination to examine language lateralization in a single person/patient or across populations. The neurobiology of language, specifically as it relates to the hemispheric specialization for language, requires significant further study as many basic questions remain unanswered, such as: What is the best way to assess language lateralization in healthy individuals and patients? Do structural asymmetries underlie functional lateralization? Are language and literacy skills associated with hemispheric specialization?

For a comprehensive analysis of hemispheric specialization for language, I used a range of neuroimaging techniques to investigate functional and structural asymmetries in both neurotypical individuals and those with language impairment. The introductory chapter of my thesis therefore covers the main aspects of what is known about the neurobiology of language and explains influential theories about the origin of hemispheric specialization; it describes how lateralization changes with age and reviews the relationship between hemispheric specialization and language abilities. At the end of this chapter, I provide an outline of my thesis and my research objectives.

1.1 A short introduction to the neurobiology of language

Language is a complex dynamic process that engages an extensive network of brain regions in the left perisylvian cortex, which includes prefrontal, frontal, temporal and parietal area. Before the availability of non-invasive neuroimaging methods, our understanding of the neurobiological basis of language rested primarily on lesion studies.

In 1861, the French neurologist Paul Broca reported a post-mortem study of a patient named Leborgne, who had been severely impaired at articulating language. His inability to speak was described by Broca as follows:

> *"He could no longer produce but a single syllable, which he usually repeated twice in succession; regardless of the question asked him, he always responded: tan, tan, combined with varied expressive gestures. This is why, throughout the hospital, he is known only by the name Tan (Broca, 1861, p. 344)."*

After Leborgne died, the biopsy of his brain revealed a large lesion in the frontal lobe of the left hemisphere – specifically, in the left inferior frontal gyrus (IFG), a region that, based on its cytoarchitecture, corresponds to Brodmann's area (BA) 44, pars opercularis and BA 45, pars triangularis. By deduction, the damaged area – later referred to as Broca's area – was linked to language production (Broca, 1861). Two years later, Broca published a paper in which he described nine more patients with left frontal lobe lesions, all of whom had lost their ability to produce language (Broca, 1863).

Similarly, the German anatomist Karl Wernicke (1874) described a patient who was able to speak but could barely understand what was said to him, despite being able to hear normally. Wernicke (1874) found that the parietal/temporal area of the patient's left hemisphere was damaged and concluded that this region was involved in language comprehension. Today, we refer to this region as Wernicke's area, which corresponds roughly to BA 22 and BA 42 in the posterior two-thirds of the lateral superior temporal gyrus (STG). The discoveries made by Paul Broca and Karl Wernicke have since been validated by modern research using non-invasive neuroimaging techniques in patients and neurotypical participants. In addition, parts of the middle temporal gyrus (MTG) and the inferior parietal lobe, as well as the angular gyrus, have been implicated in language functions such as phonological storage and reading (Dejerine, 1891).

1.1.1 The Wernicke-Lichtheim-Geschwind model of language

Karl Wernicke (1874) drew on Meynert's neuro-anatomical approach to the study of aphasia and Broca's reports on the localization of the motor speech area to further develop his neurological model that related different types of aphasia to specific brain lesions. For instance, he predicted that if there were damage to the white matter tracts that connect inferior frontal with superior temporal language regions, patients would have problems in repeating what was heard despite intact speech production and comprehension (Wernicke, 1874).

In 1885, the German physician Ludwig Lichtheim was the first to confirm this type of disconnection syndrome – now known as 'conduction aphasia'. Lichtheim (1885) also systematically summarized Wernicke's studies into a framework for classifying different types of aphasia. The 'Wernicke-Lichtheim model', which became the standard theory of neural language processing, was born. In its most simplified form, the 'Wernicke-Lichtheim model' assumed a system of connections between separate centres for acoustic-sensory aspects supporting language comprehension (Wernicke's area) and motor aspects supporting language production (Broca's area). It further predicted that lesions of the centres or the connections between them (arcuate fasciculus) would result in language processing problems (Lichtheim, 1885). For example, damage to the motor word representations in Broca's area would lead to a disruption of language production with a sparing of comprehension, whereas damage to Wernicke's area would impair comprehension *and* production, because the inputs from sensory word images were needed to select the corresponding motor word representations (Lichtheim, 1885; Wernicke, 1874).

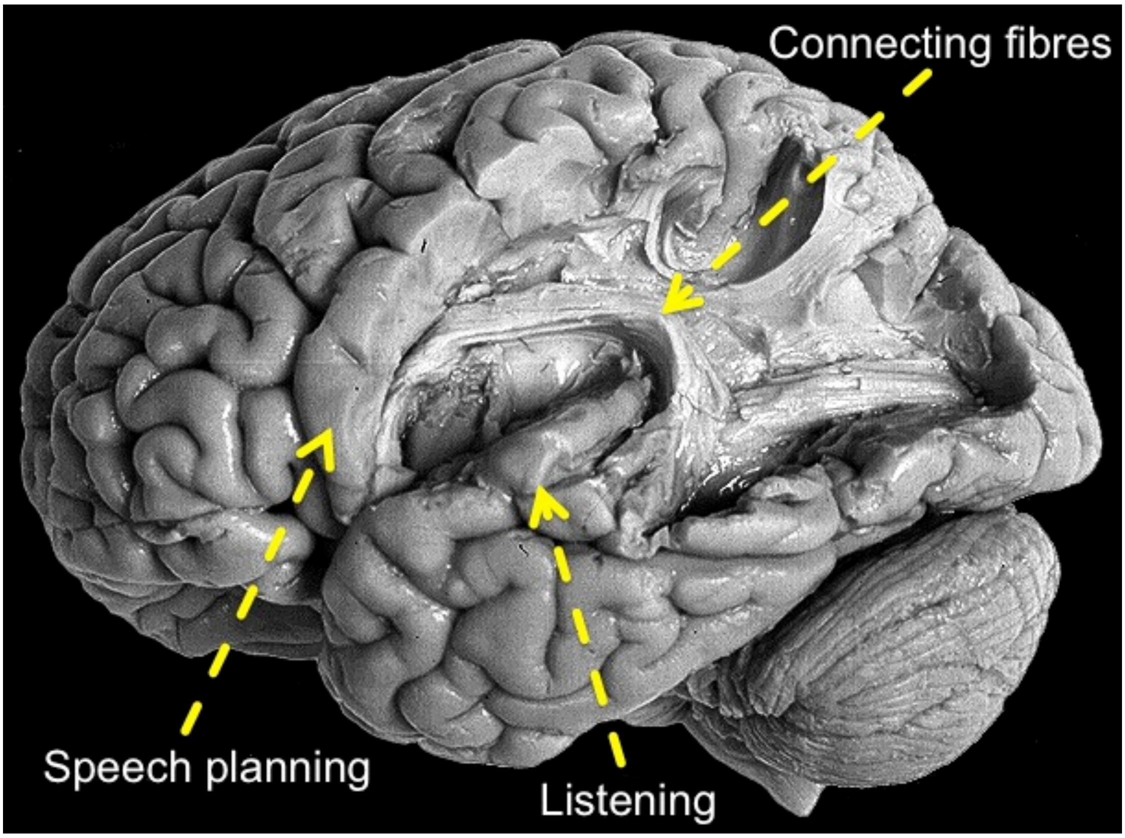

Figure 1.1 *Dissection of the arcuate fasciculus (AF). Dissection of the arcuate fasciculus (AF). The AF was dissected from the lateral aspect of the left hemisphere. The long segment of the AF (Connecting fibres), which joins superior temporal cortex (Listening) with inferior frontal cortex (Speech planning), only appears after removal of the superficial segments.*

The model was revolutionary for its time not only because it proposed an explicit information-processing account with distinct centres and sub-systems that were mapped to localized brain areas, but also because it provided a framework for classifying different types of aphasia - including those that were not yet observed but assumed to be possible based on theoretical considerations (Lichtheim, 1885). However, the oversimplified ‘Wernicke-Lichtheim model’ was severely criticized – most famously by Freud (1953) – to the extent that it lost its influence and fell into disuse in the 1950s and 60s. It was revived in 1970 by Norman Geschwind, who adopted the basic framework and added new insights into brain connectivity as derived from anatomical, physiological and neuronographic studies in humans as well as animals (Geschwind, 1965, 1970; Geschwind & Levitsky, 1968).

For almost 150 years, the classic model of neural language processing has offered a heuristic that stimulates scientific research and guides clinical diagnosis (Damasio, 1992). Although the model is generally understood to be inadequate for explaining the complexities of language processing (see Dronkers & Larsen, 2001), it is still used for the evaluation and treatment of acquired language disorders. Its resilience is due largely to how it captures the striking difference between patients who have anterior damage resulting in slow laboured articulation (Broca's aphasia) and those with posterior damage, who typically produce fluent, rapidly articulated, but unintelligible speech (Wernicke's aphasia). Recently, models with a dual-stream architecture describing dorsal and ventral language pathways have emerged as potential replacements (Hickok & Poeppel, 2007). The on-going challenge for researchers is to devise a model of brain-language relations that accounts for dynamic neural changes due to biological, developmental, and environmental influences, that also explains both normal and impaired language processing.

1.1.2 The dual stream model of language

Current models of the functional anatomy of language draw on what is known about the cortical organization of visual processing and the anatomy of the auditory system in non-human primates proposing a dual-stream framework (Hickok & Poeppel, 2004, 2007; Scott & Wise, 2004). Hickok and Poeppel's (2004, 2007) model for auditory speech processing suggests that frontal and temporal language cortices are linked via two main routes: a dorsal stream, which is involved in mapping auditory speech sounds onto articulation; and a ventral stream, which is involved in mapping sounds onto meaning. The general concept underlying this model – that the brain interfaces sensory information with two different systems – has not only proven useful in understanding neural language processing, but also in describing the major clinical aphasia syndromes: Broca's aphasia would reflect damage to the dorsal stream, while Wernicke's aphasia would be linked to lesions of the ventral stream (Hickok & Poeppel, 2004). Importantly, both streams are assumed to rely on underlying structure in the form of several white matter fibre bundles (Friederici, 2009; Saur et al., 2008).

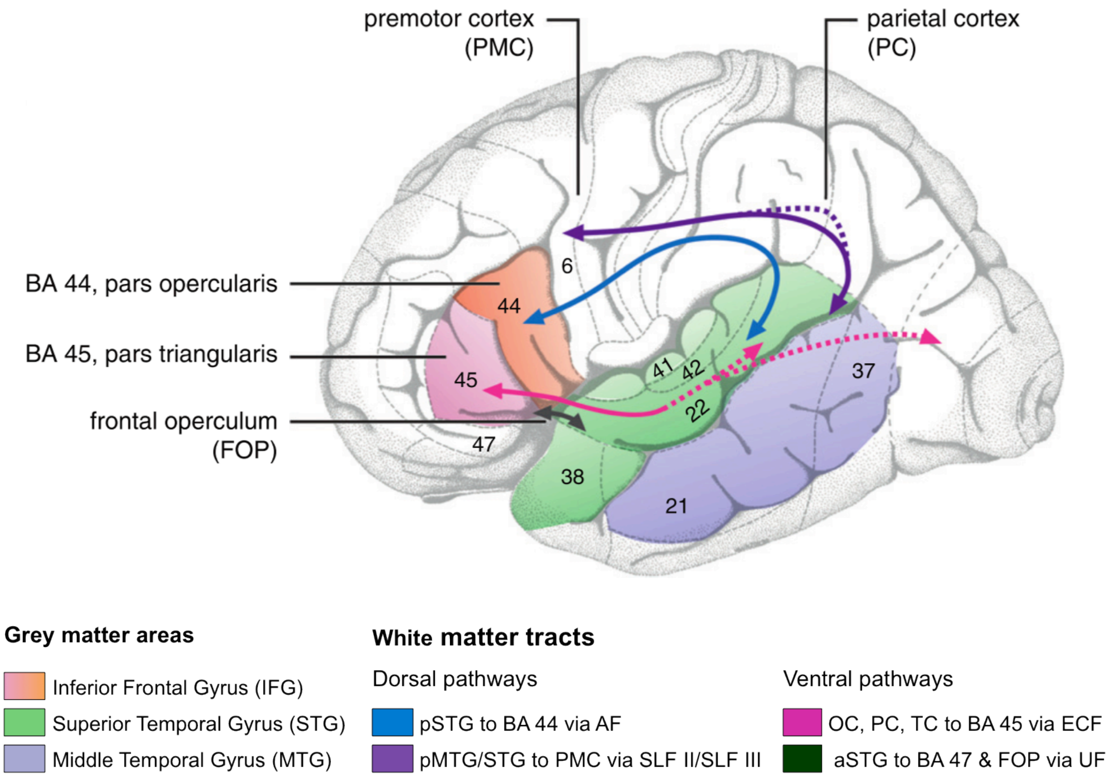

Figure 1.2. *Language-related cortical areas and fibre tracts. Schematic view of the left hemisphere. The dorsal pathway connecting the posterior STG (pSTG) with frontal cortex (FC), that is BA 44 (and others), involves the arcuate fasciculus (AF); the dorsal pathway connecting the posterior temporal cortex (pMTG/STG) with dorsal premotor areas (dPMC) involves the SLF III and/or the SLF II. The ventral pathway connecting the occipital (OC), the parietal (PC), and the temporal (TC) cortex with the inferior frontal cortex, that is BA 45, involves the inferior frontal-occipital fasciculus (IFOF) - also called the extreme capsule fasciculus (ECF); the ventral pathway connecting anterior STG (aSTG) with anterior inferior FC including BA 47 and the frontal operculum (FOP) involves the uncinate fasciculus (UF). Adapted from "The language network" by A. D. Friederici and S. M.E. Gierhan, 2013, Current Opinion in Neurobiology, 23, p. 251. Copyright 2012 by Elsevier Ltd.*

1.1.2.1 The dorsal stream: anatomy and function

The dorsal pathway comprises large association fibres running through the superior longitudinal fasciculus (SLF), which can be delineated into four subcomponents: the dorsal fronto-parietal fibres or SLF I, the middle fronto-parietal fibres or SLF II, the ventro-rostral fibres or SLF III, and a distinct fronto-temporal pathway described as the arcuate fasciculus (AF, Makris et al., 2005). The AF arches around the caudal portion of the insula and parallels the SLF until it branches laterally toward the inferior frontal and precentral gyri (Glasser & Rilling, 2008; Saur et al., 2008). It is believed to serve as the primary dorsal pathway directly linking the two language foci in the left hemisphere: Wernicke's area and Broca's area (Anderson et al., 1999). In a recent diffusion MRI study conducted by Catani and colleagues (2007), inter-hemispheric differences were found in the AF with a strong leftward lateralization in more than 50% of the subjects. The study demonstrated that the overall prevalence of asymmetrical distribution of the AF is higher (82.5%) than the one previously reported for the PT (65%). Thus, the authors proposed that the AF might represent a key anatomical substrate for language lateralization. Anatomical models of white matter connections, however, are predominantly based on diffusion magnetic resonance imaging (DTI) or post-mortem dissection methods, which are not ideal for identifying the precise course of fibre bundles and specifically their grey matter targets (Schmahmann & Pandya, 2006). In animal research, histological tract tracing techniques can be used to determine the exact origin and termination of a pathway. Studies that have used this method in the macaque brain have suggested that there is no direct connection between posterior STG (Wernicke's area homologue) and anterior IFG - Broca's area homologue (Schmahmann & Pandya, 2006, for review). As such, the nature or even existence of the dorsal connection via the SLF/AF is still unclear. Frey and colleagues (2008), for instances, used high angular resolution diffusion MRI in humans and found a clear dissociations of the trajectory form the anterior extent of Broca's area compared with those from the posterior extent: area 45 connected with STG via the extreme capsule fibre system, whereas area 44 connected with inferior parietal cortex via the third branch of the SLF. This finding is not only consistent with anatomical tracing studies in the macaque monkey (Petrides & Pandya, 1988), but also suggests that the connections of Broca's area are more differentiated than previously assumed. Although the AF may still connect superior temporal with inferior frontal language areas, research suggests that it is not the only pathway (Frey et al., 2008).

According to the Wernicke-Lichtheim model and Geschwind's modern revival of it, lesions of the AF would produce conduction aphasia, which is characterized by deficits in verbal repetition (Lichtheim, 1885; Geschwind, 1970). Research has since confirmed that this syndrome is associated with such damage (Bernal & Ardila, 2009, for review). Similarly, Breier et al. (2008) correlated white matter damage with aphasic behaviour, demonstrating its contribution to verbal repetition. Agenesis of the AF, however, does not result in conduction aphasia (Bernal et al., 2010), and fluency impairment often emerges in combination with cortical lesion(s) (Breier et al., 2008; Marchina et al., 2011). Hence, the dorsal pathway may play a more general role in phonological processing (Duffau et al., 2002; Duffau, Gatignol, Denvil, Lopes, & Capelle, 2003). Consistent with this notion, Duffau and colleagues (2002, 2003) showed that direct electrical stimulation of the AF in awake patients who performed a picture-naming task elicited phonemic paraphasia (an unintended substitution of a word with a nonword). In addition, the dorsal pathway has been implicated in the processing of complex syntactic structures (Brauer et al., 2013; Friederici et al., 2006; Wilson et al., 2011). Using DTI in patients with primary progressive aphasia, Wilson and colleagues (2011) found that microstructural damage to the dorsal language pathway was strongly associated with deficits in production and comprehension of syntax. The assumption that the dorsal stream supports higher-order language functions, such as complex grammar, is further supported by phylogenetic and ontogenetic findings. Specifically, in non-human primates that do not possess syntactic abilities, the AF is not well developed (Rilling et al., 2008). This is also true for children who have not yet mastered the processing of complex sentences (Brauer, Anwander, & Friederici, 2011). The dorsal pathway may therefore play an important role in language learning, too (Bernal et al., 2010). In fact, Yeatman and colleagues (2011) have shown that diffusion properties of the AF predict both phonological awareness and reading skills in children aged 7-11 years.

1.1.2.2 The ventral stream: anatomy and function

At least two fibre bundles have been proposed to underpin the ventral stream, namely the uncinate fasciculus (UF) and the extreme capsule fasciculus (ECF; Makris & Pandya, 2009). The UF runs laterally and ventrally through ECF to the fibres of the inferior frontal-occipital fasciculus (IFOF; Martino et al., 2010) and links the anterior temporal lobe and temporal pole with the orbitofrontal cortex and the ventro-medial located operculum (Catani & Schotten, 2012). The ECF was first discovered in the macaque monkey and is thought to convey fronto-temporal connections bidirectionally (Berke, 1960; Petrides & Pandya, 1988, 2006). Frey and colleagues (2008) confirmed its existence in the human brain; interposed between the claustrum and the insular cortex. Because the ventral part of the ECF and the external capsule have similar orientations and contribute to the inferior frontal-occipital fasciculus (IFOF), some authors identify these fibres as part of this long association fibre tract (Catani & Schotten, 2012; Duffau, Moritz-Gasser, & Mandonnet, 2013). Makris and Pandya (2009), however, demonstrated that the ECF could be differentiated from neighbouring fibre pathways such as the external capsule, the middle longitudinal fascicle, UF, AF, SLF and the inferior longitudinal fascicle. The ECF's central location within the language zone – linking Broca's and Wernicke's area as well as the inferior parietal lobule (angular gyrus) – suggests that it is the major connection of the ventral stream (Makris & Pandya, 2009).

The ventral pathway connects areas in the inferior frontal cortex that have been associated with both controlled retrieval of semantic representations and during long-term lexical storage (Lau, Phillips, & Poeppel, 2008). The majority of DTI tractography studies that related the ECF to semantic processing included patients with semantic dementia (Agosta et al., 2010), stroke (Rolheiser, Stamatakis, & Tyler, 2011), or cerebral glioma (Duffau et al., 2005). In more than 85% of patients, direct electrical stimulation of the superficial layer of ventral tract led to semantic paraphasia (i.e. replacement of one word by another real word) during picture naming (Duffau et al., 2005), while stimulation of the deeper layer of the ventral tract induced non-verbal comprehension disturbances during semantic matching as assessed by the Pyramid and Palm Trees test (PPT) in more than 90% of patients (Moritz-Gasser, Herbet, & Duffau, 2013). Strikingly, the direct electrical stimulation of superficial layers of the ventral pathway elicited semantic paraphasia with normal nonverbal semantic processing and vice versa during stimulation of the deeper layer, indicating a double dissociation (Moritz-Gasser, Herbet, & Duffau, 2013). Another study by Rolheiser and colleagues (2011) correlated the behavioural performance of stroke patients with the integrity of their language-related white matter pathways and found that semantics is purely processed by the ventral tract, while phonology is processed by the dorsal tract. In addition, studies using FMRI-based fibre tracking have suggested that the ventral pathway is involved in syntactic processing (Friederici et al., 2006; Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013).

1.2 The enigma of language lateralization

Asymmetries are widespread in nature and appear to be the rule rather than exception: from chiral molecules (Quack, 1989) over cell polarity in single-cell organisms (Nelson, 2003) to the Byron asymmetry in the universe (Sakharov, 1991). Humans are no exception from this rule – neither behaviourally, e.g. most people write with a particular hand, kick a ball with a particular foot, or peer through a telescope with a particular eye – nor structurally, e.g. internal organs including our heart, lungs, stomach and liver are arranged asymmetrically.

In the brain, the discovery of left-hemisphere specialization for language was one of the earliest indications of functional differences between the hemispheres (Broca, 1861). It has been estimated that 95% of right-handers and 73% of left-handers are left-lateralized for language (Knecht et al., 2000b). The other 5% of right-handers and 27% of left-handers display what is called 'atypical lateralization', meaning that language processing happens either bilaterally, or mostly within the right hemisphere.

In addition to functional lateralization, Geschwind and Levitsky (1968) reported an anatomical asymmetry of the of the posterior Sylvian region in favour of the left hemisphere. This triangular region - known as the planum temporale (PT) - coincides spatially with the heart of Wernicke's area. While individuals who are left-lateralized for language function show a strong leftward asymmetry in the PT, those who are right-lateralized do not - at least not consistently (Moffat, Hampson, & Lee, 1998; Ratcliff, Dila, Taylor, & Milner, 1980). In addition, Foundas et al. (1994) reported an association between PT asymmetry and degree of language lateralization in eleven patients who had language lateralized to the left hemisphere, as assessed by the Wada test. Other studies, however, failed to replicate this structure-function correlation (Eckert et al., 2006; Jäncke & Steinmetz, 1993). Since there are many different ways of defining and measuring the PT with a wide range of results, a direct link between PT structure and language function has not been clearly established.

Although recent developments in neuroimaging techniques have encouraged new research on language laterality, uncovering new possible functional and structural asymmetries in the brain (Hutsler & Galuske, 2003; Toga & Thompson, 2003, for review) theories about the origin of hemispheric specialization are still actively debated.

1.1.3 Why is the brain asymmetrical in structure and function?

There is no theory that explains why our brain is asymmetrical. Nor is there one that explains why language lateralization is associated with hand dominance. Rather, hemispheric specialization is thought to reflect several factors, such as evolutionary influences, genetic background, pre- and postnatal development, and neurobiology.

1.1.3.1 Hypotheses related to evolution, heredity and development

Evolution. Evolutionary theories postulate that having a certain function lateralized to one hemisphere represents a selective advantage. Some 3.8 million years ago, the species of the iconic Lucy fossil – the *Australopithecus afarensis* – had a brain that was about a third the size of the modern human brain (Holloway, 1983). Intracranial space did not increase in step with brain size; therefore, cortical folding increased (Zilles et al., 1989). Given increased brain size and complexity, the duplication of functions was no longer efficient compared with hemispheric specialization, which left the other hemisphere free to perform additional functions (Levy, 1977). Moreover, the distribution of functions of the two hemispheres allowed for simultaneous parallel processing (Vallortigara & Rogers, 2005).

In larger brains, action potentials have to travel longer distances, resulting in a disadvantage for performing time-critical computations unless conductivity is improved (Ringo et al., 1994). The callosal fibre diameter spectrum, however, appears to be similar across brain sizes, indicating no significant adaptation in inter-hemispheric conduction speed (Ringo et al., 1994). Instead, Ringo and colleagues (1994) proposed that local circuits within one hemisphere evolved to compensate.

Given that humans can understand speech at presentation rate of 400 words per minute (Orr, Friedman, & Williams, 1965), the compensation for transcallosal conduction delay seems to be particularly important in auditory analysis and vocal control. The prediction followed that there should be a positive correlation between brain size and degree of lateralization (Ringo et al., 1994). Consistent with this hypothesis, Anderson (1999) demonstrated that if interneuronal conduction time increases proportional to interneuronal distance in an idealized randomized system, the only way to increase the instance of synaptic events in a fixed period of time is to spatially cluster proximate interneuronal connections. Furthermore, Jäncke et al. (1997) used structural MRI to measure the size of the corpus callosum (CC) in neurotypical adults and found that larger brains had relatively smaller callosa. A smaller CC has been thought to reflect fewer and/or thinner white matter fibre bundles connecting the two hemispheres, and might therefore indicate reduced inter-hemispheric communication, possibly leading to increased hemispheric specialization, in larger brains (Jäncke et al., 1997).

The main argument against an evolutionary advantage of hemispheric specialization is that bilateral language representation is also common (Binder et al., 1996; Knecht et al., 2000b; Pujol et al., 1999). In fact, one study found that greater bilaterality of language allowed autonomous verbal processing within each hemisphere (Knecht et al., 2002). Using transcranial magnetic stimulation (TMS) to temporarily disrupt language function, Knecht and colleagues (2002) found that healthy participants with bilateral language representation were less affected by either left- or right-side TMS. This suggests that those individuals will remain relatively unimpaired in verbal functioning after unilateral brain damage as bilateral language representation allows for ready compensation (Knecht et al., 2002). In addition, language lateralization, in general, does not provide a cognitive advantage (Knecht et al., 2001). In a large study involving 326 healthy participants, Knecht and colleagues (2001) found no systematic relationship between language lateralization (degree and direction) and academic achievement, numbers of spoken languages, and engagement in artistic activities.

The consistently demonstrated relationship between handedness and language lateralization has led to another evolutionary hypothesis suggesting that left-hemisphere specialization for language evolved from its control of the right hand (Corballis, 2003). Specifically, Corballis (2003) argues that hand gestures were used for communication prior to the development of speech. The existence of an innate relationship between gestures and language is supported by research on indigenous gestural languages (Kegl & McWhortner, 1997; Goldin-Meadow & McNeill, 1999) as well as by neuroimaging studies that indicate a high degree of similarity between the neural organization of sign and spoken language (Emmorey et al., 2002; MacSweeney et al., 2002).

The fact that great apes (including chimpanzees, bonobos and gorillas) have a homologue of Broca's area (BA 44) further supports this hypothesis (Cantalupo & Hopkins, 2001). In monkeys, the so-called 'mirror neurons', which are believed to subserve the imitation of behaviours such as hand grasping and manipulation, are located in area 44. This suggests that the area may have been initially specialized for primitive forms of gestural communication. Indeed, chimpanzees living in captivity not only use manual gestures that are referential and intentional, but they also communicate with a right-hand bias, especially when gesturing is accompanied by vocalization (Hopkins & Leavens, 1998). The congruence in functional anatomy of area 44 between humans and great apes suggests that hemispheric specialization for language evolved from the pre-existing asymmetrical motor system responsible for gestural communication (Corballis, 2003).

Heredity. Genetic theories of hemispheric specialization assume that the direction and/or degree of cerebral asymmetry are inherited - or, in some cases, randomly determined (Annett, 1985, 2006; McManus, 1985). A common way to quantify the role of genes in the development of a specific human phenotype is the conducting of twin studies. Classical twin studies involve the comparison of monozygotic (MZ) twins, who are genetically identical, and dizygotic (DZ) twins, who share on average 50% of alleles from polymorphic genes, allowing researchers to evaluate the degree of genetic and environmental influence on the phenotype in question. If genes are important in determining phenotype, MZ twin pairs should show a greater phenotypic resemblance than DZ twin pairs.

Thompson and colleagues (2001) were the first to create maps of genetic influences on human brain structure. They found that the amount of grey matter in the frontal cortex was highly heritable. More importantly, genetic factors significantly influenced inferior frontal and superior temporal areas in the left hemisphere only, indicating heritability for structural asymmetry of anterior and posterior language cortex (Thompson et al., 2001). Later studies confirmed that heredity plays an important role in structuring the temporal lobe, in particular perisylvian regions (Geschwind et al., 2002; Posthuma et al., 2002). Compared to grey matter volumes (Geschwind et al., 2002; Posthuma et al., 2002; Thompson et al., 2001), gyral and sulcal patterns seem to be less genetically determined (Lohmann, von Cramon, & Steinmetz, 1999; Thompson et al., 2002). Studies of MZ twins that have explicitly examined asymmetry indices, however, reported only weak intraclass correlations for brain regions that have previously been shown to be asymmetric in structure, including the PT (Steinmetz et al., 1995) and AF (Häberling, Badzakova-Trajkov, & Corballis, 2013).

Another MRI study investigated brain asymmetry based on the integrity of white matter in 60 MZ twin pairs and 209 DZ twin pairs, as well as in their siblings (Jahanshad et al., 2010). Heritability was computed for asymmetry indices of eleven white matter fibre bundles. Jahanshad et al. (2010) found that genetic factors accounted for variance in asymmetry of four regions, namely the anterior thalamic radiation (37%), the forceps major (20%), the inferior-fronto-occipital fasciculus (33%), and the uncinate fasciculus (20%). Interestingly, the latter two tracts have been proposed to underpin the ventral language stream (Catani & Schotten, 2012; Makris & Pandya, 2009). It is important to note that only the inferior-fronto-occipital fasciculus gave heritability estimates greater than 0.25 in this study (Jahanshad et al., 2010).

The above studies described asymmetries in brain structure; it is still unclear how well structural asymmetries relate to functional lateralization of language. Only a handful of studies have examined the relationship between structural and functional asymmetry, all of which revealed inconsistent findings (Powell et al., 2006; Propper et al., 2010; Vernooij et al., 2007). Using FMRI, Badzakova-Trajkov and colleagues (2010) assessed functional lateralization for language, spatial judgement and face processing in MZ twins (half of which were concordant and half discordant pairs for handedness). While all three paradigms revealed the expected pattern of lateralization – i.e. left for language and right for the nonverbal tasks – only interclass correlations for indices of language lateralization were significant in the concordant, but not discordant group

(Badzakova-Trajkov et al., 2010). If handedness is ignored, statistical analysis of the combined sample reveals that MZ twins were no more similar than is expected by chance (Bishop, 2013).

While there is some evidence for heritability of structural and functional asymmetries, cerebral laterality cannot be influenced exclusively by one’s genotype. For example, identical twins that are discordant for handedness also differ considerably in the asymmetry of the PT (Steinmetz et al., 1994). Furthermore, the methodologies of genetic brain mapping studies should be scrutinised. First, collecting genetic as well as neuroimaging data in the same participants is laborious, time-consuming, and expensive; sample sizes of these studies are therefore relatively small. The magnitude of associations between genes and brain structure or function - especially when comparing MZ twins with DZ twins or heritability between different brain regions - is thought to be small, too (Plomin & Kosslyn, 2001). Thus, very large cohorts are usually needed to detect genetic effects. All the brain imaging studies reviewed here, however, used small samples and had the power to detect only large effects. Second, most studies have focussed on structural asymmetry; only a few examined functional lateralization, and fewer still looked at function-structure associations (e.g. Guadalupe et al., 2015).

Overall, the current literature suggests that genes may play a measurable, but relatively small, role in accounting for variation in cerebral asymmetry/lateralization. Whatever the genetic determinants may be, many pre- and post-natal factors have also been shown to modulate asymmetries in brain structure and function.

Development. Functional and structural asymmetries associated with language processing have been shown to emerge early in human development - some even before birth (LeMay, 1976). Consequently, it has been suggested that prenatal factors such as posture (Previc, 1991) and thumb-sucking (Hepper et al., 1991) lead to perceptual and motor asymmetry. In the third trimester of pregnancy, two-thirds of fetuses are positioned with their right ear facing outwards (Previc, 1991). Previc (1991) argued that the right ear is therefore better positioned to perceive and discriminate sounds (including speech), and that this asymmetry in auditory experience commences the development of cerebral lateralization for language. Previc's hypothesis is consistent with findings from studies using dichotic listening, tachistocopic viewing, electroencephalography (EEG) and other experimental paradigms, indicating that linguistic functions are localized in the left hemisphere from birth, independent of gender (see Hahn, 1987 for review).

In a complex theory, Geschwind and Galaburda (1985) proposed that the development of language lateralization is influenced by levels of fetal testosterone. A testosterone-induced delay in left hemisphere maturation may result in random lateralization; in other words the individual becomes left- or right-lateralized for manual activities and/or language (Geschwind & Galaburda, 1985). Left hemisphere specialization is therefore less likely in men, which in turn increases the chance of observing developmental language disorders in men (Geschwind & Galaburda, 1985). Despite a great interest in the Geschwind-Galaburda model, the data supporting this theory are highly inconsistent and amenable to alternative explanation (see Bryden, Mcmanus, & Bulmanfleming, 1994 for review). For example, while some studies have demonstrated an association between left-handedness and certain cognitive deficits (e.g. Annett, 1999), a more recent study of 1277 older adults found that left-handedness was not associated with decreases in quality of life factors including psychological well-being and physical health (Porac & Searleman, 2002). More importantly, Porac and

Searleman (2002) demonstrated that left-handed participants did not differ from right-handed ones in their cognitive and/or verbal abilities.

1.1.3.2 Hypotheses related to the temporal processing of speech sounds

If we assume that hemispheric specialization is advantageous for evolutionary reasons and/or the full development of language abilities, why would the left hemisphere be favoured over the right? While some have argued for a chance event, perhaps due to genetic mutation (McManus, 1991), recent evidence suggests that certain properties of the left hemisphere have enabled its predominant role in language processing. For example, Zatorre et al. (2001, 2002) proposed a model in which language lateralization is associated with timing differences between left and right auditory cortex, such that temporal resolution is better in the left and spectral resolution better in the right auditory cortex. Because speech requires the perception of rapidly changing sounds (Shannon et al., 1995), language lateralization may have emerged from this perceptual asymmetry. The organization of local, intra-hemispheric circuits (Ringo et al., 1994) might have been sensitive to initial left-hemisphere advantages in temporal processing and, therefore, may have caused a more general functional specialization for language (Zatorre & Belin, 2001; Zatorre et al., 2002). Along a similar line of argument, Poeppel (2003) has suggested that asymmetries related to speech perception may be accounted for by hemispheric differences in sampling time; left auditory areas extracting information from short (~40 Hz) and right auditory areas from long (~4 Hz) temporal integration windows.

Using positron emission tomography (PET), Zatorre and colleagues (2001) tested their hypothesis by examining auditory cortex responses to spectral and temporal variation in pure tone patterns. As predicted, increasing the rate of temporal change predominantly engaged left auditory areas, whereas increasing the number of spectral elements engaged right auditory areas (Zatorre & Belin, 2001). Several independent studies have since replicated this finding (e.g. Jamison et al., 2006; Zaehle et al., 2004, 2008). Golestani and colleagues (2002) investigated the relationship between brain anatomy and the ability to learn rapidly changing sounds, and found that fast learners had a stronger leftward asymmetry of white matter in parietal regions. In addition, functional lateralization of increased temporal processing is paralleled by a leftward asymmetry of the white matter underlying the primary auditory cortex (Penhune et al., 1996) and the planum temporale (Anderson, Southern, & Powers, 1999), suggesting that auditory areas of the left hemisphere are better equipped for processing information rapidly.

Taken together, a number of evolutionary, genetic, developmental, and neurobiological theories have been posited to explain brain asymmetry for language function and structure. Some evidence suggests maturation differences between the two hemispheres, and other that the neural architecture of a gestural system of communication (with right-hand preference) might have preceded and influenced the emergence of language lateralization. Because both speaking and handiwork require fine motor skills, it is conceivable to assume that these activities should be specialized within one hemisphere. The most plausible explanation to date is that properties particular to the left hemisphere - including temporal processing advantages - make it more suitable for hosting language function.

1.1.4 Brain asymmetry and language development

The brain changes most markedly early in life, but it never stops changing: from cradle to coffin it adapts, learns, makes memories and rewires. That said, there are clear stages of maturation of the brain from postnatal through to late adolescence, and less clear ones throughout the lifespan.

Between birth and age six the brain increases in size four-fold, reaching approximately 90% of its adult volume (e.g. Lenroot & Giedd, 2006; Reiss et al., 1996). Structural grey and white matter changes (up to adolescence) do not strictly correspond to total brain size changes; they are thought to reflect functional and behaviour-related reorganization. The development of cortical grey matter volume, for example, tends to follow an 'inverted U' trajectory with volumes in different cerebral lobes peaking at different times: frontal and parietal grey matter reach their maximal volumes at about 10 to 12 years, whereas temporal grey matter volume peaks at 16 years (Giedd et al., 1999). On average, cortical thinning (as part of brain development) seems to occur first in grey matter areas that mediate primary functions - such as motor and sensory systems - and then in the higher order association areas which integrate those primary functions (Lenroot & Giedd, 2006).

Unlike grey matter, white matter volume generally increases with age (Giedd et al., 1999). Some research groups demonstrated that white matter does not begin to decrease until age 45+ (Bartzokis et al., 2001). The growth pattern, however, reveals that white matter changes rapidly in young children before asymptotically approaching adult values (Lebel & Beaulieu, 2009; Lebel et al., 2008; Mukherjee & McKinstry, 2006). The evidence suggests that distinct white matter tracts mature at different speeds, with long projection fibres developing earliest, then commissural, then association fibres (Mukherjee & McKinstry, 2006).

Maturation of white matter tracts is characterized by increasing myelination of fibres, which is reflected in diffusion MRI as an increase in FA during infancy and childhood (Mukherjee et al. 2001; Barnea-Goraly et al. 2005; Lebel et al. 2008). In a cross-sectional study of development, Lebel and colleagues (2008) characterized the trajectory of such microstructural changes in multiple major white matter tracts. They examined a total of 202 healthy participants aged 5-30 years using DTI and found evidence for developmental differences in FA measures from a major dorsal pathway, the SLF, and a major ventral pathway, the ILF. While the ILF appeared mature in late childhood, the SLF did not reach full maturity until mid to late adolescence (Lebel et al. 2008). A more recent study by Brauer et al. (2013), who compared the development of the AF/SLF and the IFOF/ECFS in three different age groups, infants at birth, 7-year old children, and adults, reported an extended trajectory for the dorsal language pathway, too. Unlike ventral connections, which were already evident in newborns, dorsal connections revealed a distinct pattern of maturation: the dorsal tract that terminates in the premotor cortex was also observable at this early age, whereas the dorsal tract that terminates in the inferior frontal gyrus (BA44) was not (Brauer et al., 2013). Brauer and colleagues (2013) thus argue for a maturational primacy of the ventral pathway - together with the dorsal pathway connecting to the premotor cortex - during early postnatal development. In contrast, the other dorsal pathway has been suggested to unfold its involvement in more complex language functions at later stages in development (Brauer et al., 2013). The results of both studies (Lebel et al. 2008, Brauer et al., 2013) are consistent with previous findings on white matter maturation that showed slower myelination in language-related fronto-temporal areas relative to motor related white matter (Pujol et al., 2006).

Although the dorsal language tract appears to be among those fibre bundles that mature only very late in human development (Lebel et al. 2008; Giorgio et al., 2008), a very early leftward asymmetry of the AF has been demonstrated in infants (Dubois et al., 2009). Using DTI, Dubois and colleagues (2009) assessed white matter asymmetries in 23 healthy infants from 1 to 4 months of age based on local diffusion properties and tractography. The reconstruction of the AF and cortico-spinal tract revealed left-right differences during the first postnatal weeks in two white matter networks that sustain functional lateralization in adults (Dubois et al. 2009). The authors propose that the maturation of these white matter fibre bundles is related to the development of hemispheric specialization for language and motor function (Dubois et al., 2009).

These white matter changes are accompanied by major developments in motor, sensory, and higher cognitive functions including language. In a comprehensive MRI study, Skeide and colleagues (2015) measured functional activation in cortical language areas, diffusion properties of the underlying white matter connections, and performance during a child-appropriate sentence comprehension task (sentence-picture-matching) in order to assess the predictive value of brain structure and function for behaviour across development. The authors tested typically developing children from three different age groups, namely 3-4 years, 6-7 years, and 9-10 years, as well as healthy adults aged 21 to 34 years, and found that correlation between FA of the dorsal white matter tract and syntax processing speed was significantly stronger than the correlation between BOLD signal changes in the corresponding fronto-temporal language cortex and syntax processing speed. Moreover, the white matter integrity of the AF significantly predicted speed of performance even after the authors adjusted for age, memory and BOLD activity in the two language areas (Skeide et al., 2015). Skeide and colleagues (2015) concluded that the microstructure of the dorsal language pathway, as assessed by diffusion MRI, was not only the better predictor for behaviour but also explained additional variance in participants' performance above and beyond grey matter activity. The study provided compelling evidence that certain language functions are dependent on the maturation of white matter fibre bundles connecting cortical language hubs (Skeide et al., 2015).

1.1.4.1 Does lateralization change with age and language development?

Changes in language lateralization as the brain ages and develops are relative to an undetermined baseline - the asymmetries in brain function that may exist at birth.

Although many people consider functional maturation to be a biological, genetically controlled phenomenon, research suggests that our brain is sensitive to environmental and learning influences, too. Literacy, for instance, is a relatively recent human accomplishment, and it is conceivable to assume that no innate mechanisms have evolved to accommodate this skill. Nonetheless, Castro-Caldas and colleagues (1998) demonstrated that learning to read and write during childhood influenced the functional organization of the adult brain. Using PET, they compared activation patterns associated with pseudoword repetition in literate versus illiterate adults. The latter had never attended school and therefore had no formal education in reading and writing. The literate group revealed a distinct cluster of activation in the left parieto-temporal cortex, which was absent in the illiterate group (Castro-Caldas et al., 1998).

Advocates of ‘developmental lateralization’ often refer to clinical data which showed that aphasia after right hemisphere lesion is more common in children compared with adults, and that those children recover almost perfectly (Lenneberg, 1967). Based on this observation, Lenneberg (1967) proposed that all functions, including language, develop initially in parallel in both hemispheres. Subsequent studies supported this theory, suggesting that during a child’s development, language functions shift from right or bilateral to more focal processing within the left hemisphere (Bates et al., 1997; Chiron et al., 1997; Corballis & Morgan, 1978). This gradual lateralization is thought to become fully established at adolescence (Lenneberg, 1967; Miller & Turner, 1973). Other studies further established the involvement of the right hemisphere in early language development (e.g. Bates et al., 1997; Chiron et al., 1997; Mills, Coffey-Corina, & Neville, 1997).

First, Bates and colleagues (1997) - who examined the effects of focal, unilateral brain lesions on language function in infants and preschool children aged 10 to 44 months - reported that children with right-hemisphere injuries at 10-17 months of age were at greater risk for delays in language comprehension and gestural communication than those with left-sided lesions. Importantly, these deficits appeared to be transient, suggesting that the right hemisphere plays a unique role only in the first stages of language development (Bates et al., 1997).

Secondly, Chiron et al. (1997) examined cerebral blood flow changes at rest in children between 1 and 19 years of age using single photon emission computed tomography (SPECT). Their data showed that metabolic activity was greater in the right relative to the left hemisphere in infants younger than 3 years. During the fourth year, however, they observed a right-to-left shift, predominantly driven by a change in activity in the parieto-temporal associative areas (Chiron et al., 1997). Although it is difficult to infer the functional relevance of this shift - since changes in cerebral blood flow were measured at rest - Chiron and colleagues (1997) proposed that it might reflect the right-hemisphere involvement in language processing in young children.

Lastly, Mills and colleagues (1997) measured EEG activation relating to auditory comprehension of familiar and unfamiliar words. They noted activation differences between bilateral event-related responses (ERPs) that were broadly distributed over anterior and posterior regions at 13 month versus left-lateralized ERPs limited to temporal and parietal regions at 20 months of age. Strikingly, EEG patterns varied as a function of age as well as of language abilities, suggesting that the observed neurophysiological changes might be associated with the remarkable lexical development that typically occurs between 13 and 20 months of age (Chiron et al., 1999).

Despite this evidence, other authors argue that the two hemispheres are functionally differentiated at the moment of birth (Bradshaw, 1978; Mehler & Dupoux, 1994). This seems plausible, because asymmetries in brain structure are evident in utero, long before the child develops language (Habas et al., 2012; Kasprian et al., 2011; Kivilevitch, Achiron, & Zalel, 2010). In addition to these structural asymmetries, research has shown that functional lateralization for speech sound is already present in newborns and very young infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Peña et al., 2003). For example, forward- relative to backward-played infant-directed speech revealed significantly more activation in left temporal brain regions in sleeping newborns (aged 2 to 5 days), as measured by near-infrared spectroscopy (Peña et al., 2003). The authors concluded that the brain at birth is functionally organized to process speech in the left hemisphere (Peña et al., 2003). In an FMRI study with 3-month-old infants, Dehaene-Lambertz et al. (2002) also found that auditory stimulation using forward- and backward-played speech significantly activated the left STG compared to silence.

These latter studies, however, do not negate the evidence for developmental and age-related influences on language lateralization. In a recent review on the neural basis of language development, Friederici (2006) suggests that language-related ERP patterns associated with lexical-semantic, syntactic, and prosodic processing appear to change in their latency and duration, but not in their basic morphology from childhood to adulthood. Thus, the theory that some aspects of cerebral asymmetry are present at birth, but others change with age and individual experience, seems to best fit the existing data (Grabowska et al., 1994).

1.1.4.2 Is atypical language lateralization associated with language impairments?

Children with specific language impairment (SLI) struggle to master their native language for no obvious reason (Bishop, 1997). In other words, SLI is a developmental disorder (without underlying physiological abnormality) that selectively affects the domain of language processing. Affected children will develop normally, except for being slow to utter their first words, having trouble in understanding and/or using complex grammar, or having difficulties learning to read (Bishop, 2006).

Although SLI is notoriously heterogeneous, a large number of SLI children show obvious difficulties with the formal rule-like aspects of language such as phonology and syntax (Bishop, 1997). Hence, early models of SLI have suggested that those affected by SLI, or at least a subgroup, suffer from a deficit which is specific to a certain aspect of language processing, such as grammar (Clahsen, 1989; Rice & Oetting, 1993; van der Lely, 1994). Others have proposed that SLI is not caused by a processing deficit specific to language, but by a deficit in temporal auditory processing (Merzenich et al., 1993; Tallal & Piercy, 1973) or by a deficit in the procedural memory system (Ullman & Pierpont, 2005). Still others have argued that the underlying deficit of SLI is more general in nature, reflecting a limited processing capacity (Bird, Bishop, & Freeman, 1995; Bishop, 1997; Leonard, 1998). The suggestion is that the child becomes stuck in immature/limited modes of language processing, which impairs new learning; knowledge that is automated in other children remains effortful to apply in those with SLI (Bishop, 2000).

While all of these theories are based on empirical data, they are mostly behavioural experiments, because neuroimaging studies in children with SLI are rare. No neuroimaging study has yet to detect any neurological abnormality in SLI on gross inspection of the brain. Instead, the evidence is pointing to more subtle differences in the proportions of different cortical regions, white matter connections, and functional asymmetry (e.g. de Guibert et al., 2011; Gauger, Lombardino, & Leonard, 1997; Kim et al., 2006; Vydrova et al., 2015).

With respect to brain morphology, some studies suggest a reduced or reversed asymmetry of language areas in the temporal cortex in individuals with SLI relative to typical peers (e.g. Gauger, Lombardino, & Leonard, 1997; Jernigan et al., 1991; Leonard et al., 2002; Plante et al., 1991). Others also reported structural abnormalities in inferior frontal language regions in SLI (Gauger et al., 1997; Jernigan et al., 1991). Gauger and colleagues (1997), for instance, used MRI to measure the size of the IFG (pars triangularis) and PT in 11 children with SLI and 19 typically developing peers. Compared with controls, children with SLI were less likely to have a leftward asymmetry of the PT. In addition, the pars triangularis of the left hemisphere was significantly smaller in language-impaired children, and anomalous morphology in these language areas correlated with depressed language ability (Gauger et al., 1997).

Recent studies have extended the assessment of brain morphology in SLI to encompass white matter circuits underlying the cortical language network. Kim et al. (2006) were the first to evaluate the integrity of white matter fibres bundles in language-impaired children using diffusion MRI. The study found that relative to controls, children with SLI showed reduced white matter integrity - as measured by fractional anisotropy (FA) - in the genu of the corpus callosum. Since myelination of the brain progresses from posterior regions to anterior ones (Barkovich, 2000), the authors suggested that the observed FA decrease could reflect a delayed maturation of the genu of the corpus callosum in SLI (Kim et al., 2006). Other studies have since reported that children with developmental language and literacy impairments also show white matter abnormalities in dorsal and ventral language tracts (e.g. Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015). Only Vydrova and colleagues (2015), however, looked at inter-hemispheric differences of white matter pathways. They found that children with SLI were more likely to exhibit a rightward asymmetry of the IFOF (based on volume), compared with typically developing peers. A less frequent leftward volumetric asymmetry of the AF in SLI relative to controls was also described, but group differences were not statistically significant (Vydrova et al., 2015).

An important question is whether (or to what extent) these structural asymmetries influence functional lateralization for language. One of the first neurophysiological studies to investigate this was conducted by Neville et al. (1993), who compared EEG activation patterns associated with word processing in SLI and control children. Function words, which carry grammatical information and normally elicit a left anterior negativity, evoked a more bilateral or even right-lateralized negativity in children with SLI compared with controls (Neville et al., 1993). Three more studies that used single-photon emission computed tomography (SPECT) to measure regional cerebral blood flow at rest, found reduced asymmetry or hypoperfusion of the left hemisphere in children with SLI relative to typically developing peers (Denays et al., 1989; Lou, Henriksen, & Bruhn, 1990; Ors et al., 2005). Further evidence for weak cerebral lateralization in developmental language and literacy disorders is provided by studies using functional transcranial Doppler ultrasonography (FTCD; Illingworth & Bishop, 2009; Whitehouse & Bishop, 2008). Whitehouse and Bishop (2008), for example, used FTCD to measure cerebral blood flow velocity changes during a word generation task; they showed that bilateral or right lateralized blood flow responses were significantly more common in adults with persistent language impairment than in controls. Findings from recent functional MRI studies, however, are inconsistent: some studies reported differences in functional lateralization between SLI and control group (Bernal & Altman, 2003; de Guibert et al., 2011), whereas others did not (Hugdahl et al., 2004; Ellis Weismer et al., 2005).

In sum, most neuroimaging studies in language-impaired populations, such as SLI, have focused on functional and structural asymmetries of the frontal and temporal language cortex and the white matter that connects them. Given that gross brain morphology is usually normal in individuals with SLI, it has been suggested that genetic influence may affect early processes in neural maturation, resulting in a non-optimal pattern of functional and structural brain connectivity (Bishop & Snowling, 2004; J. Kim et al., 2006). Consistent with this notion, several studies have found that the usual pattern of left-hemisphere specialization for language is disrupted in SLI (see Bishop, 2013 for discussion). A key question is whether this change in lateralization is a cause of developmental language disorders or a consequence of them. Most studies have used functional neuroimaging to compare children with SLI and typically developing peers in order to examine differences in brain activation associated with a particular language task (e.g. Badcock et al., 2012; de Guibert et al., 2011). Presumably, children with SLI find it more difficult than controls to complete these language tasks, which begs the question: are the observed abnormalities in activation patterns due to inherent limitations, or relative task difficulty (Bishop, 2013)?

1.3 Thesis outline and objectives

The main objective of this thesis is to examine the neural underpinning of language processing and its representation in the two hemispheres. Specifically, I investigated how asymmetries on brain structure and function relate to language abilities, both in typically developing individuals and those with language impairment.

A distinctive feature of my work is the combination of a greater number and variety of functional and structural neuroimaging techniques than is found in most other research studies to date.

In my first study (Chapter 2), I analysed diffusion MRI data that was obtained in families with at least one language-impaired child and control families to investigate whether (abnormal) white matter connectivity underpins atypical laterality in SLI. My specific aims were to:

i) Examine differences between members of SLI and control families in the white matter microstructure as measured by diffusion properties.

ii) Compare asymmetry patterns of language-related white matter tracts in members of SLI and control families.

iii) Explore the relationship between diffusion and/or asymmetry measures and language abilities in SLI and control families.

My second study (Chapter 3) looked at functional MRI data obtained from the same members of SLI and control families who took part in my first study. Because good temporal resolution is required to understand speech, it has been suggested that language lateralization might be determined by asymmetries of lower-lever auditory processing (Efron, 1963; Schwartz & Tallal, 1980). Atypical language lateralization in SLI, therefore, might reflect changes in the pattern of functional lateralization for basic auditory processing. Hence, I compared auditory cortex activation in individuals with SLI and typically developing controls while they passively listened to pure tone sequences that varied in their temporal or spectral structure. I aimed to:

i) Replicate previous findings that neural responses to increased temporal variation are left lateralized, whereas those to increased spectral variation are right lateralized, in children and adults from control families.

ii) Determine whether this hemispheric specialization is altered in language-impaired members from SLI families.

In my third study (Chapter 4), I used FTCD to assess variations in language lateralization across different language tasks in neurotypical adults (N = 215). Recruiting a large sample of children with SLI would have been ideal, but was beyond the scope and resources of my thesis; the recruitment of children with developmental disorders is labour and time-intense and the dropout rate is high, due to excessive motion in the scanner. Evidence from neuroimaging suggests that expressive versus receptive language tasks show different magnitudes of lateralization (e.g. Badcock, Nye, & Bishop, 2012; Gaillard et al., 2004). My aims were to:

i) Investigate the reliability of FTCD in assessing language lateralization based on semantic matching versus word generation tasks.
ii) Compare functional lateralization for language based on a more expressive language task (word generation) versus a more receptive/passive language task (semantic matching).
iii) Explore the relationship between handedness and functional lateralization in the two paradigms.

For my final two studies, I identified 16 individuals with atypical language lateralization from the sample of 215 and compared them to a group of 16 individuals with typical language lateralization. I used a combination of FTCD, MRI and behavioural (visual half-field task) measures of language laterality and language abilities. My fourth study (Chapter 5) focussed on the representation of language function in typically and atypically lateralized participants. I aimed to:

i) Investigate differences in brain activity related to typical and atypical language laterality.
ii) Test whether different laterality assessments determine language lateralization concordantly.
iii) Explore the relationship between different measures of functional language lateralization and behaviour.

In my last study (Chapter 6), I used diffusion MRI to investigate changes in the white matter microstructure of language-related fibre bundles and their functional relevance in typically and atypically lateralized participants. My specific aims were to:

i) Test whether differences in the white matter microstructure and/or asymmetry of dorsal and ventral language tracts underpin differences in functional language lateralization.
ii) Assess whether the integrity and asymmetry of language-related white matter tracts are related to language abilities.

Finally, Chapter 7 summarises my findings and discuss their implications for how we best assess language lateralization and future research directions.

2

Abnormal white matter microstructure in specific language impairment

Abstract

Specific language impairment (SLI) is a developmental disorder that encompasses deficits in comprehension, expression, and use of language in an otherwise normally developing child. The aim of this study was to investigate language-related white matter pathways and their structural asymmetry in SLI.

I analysed diffusion tensor imaging data obtained from families with at least one language-impaired child and control families to look for differences in the white matter underlying cortical language areas. I found significantly reduced fractional anisotropy (FA) in children with SLI compared with controls in the genu, body and splenium of the corpus callosum as well as in the white matter underlying the left and right frontal opercular cortex and anterior insular cortex including occipito-temporal areas. Strikingly, the area of low FA centred on the body of the corpus callosum extended into the white matter of both hemispheres corresponding to the location of the arcuate fasciculus. These findings indicate that children with SLI have poor white matter integrity of the dorsal and ventral language pathway. The decreased FA of the callosal tract may reflect reduced inter-hemispheric connectivity in language-impaired children. Such abnormalities may be related to altered brain asymmetries, thus these findings provide useful insights into neural differences that underpin atypical lateralization of language associated with SLI.

2.1 Introduction

Learning to speak involves complex, dynamic interactions between a child's developing brain and his or her surroundings (Bishop, 2000). Most children acquire and develop language effortlessly. For about 7% of English speaking children, however, learning their native language is extremely difficult (Tomblin et al., 1997). This prevalence rate varies depending on diagnostic criteria, neuropsychological assessment and age group (Bishop & McDonald, 2009; Bishop & Adams, 1990) - for example, milder delays in pre-schoolers may resolve with time, thus making persistent language impairments in adulthood less common (Bishop & Adams, 1990).

Specific language impairment (SLI) describes a developmental disorder in which language learning is disproportionately impaired compared with other non-linguistic domains. By definition, this discrepancy cannot be accounted for by a general developmental delay, acquired brain injury, physical abnormality of the speech apparatus, or significant hearing impairment (Bishop, 1997, 2006). In other words, children with SLI seem impaired for no apparent reason. They typically start to talk at a later age, produce fewer words and lag behind their peers in using complex grammar and/or in language comprehension (Bishop, 1997).

Although SLI is characterised by its specificity to language, affected children may have deficits in all areas of language processing. Also, some children are more affected than others (Leonard, 1998). These differences make for a heterogeneous and difficult to assess disorder, but we now understand some core characteristics; in English-speaking children with SLI, morphology (structure of words) and syntax (structure of sentences) seem to cause the greatest difficulties (see Bishop, 1997 for review). Typical errors that a 5-year-old child with SLI would make include dropping the 's' from the end of present-tense verbs (e.g. "she ride the horse" instead of "she rides the horse”), omitting past tense (“he eat the cookie” instead of “he ate the cookie”), and asking questions without the usual ‘be’ or ‘do’ verbs (e.g. “Why he like me?” instead of “Why does he like me?”). Less apparent would be deficits in vocabulary, problems with the communicative use of language, or difficulties with phonology (sounds of words/morphemes; Bishop, 1997).

To assess phonological difficulties, language-impaired children are asked to repeat novel sequences of sounds in form of pseudowords or nonwords (Bishop, North, & Donlan, 1996; Gathercole & Baddeley, 1989). Gathercole and Baddeley (1989) demonstrated that children with SLI performed equally well compared with controls on one- and two-syllable pseudowords, but on longer pseudowords their performance dropped drastically. These results are thought to reflect deficits in phonological working memory rather than an articulatory impairment (Gathercole & Baddeley, 1989). Many studies have since confirmed that children with SLI perform poorly on pseudoword repetition (Bishop, 2001; Bishop, North, et al., 1996; Botting & Conti‑Ramsden, 2001). In fact, there is evidence that children with ‘resolved’ language impairment still have problems with this task later in life, suggesting that a limited phonological working memory capacity may be a core deficit in SLI (Bishop, North, et al., 1996).

2.1.1 Cerebral lateralization in SLI

Research to date has not identified a neurological basis for SLI, but it is reasonable to believe there is one as SLI is highly heritable (Bishop, 2002). There is some consensus that SLI is associated with subtle structural and functional deviations from the normal pattern of left-hemisphere lateralization for language (Bishop, 2013). Further neuroimaging studies have shown structural brain abnormalities in individuals with SLI: reduced volume or atypical rightward asymmetry in the anterior language cortex and the posterior language cortex including perisylvian regions and the planum temporale (De Fossé et al., 2004; Gauger, Lombardino, & Leonard, 1997; Herbert et al., 2005; Jernigan et al., 1991; Plante et al., 1991, but see Preis et al., 1998).

Collectively, these findings suggest a model to account for the association between weak cerebral lateralization and language impairments: in SLI, abnormal brain development (possibly due to a genetic risk factors) causes atypical structural asymmetries that in turn leads to abnormal functional organization (Badcock, Bishop, et al., 2012).

Badcock and colleagues (2012) tried to relate abnormal functional language organization to structural abnormalities in children with SLI. In SLI relative to controls, they reported reduced activation in the left inferior frontal cortex, right putamen, and superior temporal cortex bilaterally, in combination with increased grey matter in the left inferior frontal cortex and decreased grey matter in the right caudate nucleus and superior temporal cortex bilaterally. Despite the overlap of structural and functional abnormalities in these regions, the relationships between the two in frontal and temporal language areas were different (Badcock, Bishop, et al., 2012).

Although the majority of studies have reported atypical asymmetries of cortical language areas in SLI (e.g. Gauger, Lombardino, & Leonard, 1997; Jernigan et al., 1991; Plante et al., 1991), the underlying factors of functional language lateralization - such as asymmetries in grey matter volume or in white matter microstructure - have not been clearly delineated. Trauner and colleagues (2000) reported that 12 out of 35 children (34%) with developmental language impairment showed structural abnormalities in multiple brain areas compared with none of the 27 control children. Strikingly, the observed abnormalities were in the white matter in almost all children (Trauner et al., 2000).

Advanced neuroimaging techniques, such as diffusion-tensor imaging (DTI), have the power to demonstrate altered white matter integrity. For example, a higher chance of leftward asymmetry of white matter regions underlying primary auditory cortex (Penhune et al., 1996) and fibre bundles connecting frontal with temporal language areas (Hagmann et al., 2006) suggests that white matter tracts represent a more likely anatomical substrate for lateralization of language than cortical areas alone.

2.1.2 White matter abnormalities in SLI

Recent neuroimaging studies support the idea that language processing is not only mediated by distinct cortical areas, but also by the white matter fibre bundles that connect them (see Dick, Bernal, & Tremblay, 2013; Friederici & Gierhan, 2013; Price, 2012 for review). The dual-stream model for auditory speech processing proposes dorsal and ventral pathways that support communication between inferior frontal and superior temporal language areas (Hickok & Poeppel, 2004; Scott & Wise, 2004). Dorsal white matter fibre tracts are thought to subserve auditory-to-motor mapping and the processing of syntactically complex sentences via different branches of the superior longitudinal fasciculus (SLF) and the arcuate fasciculus (AF, Breier et al., 2008; Friederici et al., 2006). Ventral tracts have been related to semantic and basic syntactic processes via the extreme-capsule fasciculus (ECF) and the uncinate fasciculus (UF, Friederici et al., 2006; see Friederici & Gierhan, 2013 for review).

The corpus callosum (CC) is also considered critical for the development of language lateralization (Geschwind & Galaburda, 1985; Geschwind & Levitsky, 1968). It is the major neural pathway linking homologous brain regions, and it is thought to play a fundamental role in integrating information between the two hemispheres (Gazzaniga, 2000). Using both structural and functional MRI in a large group of healthy subjects, Josse and colleagues (2009) were the first to demonstrated that the size of the midsagittal surface of the CC contributes to the degree to which language is functionally lateralized.

In SLI, in accordance with studies of grey matter morphology, studies using diffusion MRI have found abnormalities in the white matter microstructure (Kim et al., 2006; Lee, Nopoulos, & Bruce, 2013; Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015). Kim and colleagues (2006) were the first to use DTI to examine white matter fibre bundles in language-impaired children. Despite normal-looking brain morphology on MRI scans, they observed a decrease in fractional anisotropy (FA) in the genu of the CC in children with SLI compared with controls. Based on this finding they suggested that individuals with language impairment have structural brain abnormalities at the microstructural level that cannot be detected by conventional MRI (Kim et al., 2006). Combining volumetric analyses with DTI, Lee and colleagues (2013) demonstrated abnormalities at the macrostructural level of the corticostriatal system, which were region-specific and included increased volume of the putamen, nucleus accumbens, and right globus pallidus. Their DTI analysis, however, revealed that whole-brain FA was lower in SLI compared with controls, indicating diffuse abnormalities at the microstructural level.

Only a few studies have used DTI to investigate language-related white matter tracts in SLI (Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015). Two studies focused on the dorsal language pathway and found abnormalities in its white matter microstructure, as indicated by increased mean diffusivity in the left AF (Roberts et al., 2014) and reduced fractional anisotropy in the SLF (Verhoeven et al., 2012). Vydrova et al. (2015) extended these findings and reported white matter abnormalities within both dorsal and ventral streams. Relative to controls, children with SLI showed decreased fractional anisotropy in the inferior longitudinal fasciculus (ILF), IFOF, UF and AF, along with increased mean and radial diffusivity in the left ILF, left IFOF and AF bilaterally.

Taken together, neuroimaging studies of SLI have not revealed gross abnormalities or differences relative to neurotypical populations. Instead, there are subtle differences in grey matter volume of brain areas (Badcock, Bishop, et al., 2012; Lee et al., 2013), altered cerebral asymmetries in areas associated with language processing (De Fossé et al., 2004; Gauger et al., 1997; Herbert et al., 2005; Jernigan et al., 1991; Plante et al., 1991), and indications of altered structural connectivity as reflected by diffusion abnormalities (Kim et al., 2006; Lee et al., 2013; Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015).

Even though a popular view is that SLI results from a disruption of the usual pattern of language lateralization, the supporting evidence is weak and inconsistent. The variation in discovered structural asymmetries related to language processing and their association with language impairments, is likely to be influences by the diverse methodologies used in this line of research. Heterogeneity within the clinical population, as well as variability within the imaging technology, make it difficult to compare and interpret results across studies. Moreover, neuroimaging studies in language-impaired children are rare. All these factors contribute to our failure to produce a comprehensive account of the neurobiological basis of SLI.

2.1.3 Aims of this study

In this study, I used diffusion MRI to examine white matter regions underlying the cortical language network in families with at least one language-impaired child and in control families. To investigate general and specific changes in white matter integrity, I combined whole-brain voxelwise analysis of diffusion measures with post-imaging reconstruction of language-related white matter tracts. I restricted my tractography analysis to fibre bundles connecting the cortical language hubs - the AF (part of the SLF) as the dorsal and the ECF (part of the IFOF) as the ventral link between Broca's and Wernicke's area. This restriction reduced the number of comparisons made in a small sample. I also analysed the CC because its important role in the development of functional lateralization.

The aims of this study were to characterize the neural underpinnings of SLI in the white matter underlying the cortical language network and to determine whether abnormal white matter connectivity (as summarized in 2.1.2) underpins atypical laterality in SLI. Based on previous findings, I predict that i) individuals with SLI will differ from typically developing peers in their white matter microstructure (e.g. Kim et al., 2006; Vydrova et al., 2015); ii) tractography analysis will reveal a leftward asymmetry of the AF and ECF in typically developing controls (e.g. Catani et al., 2007; Parker et al., 2005); iii) this asymmetry will be reduced in individuals with SLI, who showed functional and structural abnormalities in a previous study by Badcock et al., (2012).

2.2 Methods

2.2.1 Participants

Families with at least one child with SLI and control families with typically developing children were recruited from a database of research participants in previous studies (Badcock, Bishop, et al., 2012; Barry, Yasin, & Bishop, 2007). Diffusion MRI data was obtained in eight children with SLI, six unaffected siblings and ten control children. Additionally, seven parents with SLI, eight unaffected parents and 14 control parents were scanned using the same DTI protocol. *Table 2.1* summarises the demographics for each group of participants included in my DTI analyses. Kruskal-Wallis test and Chi-square statistic confirmed that the three groups of children were matched for age, gender and hand preference for writing (*Table 2.1*). This was also true for the three groups of parents - with the exception of self-reported handedness (*Table 2.1*). All volunteers were native speakers of English, had a non-verbal IQ (NVIQ) score of 80 or above on the Wechsler Abbreviated Scale of Intelligence (Wechsler & Chen, 1999) as well as normal hearing (a bilateral pure tone audiometric screening test at 25 db HL ISO for 500, 1000, and 2000 Hz) and no reported neurological impairments or psychiatric disorders. Children with SLI were originally diagnosed with language learning difficulty at school and the diagnosis was confirmed by performance on standardized tests of language or literacy ability. All SLI subjects included here scored below the 10th percentile on two or more standardized tests of language and literacy ability, but no child was included based upon two low literacy scores alone.

Table 2.1. *Group characteristics are shown for individuals with SLI (SLI), unaffected family members (SIB/PAR) and control families (CON) for children and adults data separately. P values are reported for within study group comparisons of age as well as gender and self-reported handedness based on Kruskal-Wallis test and Chi-square statistics.*

	Children				Adults			
	SLI	SIB	CON	*P* value	SLI	PAR	CON	*P* value
N	8	6	10		7	8	14	
Age range	12-17	12-22	11-18		40-61	37-54	38-55	
Median age	14	18	13.5	0.124	45	50	45	0.253
Gender (M:F)	7:1	4:2	8:2	0.600	2:5	4:4	7:7	0.611
Handedness (R:L)	6:2	5:1	9:1	0.698	5:2	8:0	14:0	0.034*

Note: Significant differences ($p < 0.05$) are indicated by an asterisk.

Members of the typically developing control group had no reported history of language or literacy problems and scored above the 10th percentile on all standardized tests. Informed written consent was obtained from all participants and their parents in accordance with ethical approval from the Mid and South Buckinghamshire Local Research Ethics Committee (04/Q1607/64).

2.2.2 Neuropsychological evaluation

All children underwent a neuropsychological evaluation to obtain their non-verbal IQ, language and handedness scores. A trained psychology assistant administered the assessment, which lasted about 1.5 h and included the following tests:

Non-verbal intelligence. Non-verbal intelligence (NVIQ) was measured using two subtests from the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler & Chen, 1999); namely the block design and matrix-reasoning task. Scores were converted into age-scaled scores.

Language. Language abilities and literacy skills were assessed using a comprehensive test battery including the Children's Communication Checklist, version-2 (CCC-2; Bishop, 2003a) or the Communication Checklist for Adults (CC-A; Whitehouse & Bishop, 2009) depending on age. These checklists evaluate the parental report of communication skills and were designed to assess strengths and weaknesses in communication, which are not readily identified by traditional language tests. A General Communication Composite (GCC) score greater than 58 reflects language skills within a normal range. An electronic version of Test for Reception of Grammar-2 (TROG-2; Bishop, 2003b) was used to look at grammatical understanding in children and adults. TROG-2 is a multiple choice sentence comprehension test and scaled scores were derived from UK test norms. The Test Of Word Reading Efficiency (TOWRE; Torgesen, Wagner, & Rashotte, 1999) was administered to assess reading skills using form B. This speeded test that gives scores for reading of real words (sight word reading efficiency) as well as non-words (phonemic decoding efficiency) and raw scores were converted to standard scores using American norms. Oromotor coordination was examined using the oromotor sequences, sentence repetition, and non-word repetition subtests of the NEuroPSYchology test battery (NEPSY, Korkman, Bortolini, & Kemp, 1998). The norms cover a maximum age of 12 years, 11 months; therefore, data from a larger control sample was used to convert raw scores to standard scores (see Barry, Yasin, & Bishop, 2007).

Handedness. Handedness was assessed using the Edinburgh Handedness Inventory (EHI, Oldfield, 1971). Children were asked to demonstrate how they would perform each of the following ten actions: (1) write, (2) draw, (3) throw, (4) use scissors, (5) brush their teeth, (6) cut with a knife, (7) use a spoon, (8) sweep with a broom (upper hand), (9) take the lid of a box, and (10) deal cards. Left, Right, or either (if child indicated both) hand was recorded in each case. The number of right hand preferences was taken as a measure of hand dominance.

2.2.3 MRI data acquisition

Whole brain MRI data was acquired using a 1.5-T Siemens Sonata scanner with a single-channel head coil. Padding was inserted around the head to restrict movement and minimize motion-related artefacts. Participants wore headphones and watched a DVD of their choice while structural brain scans were acquired. Three high-resolution T1-weighted images (1-mm isotropic voxels; 3D FLASH sequence; TR = 12 ms; TE = 5.65 ms; matrix = 256 x 256 x 208; elliptical sampling) were acquired in each participant for image registration and structural analysis. Shortly after each image acquisition (5 min), the structural scan was inspected for excessive motion, and if necessary children were reminded to keep as still as possible. This ensured that at least three artefact-free images were successfully obtained in each subject. The first and the third images were registered to the second image to correct for movements between acquisitions (rigid-body transformation; 6 DOF) and summed to create a single T1-weighted structural image. For the diffusion data, two sets of echo-planar images (EPI) were acquired (53 x 2.5 mm axial slices; in-plane resolution 2.5 mm^2) using a b-value of 1000 smm^{-2} uniformly distributed across 60 gradient directions. Three non-diffusion-weighted (one at the start, one in the middle, and one at the end of the diffusion sequence and 60 diffusion-weighted images were acquired for each set.

2.2.4 MRI data analysis

I used the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) to pre-process and analyse the imaging data. Further statistical tests were conducted using SPSS (www.ibm.com/software/analytics/spss).

2.2.4.1 Tract-based spatial statistics

The FMRIB Diffusion Toolbox (FDT; Behrens et al., 2003, 2007) was employed to process the diffusion data. During pre-processing, images were corrected for eddy currents and head motion by affine registration to non-diffusion volumes. To further improve the signal-to-noise ratio, the data were averaged across the two sets. Images were created of fractional anisotropy (FA), axial and radial diffusivity (respectively parallel [λ_1], and perpendicular [($\lambda_2 + \lambda_3$) / 2] to the principal diffusion direction). Tract-Based Spatial Statistics (TBSS, Smith et al., 2006) was run for voxel-wise statistical analysis of the FA data. TBSS aligns all participants' FA images to a target before transforming the entire dataset into 1 x 1 x 1 mm standard space using nonlinear registration. I employed the FMRIB58_FA standard-space image - obtained from a high-resolution average of 58 healthy participants - as my pre-defined registration target. All aligned FA images were averaged and thinned to create a "skeleton" that represents the centre of white matter tracts common to all participants in the study. To avoid analysis of areas of low mean FA and high inter-subject variability the “skeleton” was thresholded at FA > 0.2. For analysis, TBSS projects each participant’s FA image onto the mean skeleton, by filling the skeleton with the highest FA values from the nearest relevant tract centre. For cross-subject statistical analysis, a t-test was performed at each voxel in the skeleton. Statistical inference was carried out using Threshold-Free Cluster Enhancement (TFCE) in randomise (exhaustive permutations) and changes were considered significant at $p < .05$ (fully corrected for multiple comparisons across space). FA values were compared between the groups of SLI and control children.

2.2.4.2 Probabilistic tractography

In addition, probabilistic tractography (Behrens et al., 2003) was run to reconstruct the fibres comprising the genu, body and splenium of the corpus callosum (CC) as well as those thought to represent the dorsal (AF) and ventral language tract (ECF) in each hemisphere of each participant. This analysis used a multiple region-of-interest (ROI) approach previously described by Giorgio and colleagues (Giorgio et al., 2010) and adapted for this study. Four different types of masks were incorporated to constrain the tractography analysis: (i) seed masks that defined all voxels from which probabilistic tractography was initiated, (ii) target masks which ensured that only tracts passing through these defined masks were selected, (iii) termination masks that were drawn adjacent to seed and target masks to terminate paths beyond these regions, and (iv) exclusion masks, which removed any paths entering this region. Tracts that did not pass through the seed and target masks were automatically discarded from the calculation of the connectivity distribution. Masks were defined in standard space and if applicable symmetrical in each hemisphere.

Corpus callosum. Seed regions were placed in the genu, body and splenium of the corpus callosum. The genu was defined as the most anterior point of the corpus callosum before it bends downwards and backwards in front of the septum pellucidum, and the splenium as the posterior end of the corpus callosum at its thickest part. The seed regions followed the shape of the corpus callosum in a single sagittal slice (x = 0) extending from y = 32 to -46, and z = -4 to 28. For each segment of the corpus callosum different target, termination and exclusion masks were employed.

For the *genu*, two target masks were drawn in two adjacent coronal slices (y = 54 and y = 56) including voxels in the white matter anterior to the seed mask (i.e. in the rostral portion of the frontal lobe) and extended from x = ±26 to ±4 (left or right hemisphere), and z = -6 to 34. Termination masks immediately encompassed the left and right target masks. To separate the genu from the rest of the corpus callosum one large exclusion masks was used that comprised several coronal slices (starting at y = 16) and covered the middle and posterior part of the brain.

For the *body*, two target masks were placed at a single axial slice at (z = 40) in the white matter superior to the seed extending from x = ±32 to ±10 (left or right hemisphere), and y = -70 to 28. Termination masks were drawn immediately outside the target masks. To isolate the projections between superior cortical areas passing through the corona radiata and eliminate projections to ventral areas a total of six exclusion masks (three per hemisphere) were used. One exclusion mask was located in a single coronal slice (y = -28) and extended from x = ±18 to ±8 (left or right hemisphere) and z = 4 to 12. The other were placed in two axial slices, the first one at z = 16 extending from x = ±36 to ±4 (left or right hemisphere) and y = -26 to 0; the second one at z = -6 extending from x = ±36 to ±30 (left hemisphere or right hemisphere) and y = -42 to -18. These eliminated projections via the internal capsule and temporal stem to ventral areas.

For the *splenium*, both target masks were drawn in two coronal slices in juxtaposition with each other (y = -88 and y = -86) located in the white matter posterior to the seed mask (i.e. underlying the occipital pole). The masks extended from x = ±24 to ±4 (left or right hemisphere), and z = 6 to 44 and were immediately surrounded by termination masks. To separate the paths passing through the splenium (the forceps major) from those passing through the rest of the corpus callosum, one large exclusion mask was used that comprised coronal slices anterior to and including y = -30 and covered the middle and frontal parts of the brain.

Dorsal language pathway. A seed mask was placed in the white matter of the AF, where the tract curves around the posterior extent of the Sylvian fissure. The mask was drawn in a single coronal slice (y = -38) and extended from x = ±42 to ±30 (left or right hemisphere), and z = 20 to 34. Two target masks were located at more distal extents of the tract: an axial one (z = 10) included voxels in the white matter ventral to the seed mask (i.e. in the temporal lobe, posterior to Heschl's gyrus) ranging from x = ±44 to ±32 (left or right hemisphere), and y = -36 to -50; and, a coronal target mask (y = -6) located in the white matter anterior to the seed mask (i.e. underlying the precentral gyrus) extending from x = ±42 to ±26 (left or right hemisphere), and z = 16 to 32. Termination masks were drawn immediately inferior and anterior to the axial and coronal target masks respectively. Exclusion masks were used to remove any paths that may branch off the AF; one mask comprised voxels in a single sagittal slice at x = ±50, extending from y = -62 to -10, and z = 6 to 44 (to exclude paths to the lateral parietal cortex), a second one comprised voxels in a single sagittal slice at x = ±22, extending from y = -20 to 4, and z = -12 to 20 (to exclude paths through the internal capsule). Another exclusion mask ran through the midline (x=0; to exclude paths to the other hemisphere.

Ventral language pathway. A seed mask was drawn in the white matter of the temporal stem in a sagittal slice at x = ±32 (left or right hemisphere; lateral to the putamen encompassing the ventral portions of the extreme/external capsules). The mask extended from y = -10 to 6 and z = -12 to -2. Four target masks (two in each hemisphere) were placed in the white matter anterior (i.e. frontal lobe) as well as posterior (i.e. temporal lobe) to the seed. The first one was located in white matter lateral to the anterior horn of the lateral ventricle in a single coronal slice (y = 26) extending from x = ±28 to ±20 (left or right hemisphere) and z = -4 to 14; and the second was drawn in the middle temporal white matter ventral to Heschl's gyrus in a coronal slice (y = -28) extending from x = ±46 to ±36 (left or right hemisphere) and z = -14 to -2). Termination masks immediately surrounded all target masks. To remove erroneous paths that travelled between seed and target via more lateral or medial routes, exclusion masks were employed lateral and medial to the seed and target masks; one comprised voxels in a sagittal slice at x = ±30, extending from y = -34 to 2, and z = 0 to 34, a second one comprised voxels in another sagittal slice at x = ±50, extending from y = -62 to -10, and z = 6 to 44. An exclusion mask through the midline was also used to exclude paths that crossed into the other hemisphere.

All masks were registered to the native diffusion space of each subject using FMRIB's Non-linear Image Registration Tool (FNIRT, Andersson, Jenkinson & Smith, 2007). For the purpose of better isolation of the fibre bundles, resulting tracts were thresholded in each brain image, so that only voxels were included through which a minimum of 500 samples had passed. Masks were used to extract and calculate mean FA and total volume for each tract in each participant.

2.2.5 Statistical analysis

Unless otherwise stated, preliminary assumption testing included the following assessments: Shapiro-Wilk test was used to determine whether data were normally distributed, Levene's test and Box's M tests were used to examine homogeneity of variances and covariances, and Mauchly's test was used to assess sphericity. When the latter was violated, Greenhouse-Geisser correction was applied. Because there were only two levels of repeated measures for the AF and ECF (left vs. right), sphericity was not taken into account. Lastly, Bonferroni correction was applied for multiple post-hoc comparisons.

Between-group comparison of tract measures. For each tract, mean FA and total volume were compared using a two-way mixed analysis of variance (ANOVA), with a between-subjects factor of group (SLI vs. SIB vs. CON) and a within-subjects factor of either hemisphere (left vs. right) or portion of the CC (genu vs. body vs. splenium).

Asymmetry assessment. Individual asymmetry indices (AI) were calculated to assess hemispheric differences in the dorsal and ventral language pathway based on the formula: $AI = (T_L - T_R) / (T_L + T_R)$, where T_L and T_R refer to mean FA or volume of the tract within the left (L) and right (R) hemisphere. AIs ranged from -1 to +1 with positive indices indicating a leftward asymmetry and negative ones indicating a rightward asymmetry. One-sample t-tests were used to determine whether AI values for language-impaired individuals and typically developing controls were significantly different from zero. A mixed ANOVA with group (SLI vs. SIB vs. CON) as a between-subjects factor and tract (AF vs. ECF) as a within-subjects factor was conducted to assess differences in the asymmetry of dorsal and ventral language pathways between typical and atypical participants.

Tract measures and neuropsychological assessment. Kruskal-Wallis test was used to assess differences in behavioural test scores between groups of language-impaired individuals and typically developing peers. If applicable, pairwise comparisons were performed using Dunn's (1994) procedure. To explore the relationship between tract measures (mean FA, total volume) of the CC or asymmetry (AIs) of the dorsal/ventral language tracts and a child's performance during the psychometric assessment, Spearman's rho was calculated.

For the comparisons between the children with SLI and the controls, the sample size of 8 for the SLI group was adequate to detect a difference significant at 5% (1-tailed assuming lower values in the SLI group) at 80% power only if the effect size of this difference was very large (> 1.3 standard deviations). This means that if a difference between the groups of more than 1.3 standard deviations exists, we would have the power to detect it 80% of the time and expect to find false positive results (saying there is a difference when none exists) 5% of the time. For the comparisons involving siblings, the same calculations revealed that at 5% alpha (two-tailed) and 80% power, the effect size required needed to exceed 1.6. Similarly, for the adults with SLI (N=7; 5% 1-tailed alpha, 80% power), statistical comparisons would be sensitive only to very large effect sizes (> 1.3 compared with controls or with unaffected parents).

2.3 Results

Whole-brain TBSS analyses revealed no significant white matter differences between SLI and unaffected subjects in the adult sample: neither between SLI parents and unaffected parents with a family history of SLI, nor between SLI parents and parents from control families. Thus, the following result section will focus on the comparison of children with SLI, their unaffected siblings and control children.

2.3.1 Comparison of tract-based spatial statistics (TBSS) in SLI versus controls

There were no differences in the overall intracranial volume (ICV) and mean FA derived from all cerebral voxels between children with SLI (*M* ± *SD*: ICV 1564 cm^3 ± 216 cm^3; FA 0.21 ± 0.011), their unaffected siblings (*M* ± *SD*: ICV 1561 cm^3 ± 171 cm^3; FA 0.21 ± 0.011) and typical developing peers (*M* ± *SD*: ICV 1579 cm^3 ± 108 cm^3; FA 0.21 ± 0.010).

Whole-brain TBSS analysis revealed significantly lower FA in children with SLI compared with children from control families in three clusters (*Figure 2.1*) - fully corrected (TFCE, $p < .05$). Two clusters comprised the white matter underlying the frontal opercular and anterior insular cortex extending ventrally and posteriorly to the occipito-temporal white matter - one in each hemisphere. The third cluster was located in the white matter subjacent to the cingulate cortex indicating an abnormal reduction in FA along the callosal tract; it expanded to the white matter underlying the orbitofrontal cortex (minor forceps). Strikingly, the area of low FA centred on the callosal body extended laterally into the white matter underlying the superior and middle temporal gyri in each hemisphere. These areas correspond to the location of the temporal parts of the SLF - known as the AF.

In addition, contrasting SLI children with their unaffected siblings revealed several white matter areas where there were differences between the groups in FA. As seen in *Figure 2.2* the analysis showed lower FA in the SLI children in a single significant cluster that spanned large portions of several white matter tracts. To identify the anatomical location of the peaks within this large cluster, I raised the significance threshold to $p < .01$ (*Figure 2*). Similar to the previous comparison with control children, the most significant differences between children with SLI and their unaffected siblings were located in the body, genu and splenium of the corpus callosum. There were no white matter regions that showed increased FA in SLI compared with their unaffected siblings or control children. Finally, FA of the white matter skeleton in the group of siblings did not differ from the control group.

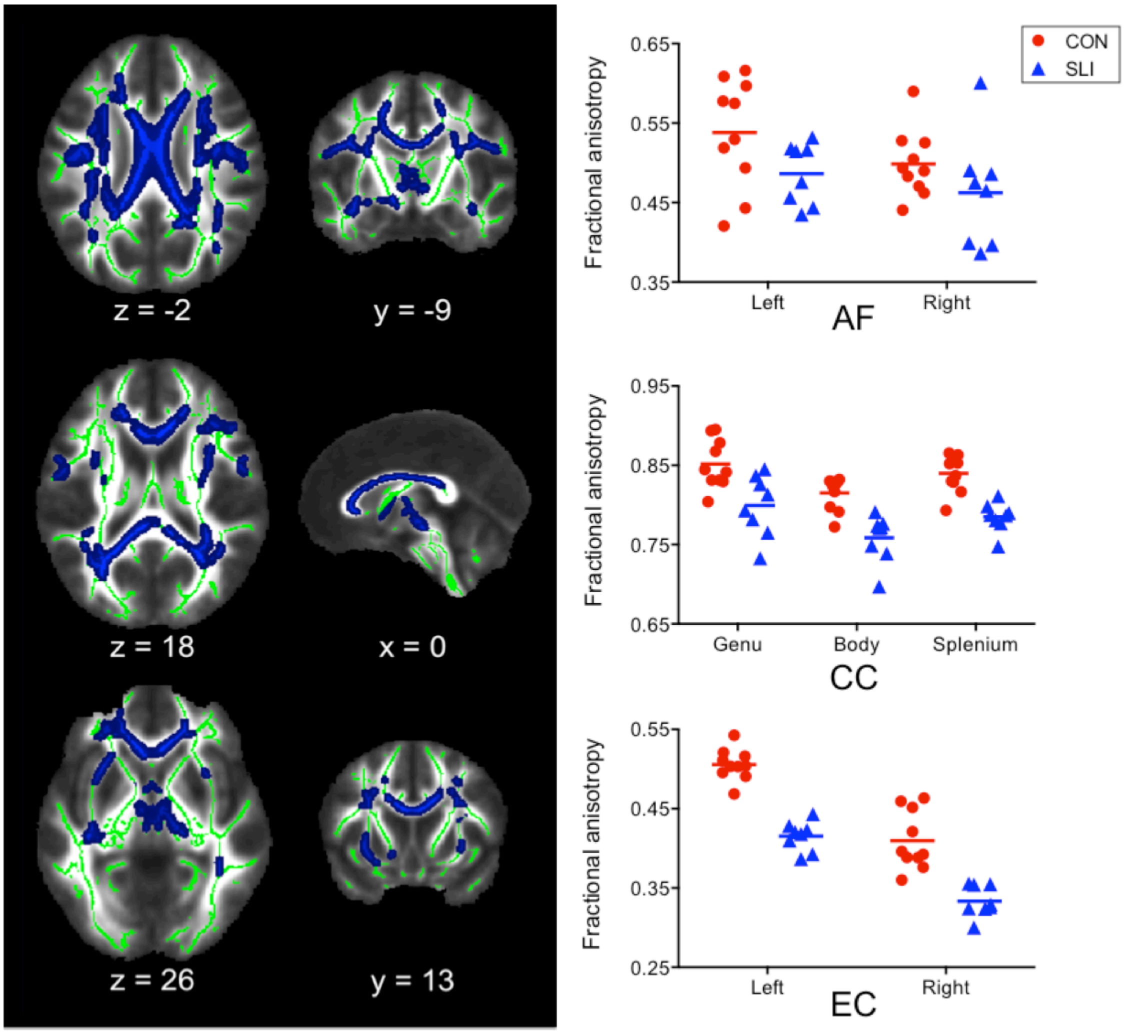

Figure 2.1. *Tract-based spatial statistics analysis (TBSS) of white matter in children with language impairments (SLI) compared with typical developing peers (CON). Blue areas indicate regions in which SLI had significantly reduced FA relative to CON. Results are thresholded at p < .05 (corrected using TFCE) and thickened for visualization purposes. Adjacent graphs displays the individual FA values extracted from the arcuate fasciculus (AF), the genu, body and splenium of the corpus callosum (CC) as well as the extreme capsule fasciculus (ECF) for CON (red circles) and SLI (blue triangles) separately.*

To further understand the microstructure of the FA differences, images of diffusivity along the principal direction of the estimated fibre orientation for each voxel (L1; axial diffusivity) and radial diffusivity (RD) - averaged across the two directions orthogonal to the principal diffusion direction for each voxel - were analysed.

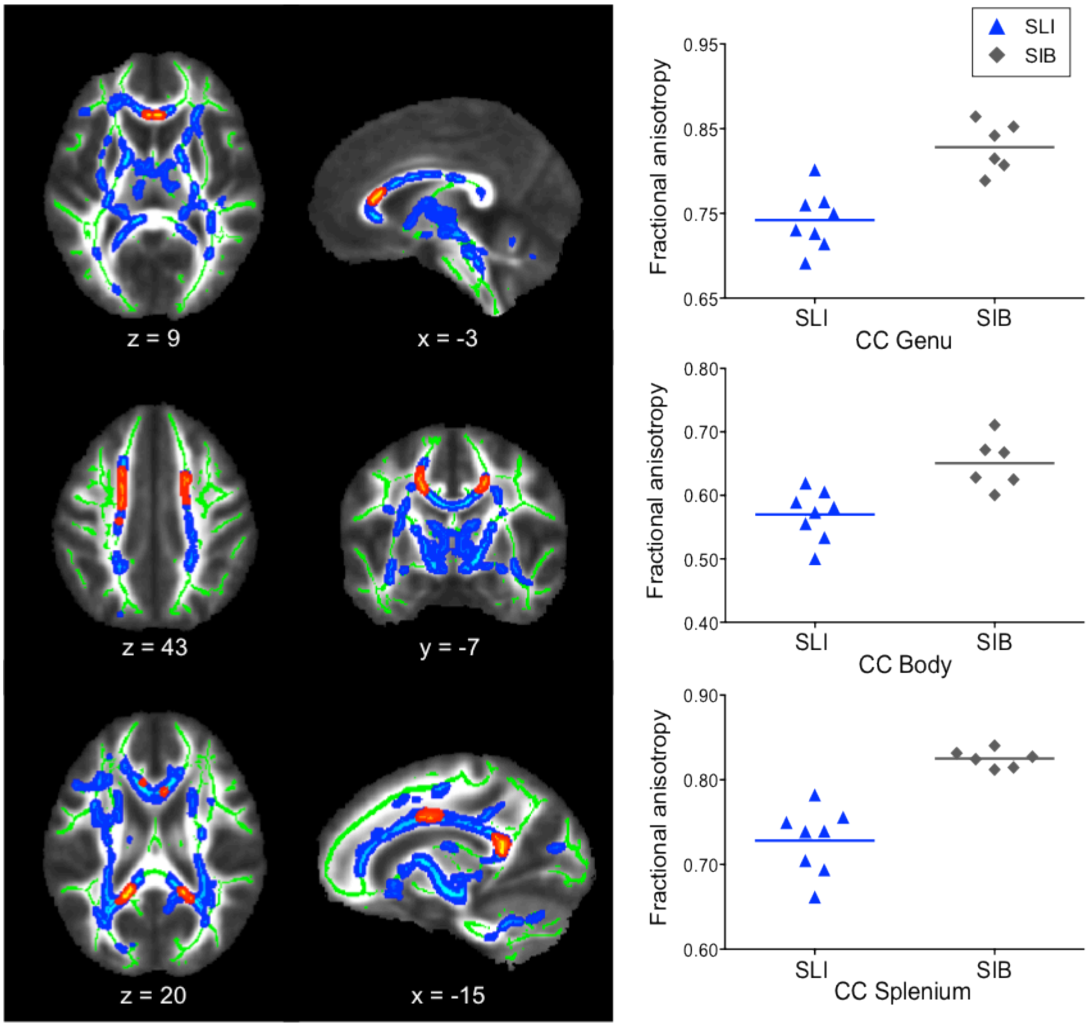

Figure 2.2. *Tract-based spatial statistics analysis (TBSS) of white matter in children with language impairments (SLI) compared with unaffected siblings (SIB). Blue areas indicate regions in which SLI had significantly reduced FA relative to SIB ($p < .05$, TFCE corrected) and red areas show peak location ($p < .01$) within the large cluster. Results are thickened for visualization purposes. Adjacent graphs displays the individual FA values extracted from the genu, body and splenium of the corpus callosum (CC) for SLI (blue triangles) and SIB (grey squares) separately.*

Children with SLI had significantly higher RD (i.e. more diffusion in the directions orthogonal to the principal diffusion direction) compared with control children in areas that previously showed reduced FA. The cluster comprised the white matter of the CC extending to the minor forceps, but was not as extensive as the one showing differences in FA. The same pattern of increased RD was observed when comparing SLI with their unaffected siblings; but RD in the group of unaffected siblings did not differ from that in control children. There were no differences between the three groups in L1 diffusivity that survived TFCE correction. Thus the reduction in FA seen in the SLI group compared to the control group and the group of unaffected siblings is explained in many areas of white matter by an increase in RD.

2.3.2 Comparison of tract measures in SLI versus controls

To explore the TBSS findings, probabilistic tractography was used to identify the genu, body and splenium of the CC, the AF - as part of the dorsal, and the ECF - as part of the ventral language pathway in each hemisphere. Each of these white matter fibre bundles was successfully tracked in all children. Volume and mean FA for the total tract were compared between groups and hemispheres/callosal portions using mixed ANOVAs. Data for SLI children, unaffected siblings and typically developing peers was normally distributed ($p > .05$). In addition, homogeneity of variances ($p > .05$) and covariances ($p > .05$) could be assumed for all tract measures, and the assumption of sphericity was met for mean FA and volume of the genu, body and splenium of the CC (FA: $p = .055$; volume: $p = .077$). To illustrate the results from statistical analyses, mean values of FA and tract volume are plotted in *Figure 2.3*.

For mean FA values obtained from the CC, the analysis revealed a significant main effect of group indicating differences between SLI, unaffected siblings and controls across all portions of the callosal tract ($F(2, 21) = 8.28$, $p = .002$, $\eta_p^2 = .44$). Post-hoc analyses showed that FA was significantly reduced in children with SLI ($M = 0.45$, $SD = 0.014$) relative to controls ($M_{diff} = 0.026$, 95% CI [0.008, 0.044], $p = .003$) as well as unaffected siblings ($M_{diff} = 0.024$, 95% CI [0.004, 0.045], $p = .017$). Siblings ($M = 0.47$, $SD = 0.012$) and control children ($M = 0.47$, $SD = 0.016$) did not differ in mean FA of the CC. As expected, across the three groups of children, FA differed between the genu ($M = 0.42$, $SD = 0.021$), body ($M = 0.48$, $SD = 0.017$) and splenium ($M = 0.49$, $SD = 0.030$) of the CC revealing a significant main effect of portion ($F(2, 42) = 117$, $p < .0005$, $\eta_p^2 = .85$). Post hoc analysis revealed that mean FA decreased significantly from posterior to anterior portions of the CC with higher FA in the splenium compared with body (M_{diff} = 0.016, 95% CI [0.004, 0.029], p = .009) and genu (M_{diff} = 0.073, 95% CI [0.058, 0.089], $p < .0005$) as well as higher FA in the body compared with genu (M_{diff} = 0.057, 95% CI [0.047, 0.067], $p < .0005$). There was no significant interaction between group and portion on mean FA values (p = .34).

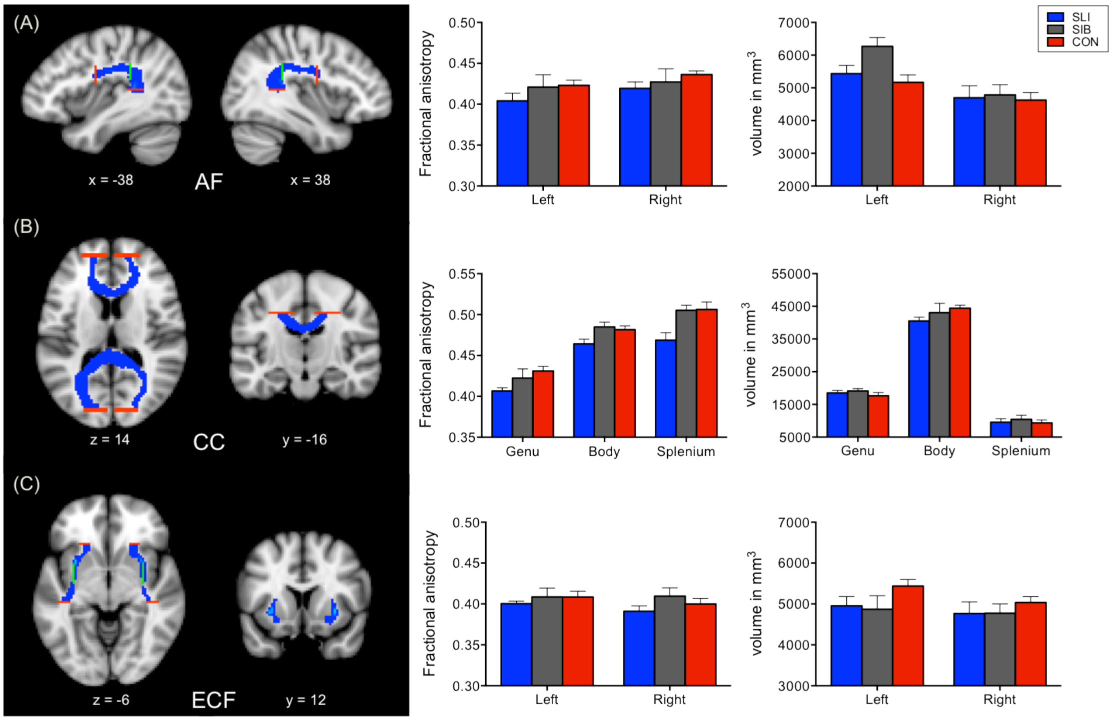

Figure 2.3. *Reconstruction of language-related white matter pathways using probabilistic tractography. Underlying brain image is the MNI152 template T1-weighted image in standard space. Blue areas are the average of the thresholded tracts across all participants between the seed masks (green) and the target masks (red). (A) Arcuate fasciculus (AF) shown on sagittal slice through the left and right hemisphere 38 mm from the midline. (B) The genu and splenium of the corpus callosum (CC) are displayed on an axial slice 14mm above the bicommissural plane and the callosal body on a coronal slice at 16 mm posterior to the anterior commissure and. (C) Extreme capsule fasciculus (ECF) is shown for both hemispheres on an axial slice at 6 mm below the bicommissural plane. Adjacent bargraphs display mean FA (left) and tract volume (right) for children with SLI (blue) unaffected siblings (grey) and controls (red). Error bars indicate the standard error of the mean (SEM).*

Looking at the volume of the CC, the analysis did not yield a significant main effect of group indicating that the volume of the CC across all three portions was similar in children with SLI, siblings and controls (p = .47). Examination of *Figure 2.3* reveals a numerically lower volume of the body of the CC in the SLI group (M = 40525 mm^3, SD = 3426 mm^3) relative to unaffected siblings (M = 43051 mm^3, SD = 2874 mm^3) and controls (M = 44417 mm^3, SD = 3026 mm^3), but this difference was not statistically significant, as the analysis did not reveal a significant interaction between group and CC portion (p = .26). The significant main effect of portion demonstrated the known differences in volume between genu (M = 18297 mm^3, SD = 2514 mm^3), body (M = 42778 mm^3, SD = 4569 mm^3) and splenium (M = 9693 mm^3, SD = 2857 mm^3) of the CC across all groups of children ($F(2, 42) = 604, p < .0005, \eta_p^2 = .97$).

For the dorsal and ventral language tracts, inspection of *Figure 2.3* reveals that children with SLI had lower FA relative to unaffected siblings and controls in the AF ($M \pm SD$: SLI 0.41 ± 0.022, SIB 0.42 ± 0.038, CON 0.43 ± 0.016) as well as ECF ($M \pm SD$: SLI 0.39 ± 0.022, SIB 0.41 ± 0.025, CON 0.40 ± 0.021) across both hemispheres. However, this difference was not statistically significant, as the analysis did neither reveal a significant main effect of group (AF: p = .32; ECF: p = .44) nor a significant interaction between group and hemisphere (AF: p = .59; ECF: p = .43). The main effect of hemisphere was significant for the dorsal ($F(1,21) = 11.3, p = .003, \eta_p^2 = 0.35$), but not ventral language pathway (p = .10). Pairwise comparison showed that mean FA of the AF was significantly higher in the right compared with the left hemisphere across children with SLI, unaffected siblings and controls (M_{diff} = 0.012, 95% CI [0.004, 0.019], p = .003).

The analysis of volume measures from the dorsal and ventral language tract revealed a similar pattern of results. There was no significant main effect of group (AF: p = .23; ECF: p = .26) or significant interaction between group and hemisphere (AF: p = .065; ECF: p = .55) for the volume of the AF or ECF. The significant main effect of hemisphere for the dorsal ($F(1, 21) = 35.3, p < .0005, \eta_p^2 = .63$), but not ventral pathway (p = .070), indicated that the volume of the AF was greater in the left relative to the right hemisphere (M_{diff} = 922 mm^3, 95% CI [599 mm^3, 1245 mm^3], p < .0005).

2.3.3. Asymmetry of language-related fibre tracts in SLI and controls

Mean AI values based on FA and volume extracted from the dorsal and the ventral language pathway are shown in *Table 2.2* for children with SLI, their unaffected siblings and typically developing peers.

Table 2.2. *Indices of asymmetry (AI) for the dorsal and ventral language pathway. Indices are shown for language-impaired children (SLI), their unaffected siblings (SIB) and typically developing peers (CON). P values are reported for one-sample t-tests against zero indicating significant leftward (positive mean AI) or rightward (negative mean AI) asymmetry for each group and tract.*

		Dorsal tract (AF)			**Ventral tract (ECF)**		
		SLI	SIB	CON	SLI	SIB	CON
AI - FA	Mean	-0.019	-0.007	-0.016	0.014	-0.001	0.011
	Std. deviation	0.029	0.013	0.017	0.022	0.019	0.022
	Minimum	-0.060	-0.021	-0.050	-0.010	-0.024	-0.030
	Maximum	0.020	0.007	0.010	0.050	0.029	0.030
	P value	**0.30**	**0.54**	**0.047***	**0.32**	**1.00**	**0.39**
AI -Volume	Mean	0.079	0.137	0.057	0.021	0.007	0.037
	Std. deviation	0.090	0.047	0.085	0.061	0.070	0.050
	Minimum	-0.070	0.056	-0.090	-0.060	-0.112	-0.030
	Maximum	0.240	0.192	0.150	0.130	0.087	0.130
	P value	**0.12**	**0.003***	**0.18**	**0.74**	**0.99**	**0.13**

Note: Significant asymmetries ($p < 0.05$, Bonferroni adjusted) are indicated by an asterisk.

Consistent with my previous findings, one-sample t-test showed that AI values were significantly different from zero for the dorsal, but not ventral language tract (*Table 2.2*). Strikingly, AIs based on mean FA indicated a significant rightward asymmetry ($t(9) = 2.95$, $p_{corr} = .047$, $d = 1.97$), while AIs based on volume indicated a significant leftward asymmetry ($t(5) = 7.09$, $p_{corr} = .003$, $d = 6.34$) of the AF for control children and unaffected siblings, respectively.

The inspection of *Figure 2.4* suggests that this pattern of AF asymmetry was consistent (but not consistently significant) across the three groups of children. To test whether mean AIs differed among the three groups (between-subjects factor) for the dorsal and ventral language tract (within-subjects factor of tract), mixed ANOVAs were run. AI values were normally distributed for the group of language-impaired children, siblings and controls, and both homogeneity of variances (*p* > .05) and covariances (*p* > .05) could be assumed.

For AI values based on mean FA, analysis revealed neither a significant interaction between group and language tract (*p* = .41), nor a significant main effect of group ((*p* = .24) indicating that indices of asymmetry did not significantly differ among the three groups. The main effect of tract, however, reached statistical significance confirming that AI values differed between dorsal and ventral tract across children with SLI, their unaffected sibling and controls ($F(1, 21) = 15.3$, $p = .001$, $\eta_p^2 = .42$). Mean AIs were significantly lower for the AF ($M = -0.015$, $SD = 0.020$) relative to the ECF ($M = 0.008$, $SD = 0.020$) suggesting a stronger rightward asymmetry for the dorsal language tract based on mean FA (*Figure 2.4*).

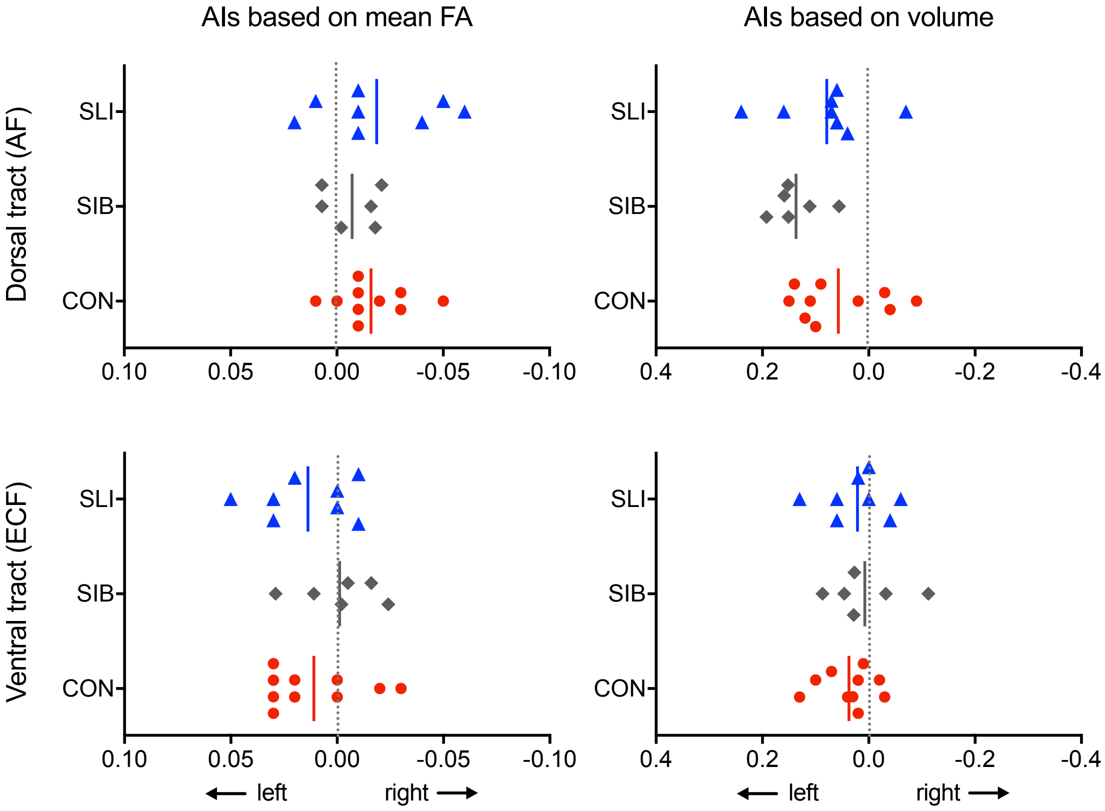

Figure 2.4. *Laterality indices (LI) for dorsal and ventral language pathways. Individual data are plotted for control (CON, red circles), unaffected siblings (SIB, grey squares) and SLI children (SLI, blue triangles). The upper row shows LIs for the dorsal white matter tract (arcuate fasciculus, AF) and the bottom row for the ventral one (extreme capsule fasciculus, ECF) based on mean FA (left) and volume measures (right). The mean of each group is marked with a line. Positive LIs indicate leftward and negative values rightward asymmetry.*

Similar results were revealed comparing AI values based on tract volume. There was no significant interaction between group and language tract (p = .30) and the main effect of group approached, but did not reach statistical significance (p = .073). In other words, children with SLI, sibling and control children did not significantly differ in their mean AIs values. Across the three groups of children, the main effect of tract revealed a significant difference in mean AIs for the dorsal and ventral language pathway ($F(1, 21) = 9.87$, $p = .005$, $\eta_p^2 = .32$). This time, indices of asymmetry were higher for the AF (M = 0.084, SD = 0.083) compared with the ECF (M = 0.025, SD = 0.057) indicating a stronger leftward asymmetry for the dorsal language pathway based volume (*Figure 2.4*).

2.3.4 Correlation of tract measures with neuropsychological data

Behavioural test scores of all children included in my analyses are summarized in *Table 2.3*. Data from one control child could not be retrieved and the child was therefore excluded from group comparisons and correlation analyses. As described earlier, children with SLI were originally diagnosed with language learning difficulty at school and the diagnosis was later confirmed by performance on standardized tests of language or literacy ability. Accordingly, the group of language-impaired children scored significantly lower on almost all standardized language and literacy compared with unaffected siblings and typically developing peers. The latter two groups did not differ (see *Table 2.3*). In addition, the three groups of children varied significantly in their non-verbal IQ (NVIQ; $\chi^2(2) = 6.69$, $p = .035$). Although all language-impaired children had NVIQ scores of 80 or above, pairwise comparisons revealed that the SLI group (mean rank = 7.00) scored lower compared with unaffected siblings (mean rank = 14.6, p = .038) and control children (mean rank = 14.7, p = .019). Again, the latter two groups did not differ in their performance (p = .97).

Table 2.3. *Demographics and behavioural test scores for children from SLI and control families. Data are shown for individuals and the median scores were calculated for the SLI, SIB and CON groups separately.*

Group	**Age**	**EHI**[a]	**NVIQ**	**GCC**[b]	**TROG-2**	**TOWRE** word reading	**TOWRE** phonemic decoding	**NEPSY**[c] oromotor sequences	**NEPSY** sentence repetition	**NEPSY** nonword repetition
SLI	12	9	84	31	88	95	72	-	85	80
SLI	13	7	109	20	88	84	80	-	65	75
SLI	15	10	118	51	97	102	78	2	105	80
SLI	17	2	81	15	78	54	54	1	55	55
SLI	17	9	102	47	102	79	69	2	85	65
SLI	14	10	96	15	102	74	76	1	75	55
SLI	14	10	88	24	60	82	70	1	60	90
SLI	12	2	89	39	67	86	89	3	80	100
	14	**9**	**92.5**	**27.5**	**88**	**83**	**74**	**1.5**	**77.5**	**77.5**
SIB	20	10	109	94	95	90	81	4	95	110
SIB	22	10	106	-	104	100	95	4	85	-
SIB	15	9	112	91	99	105	x	4	125	100
SIB	12	9	114	90	111	115	115	5	115	90
SIB	20	7	119	-	109	109	109	5	-	110
SIB	16	9	106	-	104	88	97	5	-	125
	18	**9**	**110.5**	**91**	**104**	**102.5**	**97**	**4.5**	**105**	**110**
CON	12	10	135	78	116	116	120	4	95	110
CON	13	6	116	81	102	121	123	4	100	80
CON	13	10	110	90	111	118	124	3	130	115
CON	15	10	108	89	99	89	102	5	130	100
CON	12	10	98	95	111	95	103	5	130	105
CON	15	2	99	79	104	90	95	4	110	115
CON	16	10	112	94	104	92	104	4	120	105
CON	14	10	109	81	99	95	88	3	95	100
CON	18	9	125	-	99	84	103	5	115	115
CON	11	-	-	-	-	-	-	-	-	-
	13.5	**10**	**110**	**85**	**104**	**95**	**103**	**4**	**115**	**105**
***P* values**										
SLI-SIB				0.006*	0.048*	0.017*	0.062	0.009*	0.15	0.12
SLI-CON				0.007*	0.011*	0.019*	0.002*	0.002*	0.002*	0.009*
CON-SIB				1.00	1.00	1.00	0.60	1.00	1.00	1.00

Note: Scores are standard scores (mean 100 ± 15) unless otherwise indicated.

[a] Number of actions from the Edinburgh Handedness Inventory demonstrated with the right hand (maximum = 10).

[b] Scores for the General Communication Composite obtained with the age appropriate Communication Checklist. Scores greater than 58 are considered normal.

[c] Scores represent percentile categorisations: 1 = <2nd, 2 = 2nd–10th, 3 = 10–25th, 4 = 25–75th, 5 = >75th.

The relationship between tract measures (mean FA, volume) of the CC or AIs of the dorsal/ventral language pathways and performance during neuropsychological assessment was explored by calculating Spearman’s rho for language-impaired and typically developing children separately. Because unaffected siblings and children from control families showed no significant differences in diffusion measures or in behavioural test scores, data of both groups were collapsed and treated as one group

(CON-all). To limit the number of comparisons, analyses focused on correlations between tract measures and scores obtained from language and literacy tests including GCC and TROG-2 as well as subtests from the TOWRE and NEPSY. Since there was no significant interaction between tract measures from the genu, body and splenium of the CC and group, I averaged mean FA across the three portions and calculated the total CC volume. Thus, correlations between tract and behavioural measures were assessed for combined values of the CC, but separately for the left and right dorsal and ventral language pathways. It is important to note that correlations obtained with small samples are quite unreliable and are likely to reveal spurious associations. The results presented in the following paragraph are mainly reported for completeness and should therefore be considered suggestive, rather than definitive.

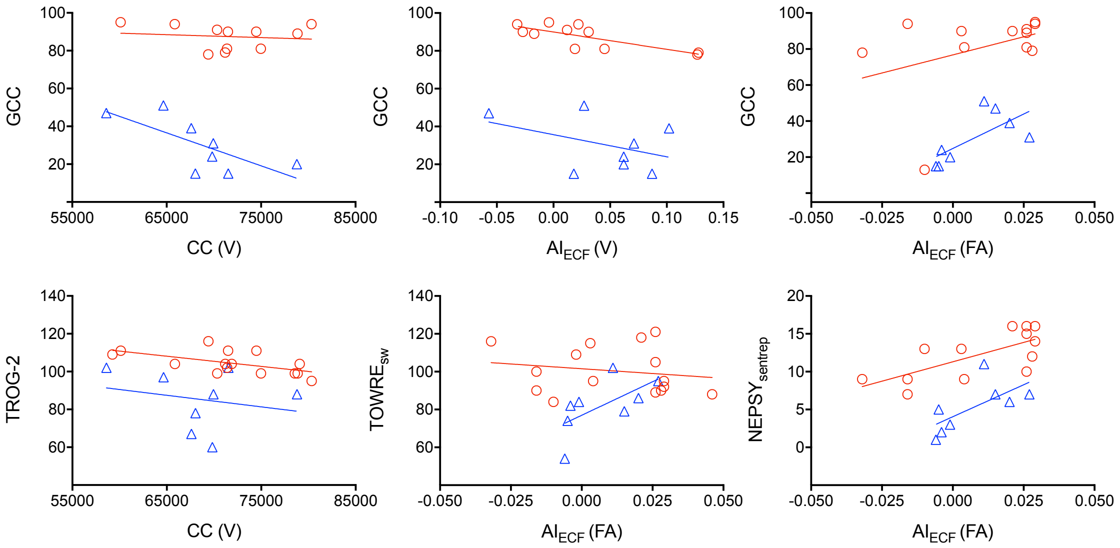

Figure 2.5*. Associations between language-related tracts and performance during neuropsychological assessment. Scatterplots display tract measures including callosal volume in mm*^{3} *(CC(V)) and asymmetry indices (AI) based on fractional anisotropy (FA) or volume (V) for the ventral language pathway (ECF) on the x-axis and behavioural measures on the y-axis. Positive AIs indicate leftward, and negative AIs rightward asymmetry. GCC - General Communication Composite, TROG-2 - Test for Reception of Grammar-2, TOWRE-sw - Test Of Word Reading Efficiency (sight word reading), NEPSY-sentrep - NEuroPSYchology test battery (sentence repetition).*

The volume of the CC correlated significantly with grammatical understanding as assessed by the TROG-2 ($r_S(15) = -.57$, $p = .026$) and with general communication skills as assessed by GCC ($r_S(8) = -.73$, $p = .040$) in the CON-all group and SLI group, respectively (*Figure. 2.5*). For both groups, Spearman's rho indicated strong negative associations indicating that children with smaller CC had higher test scores. There were no significant correlations between callosal mean FA and performance on any language or literacy test - neither for children with SLI or for control children.

For the ventral language tract, AIs based on mean FA correlated positively with performance during NEPSY's sentence repetition task in typically developing ($r_S(13) = .66$, $p = .015$) and language-impaired children ($r_S(8) = .74$, $p = .035$); stronger leftward asymmetry of the ECF was associated with higher scores on sentence repetition (*Figure 2.5*). In children with SLI, AIs based on mean FA also correlated with scores of the GCC ($r_S(8) = .73$, $p = .040$) and sight word reading as assessed by the TOWRE ($r_S(8) = .74$, $p = .037$). Again, a stronger leftward ECF asymmetry was linked to higher scores on either assessment. Indices of asymmetry based on the volume of the ventral language tract showed a positive correlation with general communication skills (GCC) in the group of typically developing children ($r_S(11) = -.65$, $p = .029$). There were no significant correlations between AIs based on ECF volume and language abilities in SLI children.

Analysis of AIs based on mean FA or volume of the dorsal language tract did not reveal any associations between AF asymmetry and performance during neuro-psychological assessment for children with SLI or typically developing children. Although correlations were primarily conducted as part of an exploratory analysis, it should be noted that none of the described associations remained significant after correcting for multiple comparisons ($p_{corr} < .003$).

2.4 Discussion

The aim of this study was to examine language-related white matter pathways and their structural asymmetry in SLI. The analysis of diffusion MRI data obtained in families with a history of SLI and control families revealed differences in the white matter microstructure of language-impaired children, but not adults. Compared with their typically developing peers, children with SLI had significantly lower FA along the entire CC including white matter areas underlying orbitofrontal cortex and superior/middle temporal gyri bilaterally; and in the white matter underlying the left and right frontal opercular and anterior insular cortex extending to the occipito-temporal areas. A similar, but more extensive pattern of low FA was seen when comparing SLI children with their unaffected siblings. Post imaging reconstruction of the genu, body and splenium of the CC confirmed that mean FA was reduced in SLI relative to unaffected siblings and control children. These findings indicate that children with SLI have poor white matter integrity along the entire callosal tract, which could reflect reduced inter-hemispheric connectivity in language-impaired relative to control children.

2.4.1 Abnormalities of language-related white matter tracts in children with SLI

My findings are in good agreement with existing studies that have found white matter differences in language-impaired children relative to typical developing peers using diffusion MRI (Kim et al., 2006; Lee et al., 2013; Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015). More importantly, the observed white matter abnormalities in children with SLI are consistent with reports of altered grey matter structure and function in the same cases (Badcock, Bishop, et al., 2012). Badcock and colleagues (2012) found that the same children with SLI had significantly more grey matter than controls in the left inferior frontal cortex and significantly less grey matter in posterior temporal areas bilaterally. Functionally, the SLI group showed significantly reduced activation during auditory naming in both inferior frontal and superior temporal region compared with unaffected sibling and controls (Badcock, Bishop, et al., 2012). These findings are not only consistent with the known roles these areas play in language, but also coincide spatially with the white matter abnormalities found in this study. Combined, our studies provide converging evidence that white matter connectivity as well as grey matter structure and function of language-related areas is altered in SLI.

The corpus callosum is the largest white matter fibre tract in the brain that links homologous brain regions and plays an important role in integrating information across the left and right hemisphere (Gazzaniga, 2000). More specifically, callosal axons from the anterior frontal lobe cross within the most anterior part (genu); pre- and post-central cortices are connected via middle regions (body), whereas temporal, parietal, and occipital areas are interconnected via the posterior callosal parts (isthmus and splenium). During normal development, age-related white matter changes have been observed in the callosal tract (Barnea-Goraly et al., 2005; Giorgio et al., 2008). Diffusion MRI studies across the lifespan with sample sizes greater than 90 have demonstrated increasing anisotropy of the corpus callosum during childhood and adolescence and decreasing trends during the aging process (Hasan et al., 2009; McLaughlin et al., 2007). Hasan et al. (2009), for example, used deterministic tractography to measure the absolute volume of the CC, callosal subvolumes (normalized with respect to each participant’s intracranial volume), and different diffusion properties in a large cohort of neurotypical right-handers aged 7–59 years. While absolute volume, normalized subvolumes, and FA values followed inverted U-shaped curves, radial diffusivity followed a U-shaped curve reflecting white matter progressive and regressive myelination dynamics that continue into young adulthood (Hasan et al., 2009).

In my study, language-impaired children showed lower FA compared with controls along the entire CC suggesting that the typical developmental trajectory may be altered in SLI. Kim and colleagues (2006) also found reduced anisotropy in the genu, but not splenium of the CC in children with SLI. Differences in my findings, marked by the extension of areas that showing a decrease in FA, may reflect different sensitivities of the two analyses rather than differences in the underlying white matter microstructure. While Kim et al. (2006) used specific ROIs that were placed according to the anatomical delineation of the callosal tract, I used probabilistic tractography allowing me to extract mean FA from the entire white matter fibre bundle including the body of the CC as well as calculating the total volume of the tract. Based on the evidence that the size of the CC reflects the degree of inter-hemispheric connections (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), several studies have looked for CC abnormalities in children with developmental language disorders (Hynd et al., 1995; Larsen, Höien, & Ödegaard, 1992; Njiokiktjien, de Sonneville, & Vaal, 1994; Preis, Steinmetz, Knorr, & Jäncke, 2000; Von Plessen et al., 2002). The reduced volume of the callosal body in the SLI group is consistent with studies that have suggested a less developed CC in dyslexia as indicated by smaller genu (Hynd et al., 1995) or differences in the shape of the posterior mid-body (Von Plessen et al., 2002). On the other hand, some studies found no differences in the absolute size of the callosal tract in children with SLI (Preis et al., 2000) or dyslexia (Njiokiktjien et al., 1994) compared with controls. The conflicting evidence regarding the size of the CC, however, may reflect the various methodologies used in this line of research. The most significant factors are great variability within neuroimaging technologies and analyses tools, different methods of measuring the CC, and more generally the heterogeneity of the study samples - especially in developmental disorders such as SLI. In my study, the combination of reduced size and abnormal structural integrity of the CC in children with SLI may affect the integration of information between the left and right hemisphere, thus leading to an abnormal pattern of cortical and/or functional language asymmetries (Geschwind & Galaburda, 1985; Hynd et al., 1995). In fact, Josse and colleagues (2009) showed that size of the midsagittal surface of the CC contributes to the degree to which language is functionally lateralized. Healthy subjects with a larger CC were more likely to show a stronger left lateralization, especially in the posterior temporal and inferior frontal language regions.

As expected, I also observed white matter differences between SLI and control children in the long association fibres that are thought to connect the two cortical language hubs, namely the AF as part of the dorsal and the ECF as part of the ventral language tracts (Dick et al., 2013; Makris et al., 2005; Makris & Pandya, 2009). Research has shown that FA of the dorsal and ventral white matter language pathways increases with age consistent with the interpretation that neural connections are strengthened during normal development (Brauer et al., 2013; Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Giorgio et al., 2010). Thus, the reduced integrity of the white matter underlying the superior and middle temporal gyri as well as frontal opercular and anterior insular cortex in both hemispheres may reflect an abnormal development of these language-related white matter fibre bundles. This accords with findings from previous DTI studies that reported abnormalities in diffusion measures of the dorsal and ventral language pathways in SLI (Roberts et al., 2014; Verhoeven et al., 2012; Vydrova et al., 2015). Using deterministic tractography, Verhoeven and colleagues (2012) found decreased FA in the white matter along the superior longitudinal fascicle, while Roberts et al. (2014) demonstrated an increase in MD measures obtained from the left AF in children with SLI compared with controls.

In accordance with these white matter abnormalities in SLI, a recent DTI study reported reduced FA and corresponding increases in RD in the AF bilaterally as well as the left IFOF and inferior longitudinal fasciculus (ILF), but reduced FA and corresponding decreases in L1 in the right IFOF in language-impaired children (Vydrova et al., 2015). They argue that the alterations in the diffusivity parameters of the left IFOF and left ILF, which are similar to the ones observed in the AF, indicate prevailing changes in the white matter microstructure of the language dominant hemisphere. Vydrova and colleagues (2015) also reported that relative to controls, children with SLI showed larger volumes of the ILF bilaterally. In my SLI group though, no differences in the size of the left or right dorsal or ventral language tracts could be seen. One can only speculate whether changes in the volume of language-related white matter fibre bundles in SLI are related to the neuropathology of the impairment, inter-individual differences during development, or compensatory mechanisms for deficiencies in the white matter microstructure of the tract (Vydrova et al., 2015). Some small discrepancies between these studies and my results such as bilateral as opposed to left hemispheric abnormalities in the white matter of the ventral tract (Vydrova et al., 2015) or less pronounced FA changes in the dorsal tract (Verhoeven et al., 2012) may be explained by differences in analysis methods (whole-brain vs. tract-specific) or tracking algorithms (probabilistic vs. deterministic) as well as definition of ROIs (central vs. all branches of the SLF) and - most likely - my rather small sample size.

2.4.2 Diffusivity measures and the maturation of white matter tracts

In recent years, diffusion MRI has become a very popular method to study the macro- and microstructure of white matter connections in the human brain. By measuring the diffusion of water along different directions, DTI provides unique insights into the morphology of brain tissue. In white matter, diffusion is restricted by tissue boundaries such as membranes or myelin, therefore the water molecules move preferentially along the axon. This characteristic allows us to infer the dominant orientation of the axon and tissue properties in each voxel, and the sum of these inferences can be used to map the organisation of white matter fibre bundles. Because we know that brain maturation and myelination result in reduced diffusion and increased anisotropy, DTI measures like FA have been proposed to be sensitive markers of white matter changes that cannot be detected by conventional MRI (Barnea-Goraly et al., 2005; Mukherjee et al., 2001). During postnatal development an increase in FA along with decreased perpendicular diffusion (RD) has been associated with a gain in myelination or compactness of fibre bundles (Snook, Paulson, Roy, Phillips, & Beaulieu, 2005), while increased FA along with increased parallel diffusivity (L1) has been suggested to reflect improved fibre coherence (Ashtari et al., 2007; Giorgio et al., 2010). In my SLI group, the decrease in FA was primarily driven by an increase in RD, especially within the white matter of the CC, suggesting that the changes in white matter integrity are caused by reduced myelin or density of the fibre bundles (Snook et al., 2005). Thicker myelin sheathes and increased axonal diameter of white matter fibre bundles can improve signal transduction, which may be critical for optimal cognitive development and language acquisition during childhood. Whether these alterations in the white matter microstructure reflect permanent axonal injuries obtained during critical times of early neurogenesis or transient abnormalities due to late maturation remains unclear.

2.4.3 Asymmetry of dorsal and ventral language pathways in SLI

Consistent with the notion that language function is mediated by the left hemisphere, DTI studies have demonstrated that the left AF has larger volume (Glasser

& Rilling, 2008; Parker et al., 2005; Powell et al., 2006) as well as higher fibre density (Vernooij et al., 2007) and increased FA (Büchel, Raedler, Sommer, Sach, & Weiller, 2004; Powell et al., 2006) compared with the right AF. These findings indicate a leftward asymmetry of the dorsal language tract. For the ventral language tract, reports on lateralization are more variable. While Thiebaut de Schotten and colleagues (2011) observed a rightward asymmetry of the IFOF, Parker and colleagues (2005) reported stronger ventral connections within the left hemisphere. A deviation from the usual pattern of left-sided brain lateralization for language has been associated with developmental language disorders (Bishop, 2013). In SLI, neuroimaging studies revealed reduced activation and weaker functional lateralization of the left hemisphere (Badcock, Bishop, et al., 2012; Bernal & Altman, 2003; Chiron et al., 1999; de Guibert et al., 2011; Ors et al., 2005; Whitehouse & Bishop, 2008) as well as atypical structural lateralization of the cortical language areas (De Fossé et al., 2004; Gauger et al., 1997; Herbert et al., 2005; Jernigan et al., 1991; Plante et al., 1991).

In my study, tract volume as well as mean FA across children with SLI, their unaffected siblings and controls was significantly different for the left compared with the right hemisphere for the dorsal, but not ventral language tract. AIs based on these tract measures, however, showed no significant asymmetry for the ECF and diametrically opposed ones for the AF. In children without language impairment, AIs based on mean FA indicated a significant rightward asymmetry of the dorsal language pathway, while those based on tract volume indicated a significant leftward asymmetry. In addition, the comparison of mean AIs did not reveal significant differences in the degree of AF asymmetry or ECF asymmetry among children with SLI, their unaffected siblings and children from control families. Because I did not replicate the expected pattern of leftward asymmetry in my control children (at least not consistently), the interpretation of my asymmetry measures is challenging.

One possible explanation may be related to the younger age of our participants compared to previous DTI studies (Catani et al., 2007; Catherine Lebel & Beaulieu, 2009; Vernooij et al., 2007). Language laterality (Holland et al., 2001) as well as volume and FA of language-related white matter tracts has been shown to increase with age (Brauer et al., 2013; Eluvathingal et al., 2007; Giorgio et al., 2010), hence asymmetry measures in this study may be affected by developmental changes. Dubois and colleagues (2006), for example, found significant correlations between age and white matter diffusion properties in infants as young as 1 - 4 months of age. Variations in FA were observed in many fibre bundles including the corpus callosum, body and splenium, as well as in the inferior and superior longitudinal fascicles (Dubois et al., 2006). The latter tract showed reduced FA in 7-year-old children compared with adults, too, arguing for an immature status of the dorsal language pathway even in older children (Brauer et al., 2011).

The rather small size of my study sample is another important consideration, especially when examining control and SLI children separately. Individual laterality measures are highly variable and mean LIs based on small groups may not be sensitive enough to reveal white matter asymmetries. Using DTI to assess white matter asymmetries of the dorsal and ventral language pathway in children with SLI, Vydrova and colleagues (2015) found similar results to mine. Although they demonstrated that leftward laterality of the AF volume in children with SLI was less frequent (24.3%) compared to data reported for healthy individuals in previous diffusion MRI studies (e.g. 81% by Lebel & Beaulieu, 2009, 82.5% by Catani et al., 2007, and 80% by Vernooij et al., 2007), it was not significantly lower relative to their control group (35.3%). In addition, the asymmetry profile of the dorsal as well as ventral language tract based on FA did not differ between SLI and control group (Vydrova et al., 2015).

2.4.4 Correlation of tract measures and language abilities

The maturation of white matter during childhood and adolescence goes hand in hand with the development of cognitive functions. Regional changes in myelination rate have been suggested to underlie these developments (Flechsig, 1920). While several DTI studies have examined the maturation of white matter with increased age (e.g. Barnea-Goraly et al., 2005; Eluvathingal et al., 2007; Giorgio et al., 2008, 2010; Krogsrud et al., 2016), only a few studies have related these white matter changes to cognitive development (Ashtari et al., 2007; Nagy, Westerberg, & Klingberg, 2004; Schmithorst, Wilke, Dardzinski, & Holland, 2005). The ones that did, reported correlations of white matter maturation, as indicated by higher FA, with measures of language and semantic memory (Ashtari et al., 2007), IQ test scores (Schmithorst et al., 2005) as well as working memory capacity and reading skills (Nagy et al., 2004). Their results suggest that age-related changes in relatively restricted white matter regions are related to the development of specific cognitive functions. For example, learning to read has not only been associated with changes in functional activity in temporo-parietal, temporo-occipital, and ventral frontal cortices (Shaywitz et al., 2002; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003), but reading proficiency has been found to positively correlate with white matter integrity in the left fronto-parietal regions (Klingberg et al., 2000; Nagy et al., 2004). In this very same region, adults with poor reading skills and a history of developmental dyslexia showed reduced FA indicating that the development of reading ability may be dependent on white matter maturation in the temporo-parietal lobe (Klingberg et al., 2000). These findings are consistent with the results from my correlation analysis where increased leftward asymmetry of the ECF based on mean FA was related to better communication skills as well as reading accuracy and sentence repetition in SLI.

My exploratory analysis also revealed that higher scores of receptive grammar in control children and general communication in children with SLI are associated with reduced volume of the CC. The negative correlation between callosal volume and language abilities is contradictory to previous reports, which indicated that the size of the CC is positively related to reading scores (Hynd et al., 1995) and verbal fluency (Hines, Chiu, McAdams, Bentler, & Lipcamon, 1992). There has been conflicting evidence, however, that a larger CC results in increased cognitive capacity, and therefore the relationship between CC morphology and cognitive abilities is still actively. For instance, some neuroimaging studies have demonstrated negative correlations between the callosal regions and measures of intellectual ability (Ganjavi et al., 2011; Hutchinson et al., 2009), whereas others reported positive (Eileen Luders et al., 2007) or no correlations (Tramo et al., 1998).

As mentioned previously, these correlations should be interpreted with caution due to the small sample size. Although all correlations were large in magnitude indicating strong associations between callosal volume or ECF asymmetry and behaviour, none survived corrections for multiple comparisons. More research in larger samples is therefore needed to assess the validity of these results.

2.4.5 Limitations and advances of this study

Despite these intriguing findings, it is important to acknowledge some limitation of the current study. The first one relates to the rather small sample size, which consequently limited the interpretation of some study result including asymmetry profiles and correlations between white matter and behavioural measures in

SLI. However, SLI at mid-childhood is rare, which makes it difficult to find affected children that are suitable and happy to undergo an MRI scan. Hence, the recruitment of volunteers is costly in terms of time.

Secondly, while DTI is sensitive to alterations in white matter microstructure, the exact anatomical interpretation of reduced FA in children with SLI remains to be elucidated. In many studies a decrease in FA has been associated with loss of structure, possibly due to axonal or myelin breakdown (e.g. Gallo et al., 2005; Rovaris et al., 2002). The DTI model, however, is an oversimplification of reality and diffusivity measures are not only affected by biological changes such as myelin thickness, axon size, and axon density (Beaulieu, 2002), but also by methodological confounds such as the presence of crossing fibres (Wheeler-Kingshott & Cercignani, 2009) and the partial volume effect (Vos, Jones, Viergever, & Leemans, 2011). As a result, the interpretation of FA changes is difficult and rests on knowledge of what is known to drive diffusion anisotropy.

Finally, FA values were averaged over the entire length of the white matter tract. Because diffusion measures vary along the trajectory of fibre bundles, averaging can obscure important information (Yeatman et al., 2012). Hence, mean values may not be sensitive enough to reveal more focal alterations within the white matter of the tract or differences between tract profiles. This may explain why the analysis based on the tractography for mean FA is not entirely consistent with the TBSS findings, which in this instance appear to have been more sensitive.

Diffusion imaging studies in children with SLI are scarce and compared to previous investigations the present study benefited from some methodological advances. For example, the data was acquired using 60 diffusion-encoding directions providing a gain in power and higher angular resolution. In order to localise white matter changes, I used TBSS for whole-brain voxel-wise analysis of diffusion parameters, followed by probabilistic tractography to further examine specific fibre bundles. While TBSS alleviates some of the problems associated with conventional approaches such as voxel-based morphometry and therefore improves the sensitivity diffusion MRI analysis (Smith et al., 2006), probabilistic tractography facilitates more accurate tracking of fibre bundles in complex white matter areas because of its inherent ability to model noise and uncertainty (Behrens et al., 2003). By combining these two methods, I was able to describe changes in the white matter microstructure in children with SLI more reliably.

2.5 Conclusions

In conclusion, I have shown that language-impaired children have reduced white matter integrity in the corpus callosum and white matter underlying the cortical language network. In spite of the small SLI sample, I was able to describe the changes in the white matter microstructure reliably by combing whole-brain TBSS analysis with probabilistic tractography. Reduced FA of the callosal tract in language-impaired children indicates changes in their inter-hemispheric connections. The corpus callosum is the major neural pathway linking homologous brain regions and has been hypothesized to play a fundamental role in integrating information across the two cerebral hemispheres (Gazzaniga, 2000). Abnormalities associated with the corpus callosum are thought to be directly related to changes in cortical asymmetry (Geschwind & Galaburda, 1985; Hynd et al., 1995). Thus, these findings provide useful insights into neural differences that may underpin atypical lateralisation of language structures associated with SLI.

3

Lateralization of brain function in specific language impairment

Abstract

Given the left hemisphere specialization for language in most typically developing children, atypical functional lateralization has been proposed to account for developmental language disorders like SLI. Yet, evidence from neuroimaging studies is weak and inconsistent. Based on the assumption that language lateralization may result from asymmetries at a more basic level of auditory processing, the present study was designed to examine patterns of brain activation and functional lateralization for non-speech sounds in SLI. The same children and adults who had participated in my first study were scanned using sparsely-sampled FMRI while listening to pure tone patterns that differed in the temporal and functional domain. The set of stimuli was identical to one used in a previous study by Jamison et al. (2006), which found that in auditory cortex, processing of temporal variation in non-speech sounds is left lateralized, whereas processing of spectral variation is more right lateralized. I found that relative to typically developing peers children with SLI showed reduced activity in the right middle temporal gyrus (MTG) as well as in right insular and left opercular cortex across the different types of auditory stimulation. When comparing SLI children with their unaffected siblings a similar pattern of reduced activation within left and right insular cortex was observed during the temporal processing. In addition, parents with SLI had increased activation in the left

caudate nucleus during increased temporal processing. However, I failed to replicate the predicted pattern of hemispheric specialization for temporal versus spectral processing in children and adults from control families. Members from families with a history of SLI did not show the expected pattern of lateralization either, but it is not clear if this was due to a deficit in the group or a problem with my experimental task

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3.1 Introduction

Although the aetiology of specific language impairment (SLI) remains largely unknown, there is growing support for the idea that a deviation from the usual pattern of left-hemisphere specialization for language is associated with SLI (Bishop, 2013). The notion of atypical language lateralization in developmental language disorders appears in the literature as early as 1925, when Orton first suggested that reading deficits may result from a poorly lateralized brain. This hypothesis was further developed by Annett (1985), who proposed a single-gene account of hemispheric specialisation. According to her ‘right shift theory’, language impairment is linked to a postulated ‘right shift’ gene that influences both human brain asymmetry and handedness: the gene promotes typical cerebral lateralization in most individuals but its absence increases the risk of language and literacy problems. For many years, there was no direct method to non-invasively assess language laterality. Therefore, early studies in this line of research focussed on handedness as a proxy measure. Handedness, however, is an indirect and often inaccurate indicator of language lateralization and a comprehensive review by Bishop (1990) did not find clear associations between handedness and SLI or dyslexia.

3.1.1 Functional lateralization in SLI

Due to advances in neuroimaging techniques, it became possible to assess language lateralization in neurotypical individuals and children more directly. Studies of brain structure and function in developmental language disorders have since revived the idea of a link between atypical cerebral lateralization and SLI (e.g. Gauger, Lombardino, & Leonard, 1997; Herbert et al., 2005; de Guibert et al., 2011; Whitehouse & Bishop, 2008). For example, different studies have used single-photon emission computed tomography (SPECT) to quantify cerebral blood flow in order to examine functional lateralization in language-impaired children. Researchers demonstrated either reduced lateralization or hypoperfusion of the left hemisphere in children with SLI compared to controls both at rest (Lou, Henriksen, & Bruhn, 1990; Ors et al., 2005) and during a dichotic listening task (Chiron et al., 1999). Functional MRI studies revealed rather mixed results: Bernal and Altman (2003) confirmed an atypical rightward lateralization in 5 out of 6 late talkers compared to a typical leftward one in 10 out of 14 control children when listening to voice recordings, while two other studies did not find reliable differences in functional lateralization between children with SLI and controls (Weismer et al., 2005; Hugdahl et al., 2004). It is important to note that the tasks used in the latter FMRI studies did not reveal a robust left-lateralized activation pattern in the control groups either. More recently, de Guibert and colleagues (2011) investigated functional lateralization in a specific subtype of SLI, in which the core components of language (especially morphosyntax and phonology) are affected and which is often referred to as typical SLI (Bishop, 2004). The authors combined FMRI with a distinct set of language tasks, including two auditory lexico-semantic tasks (semantic fluency, responsive naming) and two visual phonological tasks based on picture naming. In line with the idea of atypical lateralization in developmental language disorders, they found a significant lack of left lateralization in all core language regions along with hypoactivation of the posterior superior temporal/supramarginal junction as well as hyperactivation of the right anterior insula adjacent inferior frontal gyrus in children with SLI relative to typically developing peers (de Guibert et al., 2011). Using functional transcranial Doppler ultrasonography (FTCD) to measure blood flow velocities during a word generation task, further evidence of atypical lateralization in adults with persistent language impairment was found by Whitehouse and Bishop (2008). Compared with age-matched controls, affected adults showed either symmetrical or right hemisphere responses more commonly.

Taken together, the majority of neuroimaging studies have found evidence strongly suggestive of atypical lateralization and functioning of core language areas in SLI (Bernal & Altman, 2003; Chiron et al., 1999; de Guibert et al., 2011; Lou, Henriksen, & Bruhn, 1990; Ors et al., 2005; Whitehouse & Bishop, 2008). Methodological constraints commonly associated with functional neuroimaging have raised the question as to whether these findings are robust. One major constraint is the typically small sample sizes of these studies, due to the difficulty in recruiting children with SLI and the higher likelihood that datasets will be excluded because of motion-related artefacts. A second major constraint relates to the fact that there is little agreement about how to best measure functional lateralization: neuroimaging studies that have assessed language laterality differ greatly in all aspects of their design such as imaging technique (e.g. PET, FMRI or FTCD) and protocol (e.g. resting-state or task-related activation), paradigms used for language mapping (e.g. word generation, passive listening or reading) and modalities of stimulus presentation (e.g. visual or auditory) as well as analysis methods (e.g. whole brain vs. language areas or extent vs. magnitude of activation). These measurement inconsistencies have inevitably limited strong interpretation of findings from functional imaging studies in SLI.

3.1.2 Functional lateralization in auditory cortex

An important aspect of hemispheric specialization for language that has not been much investigated in SLI using functional MRI pertains to the processing of auditory (speech) signals. Because speech perception relies on the rapid processing of sequential information, which is encoded in a fast-fading auditory signal, one theory proposes that asymmetries at a more basic level of auditory processing may lead to cerebral lateralization of higher-order processes such as language (Efron, 1963; Schwartz & Tallal, 1980). An alternative view posits that left hemisphere specialization arises from linguistic relevance and intelligibility of the input signal (Narain et al., 2003; Scott et al., 2000) fuelling the debate over the nature of functional lateralization in auditory cortex. As a consequence more recent neuroimaging studies investigated the origin of hemispheric specialization in the absence of linguistic information using positron emission tomography (PET, Zatorre & Belin, 2001) as well as FMRI (Boemio et al., 2005; Jamison et al., 2006; Zaehle et al., 2008) suggesting that processing of greater temporal variation in auditory stimuli is associated with increased activation in the left hemisphere, whereas processing of greater spectral variation is thought to be right lateralized. The left lateralization associated with increased temporal processing has been demonstrated to be greater in posteromedial Heschl's gyrus, which represents primary auditory cortex (Jamison et al., 2006).

Along a similar line of argument Poeppel (2003) proposed that functional lateralization of auditory speech perception may be accounted for by hemispheric differences in sampling time. While left auditory regions preferentially extract information from short temporal integration windows (20-50 ms), right hemisphere homologues operate over longer ones (150-120 ms, Poeppel, 2003). According to this hypothesis initial auditory processing is roughly the same in the left and right auditory cortex, but temporal and spectral asymmetry is generated by small differences in neuronal integration constants (Poeppel, 2003). Boemio and colleagues (2005) provided supportive evidence for this model showing that both hemispheres are highly adept at temporal resolution and that right-lateralized responses in the posterior part of the superior temporal sulcus (STS) are driven by more slowly modulated signals rather than increased spectral complexity. Asymmetries in auditory processing have been hypothesized to reflect the developmental outcome of optimizing the processing of acoustic stimuli (Zatorre, Belin, & Penhune, 2002). Thus, temporal integration windows may be better thought of as relative and experience-dependent and not absolute (Jamison et al., 2006). Consistent with this notion functional lateralization associated with the processing of specific acoustic stimuli has been suggested to vary with linguistic experience (Gandour et al., 2002; Hsieh et al., 2001).

Analysis of speech requires good temporal resolution, so this functional lateralization for auditory processing might relate to language laterality. Hence, the atypical cerebral lateralization seen in SLI may arise from altered asymmetries at a more basic level of auditory processing. Previous studies claimed that children with SLI are impaired at differentiating rapidly changing sounds (Tallal & Piercy, 1973, 1974, 1975), and that these deficits are accompanied by alterations of different event-related potentials (ERP, McArthur & Bishop, 2005; McArthur & Bishop, 2010; Rinker et al., 2007). Although some researchers have argued for abnormal processing of speech-specific sounds in SLI (Holopainen et al., 1997, 1998; Shafer et al., 2005; Uwer, Albrecht, & Suchodoletz, 2007), others have argued that the deficit is a general input-processing problem affecting speech and non-speech sounds (McArthur & Bishop, 2005; Tallal & Piercy, 1973; Tonnquist-Uhlén, 1996).

3.1.3. Aims of this study

Here, I used functional MRI to examine hemispheric specialization for non-speech sounds in the same members of SLI and control families who took part in my previous study. I compared brain activation patterns in individuals with SLI and typically developing controls while they passively listened to pure tone sequences that varied in their temporal or spectral structure. By using the identical set of stimuli as

Jamison et al. (2006), my aims were i) to replicate previous demonstrations that responses to increased temporal variation are left lateralized, whereas those to increased spectral variation are right lateralized in children and adults from control families, and ii) to examine whether this pattern of hemispheric specialization is altered in language-impaired members from SLI families.

3.2 Methods

3.2.1 Participants

As for my first study, functional MRI data were obtained in children with SLI, their affected and unaffected siblings and parents as well as in control families. Inclusion criteria and the neuro-behavioural assessment of participants have been previously described (see chapter 2.2 for details).

Table 3.1 *Demographics of SLI and control participant included in FMRI study. Group characteristics are shown for individuals with SLI (SLI), unaffected family members (SIB/PAR) and control families (CON) for children and adults data separately. P values are reported for within study group comparisons of age as well as gender and self-reported handedness based on Kruskal-Wallis test and Chi-square statistics respectively.*

	Children				**Adults**			
	SLI	SIB	CON	*P* value	SLI	PAR	CON	*P* value
N	7	6	13		7	9	13	
Age range	12-17	12-22	11-18		40-61	37-54	38-55	
Median age	14	18	13	0.128	45	49	45	0.337
Gender	6M : 1F	4M : 2F	8M : 5F	0.529	2M : 5F	4M : 5F	7M : 6F	0.555
Handedness	5R : 2L	5R : 1L	12R : 1L	0.465	5R : 2L	9R : 0L	13R : 0L	0.034*

Note: Significant differences ($p < 0.05$) are indicated by an asterisk.

For this study, eight children with SLI, six unaffected siblings, and fifteen young volunteers with no family history of SLI were scanned using FMRI. Due to excessive motion, the datasets of one SLI child and two control children had to be excluded from further analysis. In the adults, functional data was acquired in seven language-impaired parents of the children with SLI, nine unaffected parents of the children with

SLI and thirteen parents from control families. Demographics and group statistics are shown in *Table 3.1*. The study was approved by the Mid and South Buckinghamshire Local Research Ethics Committee (04/Q1607/64) and in accordance with ethical approval both children and parents were informed about the experiment and gave written consent before taking part. As assessed by Kruskal-Wallis tests, neither language-impaired children (p = .13) nor adults (p = .34) differed significantly from their unaffected family members and control participants in their age (*Table 3.1*). In addition, the three groups of children (SLI, siblings, control) were similar for sex (p = .53) and handedness (p = .47). There were, however, significant differences among the adult groups related to handedness ($\chi^2(2) = 6.75$, p = .034). This was due to the SLI group containing two left-handers.

3.2.2 MRI data acquisition

MRI data was acquired using a 1.5-T Siemens Sonata scanner with a single-channel head coil and inserted padding around the head to restrict movement and thus minimize motion-related artefacts. As described in chapter 2, three high-resolution T1-weighted images (1-mm isotropic voxels; 3D FLASH sequence; TR = 12 ms; TE = 5.65 ms; matrix = 256 x 256 x 208; elliptical sampling) were acquired in each participant for image registration.

During functional scanning participants, listened to pure tone stimuli presented binaurally via MRI compatible headphones (MR Confon: http:// www.mr-confon.de) at a comfortable listening level (estimated ~70 dB). Auditory stimuli were similar to those used by Jamison et al. (2008) and varied systematically in frequency and duration of the individual elements forming three main conditions: (i) stimuli in the "standard" condition comprised trains of tones alternating at random durations (shortest duration 667 ms) between two frequencies an octave apart (one at 500 and one at 1000 Hz); (ii) stimuli in the "temporal" condition were identical to those in the standard condition but alternated at a greater rate (shortest duration 21 ms); (iii) stimuli in the "spectral" condition had the same rate of alternation as those in the standard condition but the number of frequencies sampled between 500 and 100 Hz was increased (minimum interval between two tones was 1/32nd octave).

Participants were familiarized with the stimuli prior to scanning and instructed to listen to the pure tone patterns without performing an explicit task while lying as still as possible in the scanner with eyes closed. For functional scans, whole- head T2*-weighted echo-planar images were acquired every 8s (TE = 50 ms, delay in acquisition = 6 s, in-plane resolution 3 x 3 mm, 23 axial slices 4 mm thick). Employing this sparse-sampling design (D A Hall et al., 1999) enabled us to present auditory stimuli during the 6-s silent delay (between image acquisition), thus reducing signals in the images relating to the scanner acoustic noise.

3.2.3 MRI data analysis

Functional MRI data were analysed using the General Linear Model implemented in FMRI Expert Analysis Tool (FEAT), part of the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) and further statistical tests were conducted in SPSS (www.ibm.com/software/analytics/spss). For each subject, EPIs were brain extracted using the Brain Extraction Tool (BET) and realigned to compensate for small head movements (Jenkinson et al., 2002). Functional images were first registered to the participant's structural scan using boundary-based registration (BBR; Greve & Fischl, 2009) and then non-linearly to the MNI152 standard brain (FNIRT). An 8-mm full-width-half-maximum Gaussian kernel (FWHM) was applied to spatially smooth the data and high-pass temporal filter with a cut off of 50 s was used to remove low frequency drifts. Time-series statistical analysis was carried out using

FILM with local auto-correlation correction (Woolrich et al., 2001). The three conditions were modelled separately; convolution with haemodynamic response function (HRF) was turned off as it was assumed that the volume was acquired during a time when the HRF had reached its peak. The six parameters obtained from the motion correction (rotations and translations in x, y and z were included in the model as regressors of no interest. Statistical analysis was performed using the general linear model (GLM): individual contrast maps were generated at a single-subject level to show patterns of activation related to each type of auditory stimulation compared to baseline. Higher-level analysis was carried out using FMRIB's Local Analysis of Mixed Effects (FLAME, Woolrich et al., 2004): statistical maps (cluster-forming threshold $Z > 2.3$, extent $p = .05$, corrected) were generated to show patterns of activation during each condition separately and in comparison with each other identifying areas that are differentially responsive to increased temporal or spectral variation.

A mask comprising the auditory cortex (areas TE1.0, 1.1 and 1.2; Morosan et al., 2001) was anatomically defined based on the probabilistic Jülich histological atlas, which is implemented in FSL. Primary auditory cortex (HG) is located in the posteromedial half of Heschl's gyrus, so I divided the ROI into a medial and lateral part for the left and right hemispheres separately. To test the assumption that neural responses to greater temporal variation are left lateralized, whereas those to increased spectral variation are right lateralized, I extracted the mean percent signal change in the blood oxygen level-dependent response (BOLD) from the four ROI's. To test for differences in mean percent signal change associated with greater temporal or spectral stimulation mixed analyses of variance (ANOVA) were performed with group (SLI vs. unaffected family member vs. control) as a between-subject factor and hemisphere (left vs. right) as a within-subjects factor for children and parents separately. Furthermore laterality indices ($LI=(BOLD_{left} - BOLD_{right})/(BOLD_{left} + BOLD_{right})$) were calculated for each subject and averaged across groups. Positive LIs indicate a left, negative values a right lateralization of activation patterns. Values of $-0.2 \leq LI \leq 0.2$ were considered as bilateral (not lateralized) findings (Wilke & Lidzba, 2007; Wilke & Schmithorst, 2006). Employing a Kruskal-Wallis test, I compared the LIs between groups for children and parents separately.

As for the analyses presented in Chapter 2, power calculations revealed that the sample sizes of our groups with SLI were sufficient only to detect effects that were of very large size (see section 2.2.5).

3.3 Results

To examine differences in NVIQ as well as language and literacy abilities among individuals with SLI, unaffected family members and control participants, I conducted Kruskal-Wallis tests for children and adults separately.

As expected from my previous analysis (Chapter 2.3), the three groups of children differed significantly in NVIQ ($\chi^2(2) = 6.69$, $p = .035$). Post-hoc analysis revealed that SLI children scored lower relative to unaffected siblings and control children (see *Table 3.2*). The latter two groups had similar NVIQ scores. With the exception of sight word reading measured by the TOWRE, statistical analyses confirmed that children with SLI, their unaffected siblings and typically developing controls differed significantly in their performance during language and literacy assessments, too. *Table 3.2* summarizes the group statistics for the children's neuropsychological assessment, which showed that SLI children scored lower on most standardized tests of language and literacy relative to controls and unaffected siblings. Only scores of sentence repetition as assessed by the NEPSY did not significantly differ between children with SLI and unaffected siblings.

Table 3.2. *Demographics and behavioural test scores for children from SLI and control families. Data the median scores ± interquartile range for the SLI, SIB and CON groups separately. P-values indicate significant differences in performance, as assessed by Kruskal-Wallis tests*

	CHILDREN			
	SLI	SIB	CON	*P* value
N	7	6	13	
Gender	6M : 1F	4M : 2F	8M : 5F	*.529*
Handedness	5R : 2L	5R : 1L	12R : 1L	*.465*
Age	14 ± 3	18 ± 6.25	13 ± 4	*.128*
NVIQ	96 ± 15	110 ± 9	111 ± 22.3	*.031**
GCC[a]	31 ± 27	91 ± 1	89.5 ± 15.2	*.001**
TROG-2	97 ± 35	104 ± 11.5	104 ± 12	*.019**
TOWRE-sw	86 ± 16	102 ± 21	95 ± 27	*.052*
TOWRE-pd	76 ± 13	97 ± 24	103.5 ± 25.5	*.001**
NEPSY-oro[b]	2 ± 1.25	4.5 ± 1	4.50 ± 1	*.001**
NEPSY-sentrp	80 ± 25	110 ± 22.5	105 ± 15	*.002**
NEPSY-nwrp	80 ±10	105 ± 35	115 ± 28	*.005**

Note: Scores are standard scores (mean 100 ± 15) unless otherwise indicated.

[a] Scores for the General Communication Composite obtained with the age appropriate Communication Checklist. Scores greater than 58 are considered normal.

[b] Scores represent percentile categorisations: 1 = <2nd, 2 = 2nd–10th, 3 = 10–25th, 4 = 25–75th, 5 = >75th.

3.3.1 Between-group comparisons

Activation maps comparing each type of auditory stimulation (standard, temporal, spectral) to silent baseline were generated for SLI children, unaffected siblings and control children as well as SLI parents, unaffected parents and control parents. In all six groups whole brain analysis showed similar patterns of activation for the three conditions. As expected, significant activity was observed in extensive clusters in auditory cortex encompassing Heschl's gyrus (HG) and the superior temporal gyrus (STG) as well as planum temporale (PT) in each hemisphere (cluster thresholded at $Z > 2.3$ and $p < .05$, corrected).

Group differences in activation patterns between SLI, unaffected family members and control participants were examined by calculating statistical contrasts within the

GLM. Differences between groups in areas that were not activated during auditory processing for the individual group average (namely outside the posterior and middle temporal cortex, see *Figure 3.1*) are difficult to interpret, as they were not hypothesized. Such differences may reflect differences in subthreshold or even negative activation between groups. I report them here for completeness but they are not discussed further.

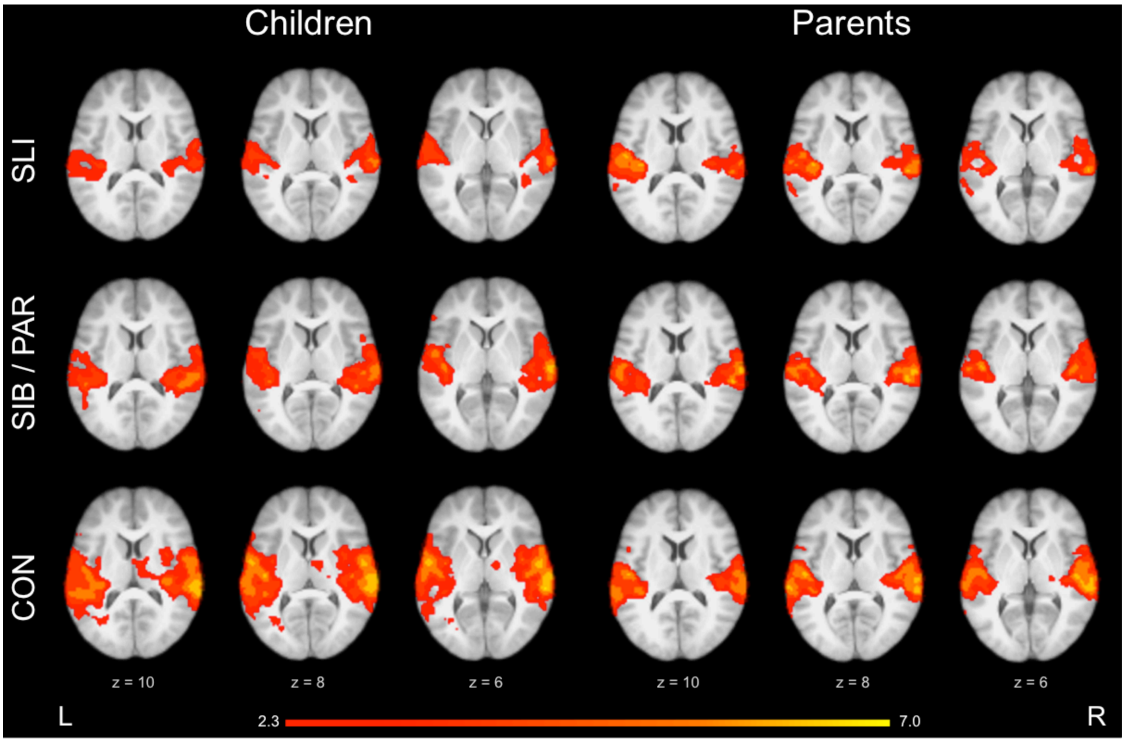


Figure 3.1 *Areas of activation associated with auditory processing for the contrast standard > baseline. Statistical maps (at Z >2.3; p < .05, corrected) are superimposed on to the MNI-152 brain: axial slices 6, 8, and 10 mm above the bicommissural plane.*

Relative to typically developing peers, children with SLI showed significantly reduced activity in the posterior part of the right middle temporal gyrus (MTG) when listening to the standard stimulus, in the right insular cortex and right thalamus when listening to the temporal stimulus, and in the right insular cortex extending to opercular cortex and left insular cortex encompassing IFG when listening to the spectral stimulus (*Figure 3.2)*. When comparing SLI children with their unaffected siblings a similar pattern of reduced activation within left and right insular cortex was observed during the temporal processing. While the left cluster extended into orbito-frontal cortex, the right included the caudate nucleus as well as opercular cortex (*Figure 3.2)*. For the spectral condition, I did not find any differences in activation to auditory stimulation between the two groups. The only group difference observed within the regions activated by auditory processing in all group averages (see *Figure 3.1*), was one of reduced activity in the posterior right MTG in the SLI group for the standard stimulus (see *Figure 3.2*, yellow areas). These results indicate a reduced response to auditory stimulation in children with SLI relative to typically developing controls and unaffected siblings. Differences in activation between the latter two groups were observed for the temporal condition only, during which unaffected siblings showed greater activation in the left insular cortex extending into left orbito-frontal areas (*Figure 3.2*).

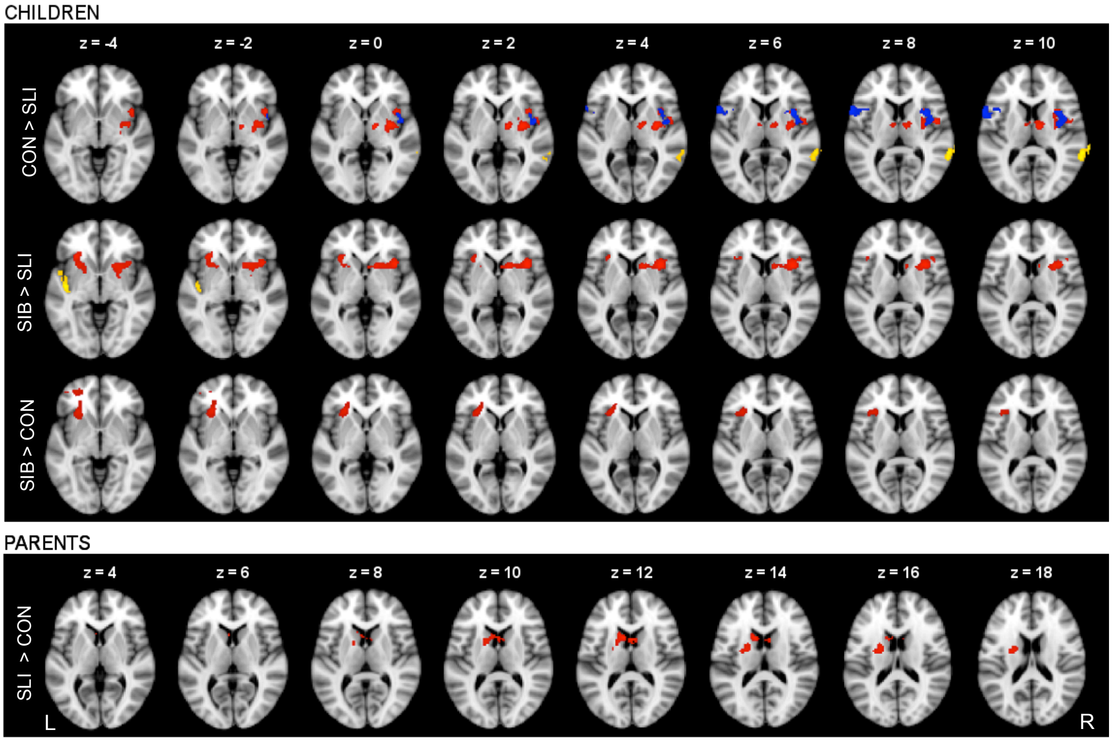


Figure 3.2. *Group differences in brain activity for the standard (yellow), temporal (red) and spectral (blue) contrast. Coloured maps show the Z-statistic (cluster threshold at $Z > 2.3$; $p < 0.05$, corrected) for comparisons between groups: Controls (CON), Siblings (SIB), and SLI as indicated on the left side. Statistical Maps are presented on the standard MNI152 T1-weighted brain. Numbers above axial slices indicate the z-coordinate in mm relative to the bicommisural plane.*

Group comparisons within the adult sample, revealed significantly increased activation in the left caudate nucleus during temporal stimulation in parents with SLI compared to control parents. No differences in activity in posterior temporal cortex were observed between SLI and unaffected parents, or unaffected and control parents.

3.3.2 Increased temporal and spectral processing

To look for the predicted pattern of hemispheric specialization, I examined functional activity associated with increased temporal or spectral variation compared to the standard tone in children and parents of SLI and control families.

The *temporal* > *standard* contrast revealed two distinct clusters within the left and right temporal lobe: with greater temporal processing, activation was significantly increased along HG and STG bilaterally comprising the PT (cluster thresholded at $Z > 2.3$ and $p < .05$, corrected). As shown in the upper row of *Figure 3.3*, this pattern of activation was seen all six groups of participants. Examination of this activity's spatial extent (number of voxels where $Z > 2.3$) and peak values (magnitude of Z-statistic) for the group averages indicated inconsistent left or right asymmetries across the different groups (*Table 3.3*). Contrary to my prediction, the size of the left hemisphere cluster was numerically smaller than the one observed in the right, in both control parents and control children. With the exception of language-impaired parents, the opposite was seen in members from families with a history of SLI, i.e. the spatial extent of auditory cortex activation was larger in the left relative to the right hemisphere in children with SLI, their unaffected sibling and parents (i.e. it was lateralized as expected). In control families, the height of peak voxels in the left and right clusters did not show large differences favouring the left hemisphere either. Similar patterns of peak values were observed in the different groups of SLI family members (*Table 3.3*). While the height of peak voxels was slightly bigger in the left hemisphere cluster in children with SLI and unaffected siblings, unaffected parents and parents with SLI showed numerically higher peak values in the right relative to the left hemisphere. The three groups of children as well as parents with SLI, unaffected parents and control parents did not differ from each other in auditory cortex activation associated with increased temporal processing.

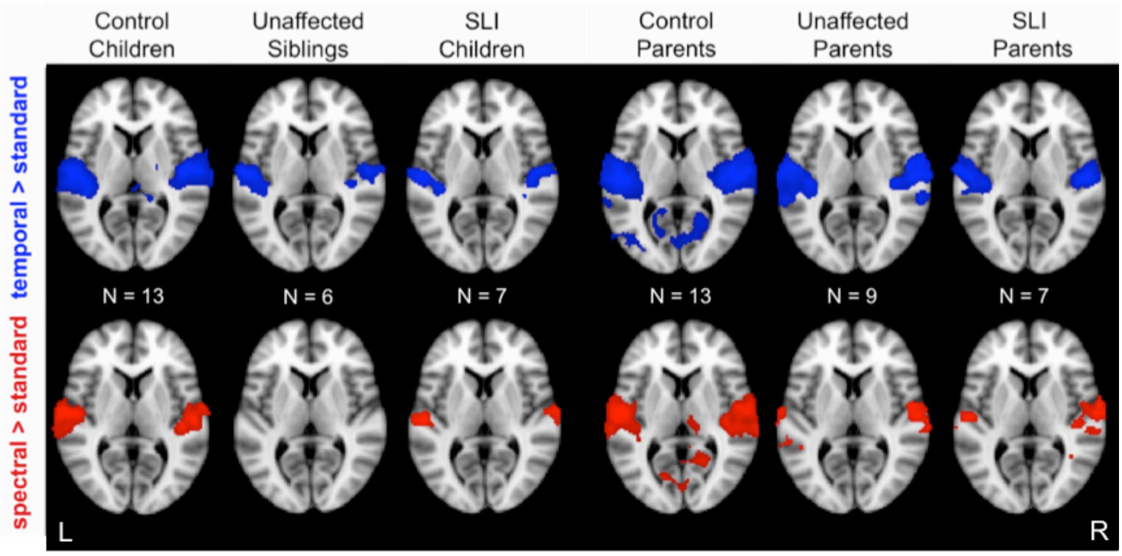


Figure 3.3 *Areas of significant activation are shown for the contrast temporal > standard (blue) in the upper and spectral > standard in the bottom row (red) for all six groups. Statistical maps (cluster threshold at Z>2.3; p<0.05, corrected for multiple comparisons at the whole-brain level) are superimposed on to the MNI-152 brain: axial slices 6 mm above the bicommissural plane.*

For the contrast *spectral > standard,* significant activation was seen bilaterally in areas centred on HG including surrounding regions of the STG in all groups except for unaffected siblings (*Figure 3.3,* bottom row); there were no clusters whose size exceeded the extent threshold correcting for multiple comparisons at the whole-brain level for this contrast in this small group. Consistent with my hypothesis, the spatial extent of the right temporal lobe cluster was numerically bigger than the one in the left hemisphere in children and parents from control families as well as in unaffected parents from SLI families (*Table 3.3*). Similar differences in cluster size favouring the right hemisphere were seen in language-impaired children and adults. While peak values were slightly higher in the right compared with the left hemisphere cluster in typically developing children, unaffected parent as well as SLI parents, control parents and children with SLI showed the opposite pattern. Auditory cortex activation that was related to greater spectral processing did not significantly differ among the three groups of children or the three groups of parents.

Table 3.3. *Peak coordinates and extent of significant clusters of activity in auditory cortex*

		Left auditory cortex					**Right auditory cortex**				
		X	*Y*	*Z*	*Max Z*	*Cluster size*	*X*	*Y*	*Z*	*Max Z*	*Cluster size*
temporal > standard	**Children**										
	SLI	-50	-16	4	4.59	1116	50	-14	2	4.21	873
	SIB	-56	-16	6	4.50	1176	52	-12	2	4.45	1041
	CON	-54	-14	8	5.67	3429	48	-14	2	5.89	3851
	Parents										
	SLI	-46	-18	4	4.76	1070	44	-20	10	4.98	2057
	PAR	-60	-10	2	4.32	3315	58	-18	10	5.1	2711
	CON	-58	-22	12	6.05	3511	58	-16	6	6.02	4069
spectral > standard	**Children**										
	SLI	-54	-20	8	3.52	394	60	-10	-4	3.34	443
	SIB	-	-	-	-	-	-	-	-	-	-
	CON	-56	-20	6	4.36	1380	62	-12	6	4.83	1579
	Parents										
	SLI	-52	-16	2	3.48	241	64	-10	8	3.86	995
	PAR	-66	-10	2	3.38	542	60	-16	8	3.72	1079
	CON	-58	-18	8	4.95	2605	54	-8	8	4.47	3025
temporal > spectral	**Children**										
	SLI	-32	-32	20	3.32	311	48	-16	10	4.08	452
	SIB	-50	-18	12	4.12	682	46	-24	6	3.68	1229
	CON	-56	-20	12	5.43	6243	48	-16	10	5.81	2365
	Parents										
	SLI	-52	-10	4	4.16	747	42	-22	12	3.82	591
	PAR	-58	-12	-2	4.18	1470	38	-20	8	4.10	1285
	CON	-62	-22	12	4.11	1261	44	-20	10	4.51	1396

Note: Clusters for the contrasts *temporal* > *standard*, *spectral* > *standard* and *temporal* > *spectral* were formed by thresholding at Z > 2.3, p < .05 (corrected). There were no significant differences in auditory cortex for the *spectral* > *temporal* contrast for any of the groups.

Overall, the inspection of cluster size and peak values of activity associated with increased temporal or spectral processing did not reveal a consistent pattern of functional lateralization - neither for control families, nor for families with a history of SLI.

3.3.3 Lateralization of increased temporal and spectral processing

Auditory cortex activation was further examined and statistically compared using a region of interest (ROI) approach. Based on Jülich histological atlas, I created masks comprising left and right primary auditory cortex (HG) to extracted mean %BOLD signal change within each hemisphere. A mixed ANOVA was carried out for children and adults separately on signal change in HG with a within-subject factor of hemisphere (left vs. right) and a between-subject factor of group (individuals with SLI vs. unaffected members of SLI families vs. control participants).

For the *temporal > standard* condition, analysis revealed that hemisphere did not significantly interact with group affiliation in children ($p = 0.17$) or parents ($p = 0.67$). In addition, neither the main effect of hemisphere (children: $p = 0.36$; parents: $p = 0.33$) nor the main effect of group (children: $p = 0.34$; parents: $p = 0.41$) reached statistical significance indicating that mean %BOLD signal change, which was associated with greater temporal processing, did not differ between left and right HG or among individuals with SLI, unaffected family members and control participants. In addition, laterality indices (LI) were calculated from the extracted values of this contrast. As shown in *Figure 3.4*, median LIs did not exceed the critical range of ±0.2 suggesting that activity in HG is not clearly lateralized during increased temporal processing in children (*Mdn* ± *IQR*: SLI -0.027 ± 0.30 SIB 0.009 ± 0.21 CON 0.104 ± 0.21) or parents (*Mdn* ± *IQR*: SLI -0.094 ± 0.16 PAR -0.025 ± 0.28 CON -0.019 ± 0.10). Kruskal-Wallis tests were conducted to evaluate differences in LI medians between children with SLI, their unaffected siblings and control children as well as among language-impaired parents, unaffected parents from SLI families and control parents. LIs did not differ among groups for either the children or the parents.

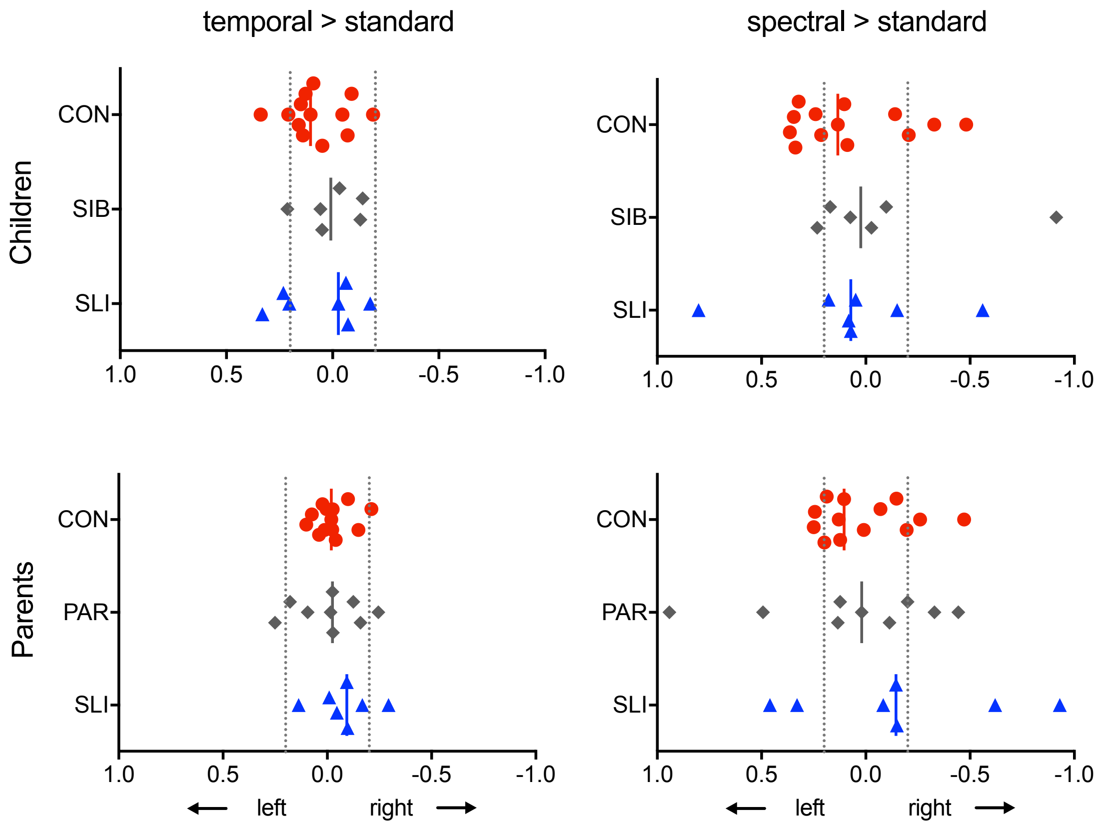


Figure 3.4 *Laterality indices for functional activation in primary auditory cortex (HG). Individual data are plotted for control (CON, red circles), unaffected (SIB or PAR, grey squares) and SLI (blue triangles) children (upper row) and adults (bottom row) for the contrasts: temporal > standard (left) and spectral > standard (right). The LI median of each group is marked with a line. Positive laterality indices indicate left and negative values right lateralization. Values falling within the range of ±0.2 as indicated by the dotted lines, were considered bilateral.*

For the *spectral > standard* condition, the mixed ANOVA did not show a significant interaction between hemisphere and group (children: $p = 0.79$; parents: $p = 0.42$) or significant differences in mean %BOLD signal change between the two hemispheres (children: $p = 0.95$; parents: $p = 0.35$) or among the three groups (children: $p = 0.63$; parents: $p = 0.20$) of children and adults. As indicated by median LIs plotted in *Figure 3.4*, there was no clear lateralization of HG activity in individuals with SLI (*Mdn* ± *IQR*: children 0.072 ± 0.32, parents -0.15 ± 0.94), unaffected family members (*Mdn* ± *IQR*: children 0.024 ± 0.48, parents: 0.019 ± 0.57) and control participants (*Mdn* ± *IQR*: children 0.13 ± 0.49, parents: 0.10 ± 0.36), too. Statistical analyses, using Kruskal-Wallis test, confirmed that median LIs of children and parents did not significantly vary.

Previous studies have shown that increased spectral variation is rather right-lateralized in the lateral part of HG whereas temporal variation is more left-lateralized in the medial part of HG (Jamison et al., 2006). Therefore, I split my mask into a medial and lateral section to see if this might reveal the expected lateralization. A three-way mixed ANOVA was run to examine differences in mean %BOLD signal change in HG with hemisphere (left vs. right) and area (medial vs. lateral) as within-subject factors and group (SLI vs. unaffected family members vs. controls) as a between-subject factor.

For the *temporal* > *standard* contrast, the analyses of children's and parent's data revealed no significant three- or two-way interactions between hemisphere, area and group on signal change suggesting that activity in medial and lateral parts of HG in the left and right hemisphere was similar for individuals with SLI, unaffected family members and control participants. While in children with SLI this activity was right lateralized in the lateral part of HG, median LIs from all other groups did not indicate a clear lateralization of HG activation in medial or lateral areas (*Figure 3.5*). Kruskal-Wallis tests were conducted to evaluate differences in LI medians for the lateral and medial HG portion between the three groups of children and parents. Consistent with my previous findings, neither children with SLI, their unaffected siblings and control children, nor language-impaired parents, their unaffected partners and control parents differed significantly in LIs based on activity in medial or lateral HG areas.

The mixed ANOVA revealed similar results for the *spectral* > *standard* contrast: hemisphere, area and group did not significantly interact with each other and there were no differences in mean %BOLD signal change between the three groups of children or parents. In addition, median LIs for all six groups fell within the critical range of ±0.2 indicating no clear lateralization for this activity in the medial or lateral portion of HG (*Figure 3.5*). Kruskal-Wallis tests confirmed that there were no significant differences in LI medians between individuals with SLI, unaffected family members and control participants in the group of children or parents based on activity along the medial or lateral part of HG.

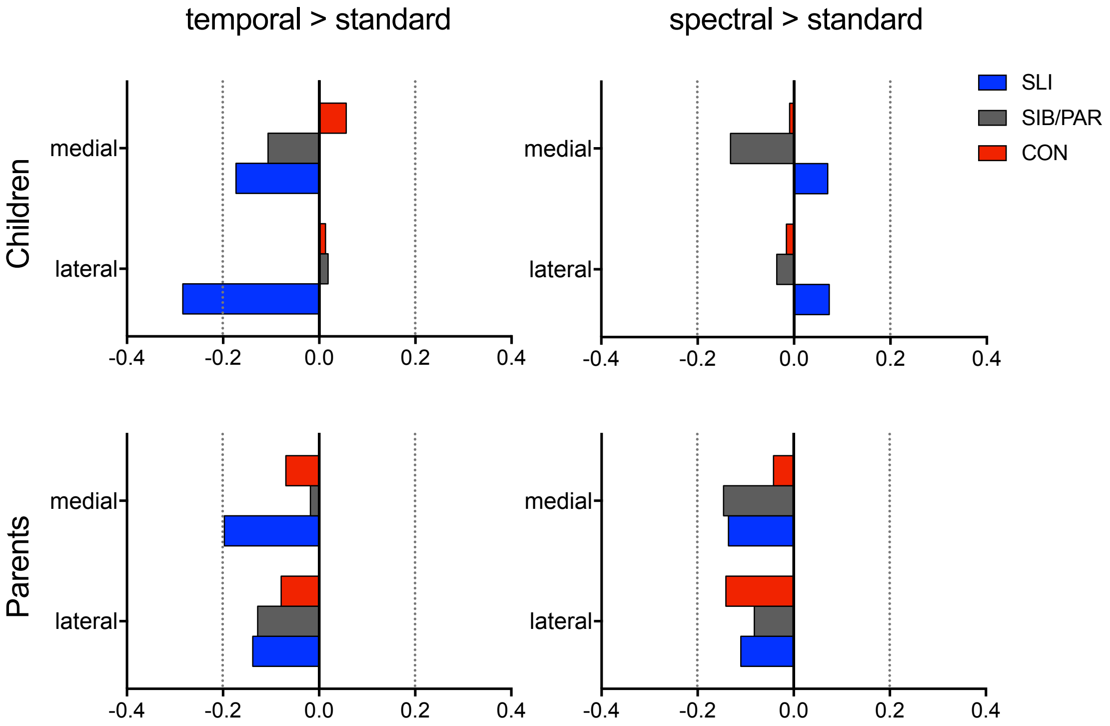


Figure 3.5. *Laterality indices based on functional activation observed in lateral and medial parts of Heschl's gyrus. Median laterality indices (LI) are plotted for control (CON, red), unaffected (SIB/PAR, grey) and SLI (blue) children (upper row) and adults (bottom row) for the contrasts: temporal > standard (left) and spectral > standard (right). Positive LIs indicate left and negative values right lateralization. Values falling within the range of ±0.2 as indicated by the dotted lines, were considered bilateral.*

Taken together, my statistical analyses of HG activity associated with increased temporal and spectral processing did not reveal the expected pattern of functional lateralization in children and adults from control families or SLI families.

3.4 Discussion

In this study, I examined functional lateralization associated with auditory processing of non-speech stimuli in children and parents of SLI and control families. The presentation of standard, temporal and spectral pure tone patterns revealed extensive clusters of bilateral activation encompassing HG, STG and PT in children with SLI, their unaffected siblings and control children as well as parents with SLI, their unaffected partners and control parents. This network of activation is consistent with the auditory processing demands of my experimental task. Between-group comparisons indicated a reduced response to auditory stimulation in children with SLI relative to typically developing controls and unaffected siblings, while language-impaired parent showed an increased response compared with parents from control families. When listening to sound sequences with greater temporal or spectral variation, all six groups showed bilateral activation in auditory cortex centred on HG. However, I failed to replicate the expected pattern of functional specialization associated with temporal versus spectral stimulation, which has been reported in groups of neurotypical adults (Jamison et al., 2006; Zatorre & Belin, 2001). Children and parents from my control families did not demonstrate left-lateralized activation to increased temporal variation, or right-lateralized activation to increased spectral variation in auditory cortex. The activation in parents and children with a history of SLI did not show the predicted pattern of lateralization either, but it is not clear if this is due to a deficit in the group or a problem with my experimental task.

3.4.1 Between- group differences in auditory activation patterns

Compared with typically developing children, children with SLI showed hypoactivation in the right MTG when listening to different variations of pure tone trains. The reduced activity that centred on the junction of the posterior MTG and supramarginal gyrus (SMG) in SLI, adjoined to superior temporal areas. In line with this finding, studies of SLI using SPECT at rest have demonstrated hypoactivation in posterior perisylvian areas bilaterally (Lou, Henriksen, & Bruhn, 1984) and in the right parietal region (Ors et al., 2005). Using FMRI while listening to series of isolated vowel sounds, pseudowords, and real words, Hugdahl and colleagues (2004) found reduced activation in the MTG region bordering the superior temporal sulcus in a family with SLI. The authors concluded that language-impaired individuals showed deficits in brain regions that are critical for speech processing and phonological awareness (Hugdahl et al., 2004). More importantly, Badcock and colleagues (2012) have previously reported that the same children with SLI, who participated in the present study, showed reduced activation in the STG bilaterally during an auditory responsive naming task using FMRI. These findings of temporo-parietal hypoactivation in SLI are consistent with neuroimaging studies indicating structural abnormalities such as reduced volume of the perisylvian temporo-parietal region (Jernigan et al., 1991) or smaller PT (Preis et al., 1998) and an atypical asymmetry of posterior perisylvian areas (Gauger, Lombardino, & Leonard, 1997; Plante et al., 1991) in language-impaired populations.

In sum, the alterations in the neural response to auditory stimulation seen in SLI compared with typically developing peers suggest deficits in brain areas that are critical for auditory processing. This finding is in line with the discussed neuroimaging studies reporting both structural and functional anomalies in the same or neighbouring brain regions. Language disorders, however, are heterogeneous and previous studies vary in their imaging technique and activation task used. Thus, further investigations are needed to clarify whether these functional abnormalities reflect common deficits and neural markers or more method-specific effects.

3.4.2 Functional asymmetry in auditory cortex

My data did not show the expected pattern of functional lateralization associated with the auditory processing of pure tone trains that varied either temporally or spectrally. Given the impressive number of independent studies, which have shown that low-level features of auditory stimulation drive hemispheric specialization (Boemio et al., 2005; Jamison et al., 2006; Schönwiesner, Rübsamen, & von Cramon, 2005; Zatorre & Belin, 2001), the null results in children and parents from control families are somewhat surprising. For example, using PET Zatorre and Belin (2001) were demonstrated that primary auditory cortex responded bilaterally to temporal variation, whereas the left and right anterior STG responded to spectral variation. Moreover, the magnitude of auditory cortex responses was greater in the left compared with the right hemisphere during increased temporal, and vice versa during increased spectral stimulation (Zatorre & Belin, 2001). These findings were replicated and extended by Jamison et al. (2006), who used FMRI combined with similar stimuli, and found the same pattern of functional lateralization even at an individual subject level. Further evidence came from another FMRI study, which employed noise-like sounds that allowed an independent parametric variation of spectral and temporal complexity (Schönwiesner, Rübsamen, & von Cramon, 2005). While neural responses within the left and right Heschl's gyrus covaried with the spectral parameter, an area on the left STG covaried with the temporal one (Schönwiesner, Rübsamen, & von Cramon, 2005). The left hemisphere involvement during rapid temporal relative to spectral discrimination - independent of whether the acoustic stimuli were speech or not - was again confirmed by Joanisse and Gati (2003). More recently, it has been suggested that functional lateralization in auditory cortex results from distinct feature extraction based on differences in sampling time (Boemio et al., 2005; Poeppel, 2003). Boemio and colleagues (2005) varied parametrically the temporal properties of non-speech stimuli and found that both left and right auditory cortex is very sensitive to this parameter. In the higher-order superior temporal sulcus, however, a clear asymmetry was observed where more slowly modulated signals preferentially drive the right hemisphere (Boemio et al., 2005). Although there are substantial discrepancies between these studies in terms of the precise areas within auditory cortex that show hemispheric differences, the consistency of the overall pattern - despite the different paradigms and stimuli used - is striking. Of particular interest is the repeatedly observed evidence that acoustic stimuli without any linguistic information can elicit functional lateralization that is not only predictable based on acoustical features, but also occurs in auditory cortex areas that coincide with those involved in speech processing (Zatorre & Gandour, 2008).

Consistent with these findings, all six groups in my study reliably activated left and right HG including surrounding areas of STG during increased temporal and spectral stimulation - with the exception of unaffected siblings, who did not show significant extent of activation in auditory cortex in response to greater spectral variation; which may be explained by the small number of participants in this group. Neither typically developing children, nor parents, however, exhibited a robust left lateralization for greater temporal and right lateralization for greater spectral stimulation. Failing to replicate these hemispheric differences in children and parents from control families makes it difficult to interpret the functional pattern seen in language-impaired individuals. It is not clear whether the lack of lateralization in SLI is indicative of a genuine deficit in this group or caused by a problem with my experimental task/design.

One could think of different reasons why this study did not yield the predicted differences for temporal versus spectral processing. The most plausible one relates to the small number of participants in each group. Brain imaging studies in neurotypical adults have indicated a great inter-subject variability in brain function across several domains including auditory perception and language (e.g. Seghier et al., 2004; Voyvodic, 2012; Xiong et al., 2000), which in turn affects measures of functional laterality. Hence, the absence of hemispheric specialization in this study could be the consequence of lack of power. In FMRI, activity of interest is commonly expressed as a group effect. Mean activation patterns, however, are not necessarily representative of all individuals belonging to that group. While only a few subjects could drive significant group effects, non-significant ones may reflect heterogeneity in the sample with some participants responding differently to others (Seghier & Price, 2016). Both inter-individual differences in anatomical structure (Brett, Johnsrude, & Owen, 2002; Rademacher et al., 2001) and in cognitive strategies (Grafton, Woods, & Tyszka, 1994; Kirchhoff & Buckner, 2006) have been suggested to account for the variability in spatial location and magnitude of functional activation. The assessment of inter-individual variability is of particular importance when using FMRI in clinical context: only when we have determined what can be considered as 'normal' in neurotypical subjects, we will be able to identify and characterize meaningful anomalies in brain function of patients (Seghier & Price, 2016). To better understand the relationship between cortical activity and cognition systematic investigations of these individual differences are needed. Thus, standard FMRI group analyses should be complemented with measures that indicate the variability/consistency of functional activation across participants such as overlap or probabilistic maps (Rademacher et al., 2001; Seghier & Price, 2016; Seghier et al., 2008).

Because measures of hemispheric specialization vary in relation to many methodological factors including the employed activation task or the formula used to calculate LIs, the variability of functional activation and its lateralization is further magnified. Moreover, LI values depend on subjective decisions about the quantities measured (i.e. extent of activation or magnitude of signal), applied statistical thresholds or the selected ROI, thus affecting the conclusions about lateralization of brain functions. This can be particularly problematic in subjects with different functional lateralization in distinct cortical areas. For example, Jansen and colleagues (2006) described a neurotypical subject who showed left-lateralized activity in frontal, but right-lateralized activity in temporal language areas during a verbal fluency task. Similar cases of crossed language laterality have been noted in epileptic patients (Baciu et al., 2003; Ries et al., 2004). Research to date has not been able to clarify whether different LIs within an individual represent a genuine plasticity in functional lateralization or poor reliability of measurement; as a consequence it remains to be elucidated whether functional laterality is an unidimensional or multifactorial trait (Bishop, 2013). In order to obtain a better picture of functional lateralization associated with a given task, it might be beneficial to use both regional and global (whole hemisphere) ROIs for LI assessment in individual participants. In addition, Wilke et al. (2007; 2006) have suggested that a bootstrapped method using multiple thresholds is less affected by inter-individual differences in activation strength.

Another important consideration relates to the debate over the nature of hemispheric specialization. Brain imaging studies that did not find hemispheric differences in auditory processing of low-level non-speech sounds (e.g. Giraud et al., 2000; Hall et al., 2002) have raised the question as to whether or not acoustic stimuli that have no linguistic relevance can evoke functional lateralization. Giraud and colleagues (2000), for example, studied FMRI responses to amplitude modulated (AM) noise and reported no left hemisphere advantage for faster AM rates. Bilateral activation that showed symmetrical plots of activation was also seen in both HG and STS during the presentation of increased frequency-modulated tones compared with static tones (Hall et al., 2002). Moreover, the opposite pattern of lateralization usually associated with greater temporal resolution has been demonstrated in a study by Harm and Melcher (2002): with faster stimulus presentation rates, the authors observed greater changes in response magnitude in the HG and STG of the right as opposed to the left hemisphere. Because of these inconsistencies, it has been argued that the acoustic basis for hemispheric specialization within auditory cortex must be more complex than a simple temporal/spectral trade-off (Scott & Wise, 2004). The acoustic features that reliably reveal left hemisphere lateralization in the absence of linguistic information remain unclear.

3.4.3 Limitations and future directions

As with my previous study, the major limitation of this research relates to the sample size - especially the individual groups of SLI, unaffected family members and control children or parents are very small. Nonetheless, these group sizes are comparable with the ones from other studies of brain structure and function in language-impaired populations (e.g. (De Fossé et al., 2004; Ellis Weismer et al., 2005; Hugdahl et al., 2004). More importantly, this study benefited from the inclusion of typically developing siblings as an additional control group, thus enabling me to control for family background. Another well-known difficulty with SLI is its clinical heterogeneity: the phenotypical profile is not only characterized by deficits in morphosyntax and phonology, but also impairments of articulatory, auditory receptive or pragmatic aspects of language. This heterogeneity may be an important source of variance in neuroimaging findings, and therefore children with SLI in this study were primarily selected based on expressive language deficits. As a consequence, it could be that changes in activation patterns are more likely to occur in areas involved in speech production (i.e. Broca’s area) and not in speech perception (i.e. auditory cortex) and further research is needed to examine whether distinct subtypes of SLI are associated with different abnormalities of brain function. Investigations that elucidate both receptive and expressive components independently will be of particular interest. In addition, the choice of a passive listening design revealed some drawbacks. First, it was not possible to directly assess a participant's attention during the scan. Requiring responses would allow online performance monitoring, but it also increases the risk of movement, which is an important consideration when scanning children with developmental disorders (O'Shaughnessy et al., 2008). Secondly, because the task was done at the end of the scanning protocol, children and parents may have found it difficult to attend to the auditory stimulation. Active listening, however, can increase both the magnitude and extent of haemodynamic response within auditory cortex (Grady et al., 1997; Hall et al., 2000; Woodruff et al., 1996). Differences in attention could therefore potentially mask differences in auditory activation (Hall et al., 2000). Hence, it may be important to minimize and control for any influence of task demands in future investigations of laterality. Further research is needed employing larger samples of healthy controls to clarify the concept of cerebral specialization. Combining different imaging techniques in larger-scale experiments that use distinct tasks on repeated occasions will help to determine how to best measure functional lateralization. Only then, research will be able to reconcile inconsistent brain imaging findings and to elucidate the question whether language laterality is related to language abilities.

3.5 Conclusion

In conclusion, the results from functional imaging indicate that language-impaired children have reduced responses to auditory stimulation relative to typically developing peers and unaffected siblings. The laterality assessment of auditory cortex activation, however, did not reveal the expected pattern of hemispheric specialization associated with the processing of temporally or spectrally increased non-speech sounds. Because I failed to replicate findings of left-lateralized activation during greater temporal and right-lateralized activation during greater spectral stimulation in children and parents from control families, the non-lateralized pattern observed in individuals with SLI is difficult to interpret. It appears that we need a better understanding of group activation patterns and their consistency across as well as within neurotypical subjects in order to be able to draw meaningful conclusions from functional anomalies seen in language-impaired children and adults.

4

Using functional transcranial Doppler ultrasonography to assess lateralization based on different language tasks

Abstract

The assessment of hemispheric specialization for language is of theoretical and clinical relevance. Evaluating functional lateralization based on one single task, however, can only lead to a limited understanding of language processing. In this study, I used functional transcranial Doppler ultrasonography to measure blood flow velocities in the left and right middle cerebral artery to obtain information on hemispheric specialization for language in neurotypical participants. A large number adults aged 18 to 46 completed an active, expressive language task (word generation) and a more passive, receptive language task (semantic matching). Test-retest reliability was evaluated in a subsample of randomly selected participants. Both paradigms elicited left hemisphere lateralization, which was more pronounced for word generation than semantic matching. Analyses revealed significant differences in lateralization between the two tasks with respect to the number of left-lateralized individuals and overall LI values. Lateralization of cerebral blood velocities was associated with handedness, i.e. atypical lateralization for language production and semantic matching was observed more frequently in left-handers compared with right-handers. On repeated examination, indices of language lateralization showed good levels of internal consistency and a high test-retest reproducibility for word

generation as well as semantic matching. My results show that FTCD is a reliable tool for the quantitative measurement of functional lateralization. Nonetheless, the use of different tasks that tap into different aspects of language appears to be crucial in providing a more comprehensive view of its cerebral representation and functioning.

4.1 Introduction

Investigating the lateralization of cognitive functions is not only important for theoretical reasons as it provides insight into the development of functional specialization (Whitehouse & Bishop, 2009), but also for clinical ones. In epileptic patients, for instance, the evaluation of language lateralization in the preoperative assessment is particularly important, because this population may have a higher incidence of atypical language representation due to altered brain activity (e.g. Moser et al., 2011;Pahs et al., 2013; Rasmussen & Milner, 1977; Woods, Dodrill, & Ojemann, 1988). Moreover, neuroimaging studies demonstrated that presurgical language mapping in patients with epilepsy can predict postsurgical language deficits (Binder et al., 1996; Sabsevitz et al., 2003). In line with these findings, Knecht and colleagues (Knecht et al., 2002) have shown that in healthy participants both the side and the degree of hemispheric specialization determines the susceptibility to language disruption when inducing transient focal virtual lesions in one hemisphere using transcranial magnetic stimulation (TMS). Another field of laterality research is the study of neurodevelopmental and psychiatric patients. For example, alterations in functional lateralization have been associated with disorders like attention deficit hyperactivity disorder (Hale, Bookheimer, McGough, Phillips, & McCracken, 2007; Hale, Zaidel, McGough, Phillips, & McCracken, 2006), autism (Flagg et al., 2005; Kleinhans et al., 2008), and schizophrenia (Bertolino et al., 2004).

Before the advances of neuroimaging, the intracarotid amobarbital procedure, otherwise known as the Wada test, was the only reliable method to determine functional lateralization. During the procedure an anaesthetic medication (sodium amobarbital) is injected into the left or right carotid artery to temporarily disrupt the function of one hemisphere, thus making the Wada test highly invasive (Wada &

Rasmussen, 1960). Although very effective, this procedure carries the risk of fatal complications, and is therefore only used in patients undergoing brain surgery. Modern attempts to provide a non-invasive alternative for the assessment of functional lateralization have focused on the measurement of the hemodynamic response to language tasks (Binder et al., 1996; Desmond et al., 1995). Despite the fact that perfusion-sensitive techniques like FMRI have started to replace the Wada technique in clinical settings, they are still too expensive and remain uneconomical for most research - especially when testing a large number of people (Pelletier, Sauerwein, Lepore, Saint-Amour, & Lassonde, 2007). Another disadvantage is that the person being scanned needs to stay still and cooperate with the given task, which makes FMRI less suitable for children and special populations (Pelletier et al., 2007).

4.1.1 Reliability and validity of laterality indices from FTCD

Functional transcranial Doppler ultrasonography (FTCD), on the other hand, is an inexpensive and easily applied method that has presented itself as a promising tool in the study of hemispheric specialization. Like FMRI, it works under the premise of neurovascular coupling: regional cerebral blood flow increases during the performance of a cognitive task in order to compensate for the rise in glucose and oxygen consumption that results from enhanced local brain activation (Kuschinsky, 1991). The changes in cerebral perfusion are associated with blood flow velocity modulations in the feeding basal arteries and can be measured by FTCD (Aaslid, Markwalder, & Nornes, 1982). By comparing event-related blood flow changes within the left and right middle cerebral artery (MCA), FTCD can be used to assess functional lateralization (Deppe, Ringelstein, & Knecht, 2004). The MCAs supply approximately three quarters of the cortex covering the majority of the lateral surface including Broca's and Wernicke's area (van der Zwan, Hillen, Tulleken, & Dujovny, 1993).

In recent years, the interest in FTCD as a research tool has grown because of advances in its software and analysis. Deppe and colleagues (1997), for instance, came up with new analytic methods that accounted for spontaneous oscillation in cerebral blood flow velocities (CBFV) related to heart beat and breathing as well as differences in left and right CBFV due to measurement artefacts. These developments considerably improved the sensitivity of FTCD, thus making it a reliable method for evaluating cerebral lateralization of language (Deppe, Ringelstein, & Knecht, 2004).

A common paradigm used with FTCD is the word generation task (WG), in which participants are asked to silently generate words that begin with a given letter. This task allows the investigation of language production while minimizing movement artefacts associated with articulation. After the interval of silent word generation, the participant may also be asked to report the generated words to establish task performance and cooperation. Previous studies of small samples found high reproducibility of laterality indices based on the WG task (Knecht et al., 1998b) and good concordance with results from the Wada technique (Knake et al., 2003; Knecht et al., 1998a) and FMRI (Deppe et al., 2000; Somers et al., 2011). To date, various FTCD studies have reported robust left hemisphere lateralization in right-handers using this paradigm (Knecht et al., 1996, 2001; Knecht, Deppe, et al., 2000; Lust, Geuze, Groothuis, & Bouma, 2011; Rosch, Bishop, & Badcock, 2012) and the consistency of findings has led to it becoming the gold standard method for evaluating language laterality with FTCD. Knecht and colleagues (2000), for example, found that 92.5% of 188 right-handed participants showed a left hemisphere bias for the WG task, which is consistent with other reports of language lateralization in terms of the proportions of people measured as left lateralized (Rasmussen & Milner, 1977; Satz, 1979; Szaflarski et al., 2012).

4.1.2 Variation in functional lateralization during different language tasks

Using FMRI, expressive language tasks such as WG have been shown to reliably reveal left-lateralized activation that is most marked within the frontal language areas (Pelletier et al., 2007). Other important components of language that involve more temporal regions, however, might not necessarily agree with respect to lateralization. In fact, evidence from neuroimaging suggests that expressive versus receptive language tasks show different magnitudes of lateralization as measured by FTCD (Badcock, Nye, & Bishop, 2012; Buchinger et al., 2000; Stroobant, Buijs, & Vingerhoets, 2009) and FMRI (Gage et al., 2011; Gaillard et al., 2004). Stroobant and colleagues (2009), for example, investigated four different language paradigms combined with FTCD and found a left hemisphere bias in 90%, 80%, 73.3% and 66.7% of the participants for word generation, sentence construction, reading, and semantic decision respectively. In addition, mean laterality indices differed significantly between the tasks indicating that the productive as well as syntactic tasks lateralized stronger than receptive language tasks (Stroobant et al., 2009). Compared with expressive language, other studies using FTCD have also demonstrated reduced functional lateralization for sentence comprehension and passive listening (Badcock, Nye, et al., 2012; Buchinger et al., 2000). The processing involved in language production, however, overlaps with that involved in language comprehension (Papathanassiou et al., 2000). Binder and colleagues (1996) therefore suggested that the semantic component of language tasks drives the left hemisphere bias for language. They developed a single word semantic decision task, which evoked robust left-lateralized activation in each individual participant using FMRI (Binder et al., 1995). This task was later validated by direct comparison with the Wada technique (Binder et al., 1996). Another semantic task, in which one picture is presented over two others and the participant is asked to indicate which of the bottom pictures best matches the top one, has also been shown to reliably reveal left lateralized activation in both inferior frontal and superior temporal language cortices (*Figure 4.1*; Mummery, Patterson, Hodges, & Price, 1998; Seghier & Price, 2009; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007). As a measure of semantic access, this task is commonly used in clinical practice and known as ‘pyramids and palm trees’ (PPT, Howard & Patterson, 1992). The strongly lateralizing effect of semantic processing has since been replicated by many studies (e.g. Bulla-Hellwig et al., 1996; Cousin et al., 2007; Poldrack et al., 1999; Vingerhoets & Stroobant, 1999).

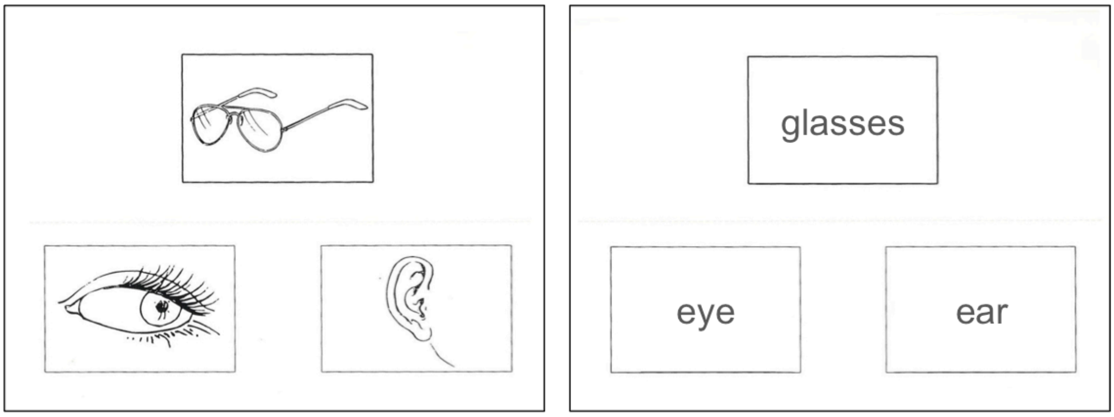


Figure 4.1*. Example stimuli of the ‘pyramids and palm trees’ (PPT) task. A triad of pictures (left) or words (right) is visually presented and the participant is asked to indicate which of the bottom pictures/words best matches the top one (semantic match).*

Taken together, research has demonstrated that functional language lateralization varies dependent on the paradigm used, which suggests that language production is more strongly lateralized than comprehension (Badcock, Nye, & Bishop, 2012; Bishop, Watt, & Papadatou-Pastou, 2009; Buchinger et al., 2000; Stroobant, Buijs, &

Vingerhoets, 2009). Yet, not all expressive tasks revealed robust lateralization at the group level (Haag et al., 2010) and the strength of individual language lateralization varied between expressive language paradigms, too (Bishop, Watt, & Papadatou-Pastou, 2009). How far this variability relates to non-linguistic factors such as task demands or individual strategies remains unclear.

4.1.3 Relationship between laterality on FTCD and handedness

One factor that has long been associated with language laterality is handedness. Since Broca's first descriptions of left hemisphere language specialization in right-handed patients, it has been speculated that the reverse pattern of language lateralization might be true for left-handers. Clinical studies challenged this claim suggesting that this principle could not be universally true because even in left-handed patients, aphasia commonly occurred after a left hemisphere lesion (Luria, 1976). Since then, research has shown that the relationship between language laterality and handedness is much more complex. Using FTCD, Knecht and colleagues (2000b) assessed functional lateralization for language production in a large sample of neurotypical adults and found that language laterality was dependent on both the direction and degree of handedness. More specifically, the more left-handed the participants were, the higher was the relative incidence of right hemisphere language, which increased linearly from 4% in strong right-handers to 15% in ambidextrous individuals and 27% in strong left-handers (Knecht et al., 2000b). In addition, functional MRI studies have demonstrated that over 90% of right-handers have left hemisphere lateralization for language (Pujol et al., 1999; Szaflarski et al., 2012) and similar proportions were reported by FTCD studies (Knecht et al., 2000a, 2000b). Although significant, the association between language laterality and handedness is not perfect. Firstly, the majority of left-handers (73-85%)

still have language abilities lateralized to the left hemisphere (Knecht et al., 2000b; Pujol et al., 1999; Szaflarski et al., 2012); and secondly, about 4-7.5% of right-handers show an atypical right hemisphere bias for language (Knecht et al., 2000a; Pujol et al., 1999). For these reasons, an FTCD study by Groen and colleagues (2013) examined the validity of different handedness assessments as a proxy measure of language lateralization. While significant correlations between language laterality and manual preference were observed for performance on a reaching task and indices based on a handedness inventory, these measures only accounted for 8-16% of the variance in functional lateralization (Groen et al., 2013). The results demonstrated that handedness is not a reliable indicator of language laterality and suggest that lateralization of language and motor functions show considerable independence from one another (Groen et al., 2013).

The question of how to assess handedness and whether existing methods are reliable and valid may contribute to the inconsistent pattern of findings. A simple and commonly used method is to classify people as left- or right-handed based on the hand used to hold the pen when writing (McManus, 1984). When asking the following question some major drawbacks of this definition become apparent: in which category fall individuals who are left-handed by nature but were taught to use their right hand or those who write left-handed but prefer to use their right hand for chopping vegetables, navigating a computer mouse and many other tasks? As illustrated this basic dichotomy does not account for the explicit discouragement of left-handedness in some cultures and may be too insensitive for people who use different hands for different activities (Bishop, 1990). Moreover, in young children or illiterate adults writing hand cannot be assessed. Consequently, handedness inventories were developed to evaluate manual preference for a wide range of activities (Annett, 1970; Bryden, 1977; Oldfield, 1971). The Edinburgh Handedness Inventory (Oldfield, 1971) and its abbreviated version, for instance, have been widely used in different studies. Although these questionnaires were designed to move away from classifying individuals as left- or right-handed, in practice, they are often used to divide participants into hand preference groups (Bishop, 1990). Another problem with handedness inventories relates to the arbitrary selection of activities, which are still affected by experience and social pressure (Bishop, 1990). Finally, some researchers used a behavioural continuum in order to quantify an individual's manual preference (Bryden, Singh, Steenhuis, & Clarkson, 1994; Calvert & Bishop, 1998). These assessments are based on the assumption that a person with a strong preference for one hand will keep using that hand to perform a uni-manual activity even when it gets uncomfortable to do so (Bryden, Singh, et al., 1994). For example, participants were asked to reach across widely separated locations to either move pegs (Bryden, Singh, et al., 1994) or pick up cards (Calvert & Bishop, 1998). The latter has been shown to positively correlate with language lateralization (Groen et al., 2013).

4.1.4 Aims of this study

In this study, I used FTCD to assess hemispheric lateralization of perfusion during two distinct language tasks in a large number of participants without developmental or other known medical disturbances. Word generation was chosen as an activation paradigm because it is one of the most effective and widely used measures to determine language laterality. In addition, I tested the sensitivity of FTCD for a new language paradigm - a semantic matching task that was adapted from the picture version of the 'pyramids and palm trees' test (PPT). The two tasks were chosen to include a range of language functions thought to involve both frontal (expressive) and temporal (receptive) areas. I also obtained standardized measures of manual preference to investigate the variability of language lateralization with respect to handedness. Altogether, I aimed i) to investigate the reliability of FTCD activation elicited by the semantic matching task and to replicate previous findings for word generation; ii) to compare cerebral lateralization for language based on an expressive (WG) versus more receptive task (PPT): I expected an overall left-hemispheric lateralization for both paradigms, but a more strongly lateralized pattern for the WG compared with the PPT task; iii) to explore the relationship between handedness and functional lateralisation in the two paradigms.

4.2 Methods

4.2.1 Participants

I recruited 231 participants via the 'Oxford Psychology Research' participant scheme to take part in this study. I could not find a suitable temporal window to record a Doppler signal in twelve participants (5.19%). Four more participants were excluded from further analyses due to the following reasons: after testing one participant reported to be deaf on the right ear, one was not a native speaker of English, one had been previously assessed using FTCD for medical reasons and showed a very weak overall signal, and lastly one had difficulties in attending to the tasks. The final 215 participants were native speakers of English with normal or corrected to normal vision and no reported history of neurodevelopmental, neurological or psychiatric disorders; 138 were women and 77 were men aged 18 to 46 years (*M* = 23 years, *SD* = 4.31 years). Based on participants' self-report the sample included 189 right-handers (66 men) and 26 left-handers. Two participants considered themselves a being left-handed but were taught to use the right hand for writing. All participants gave written informed consent and were compensated for their participation according to the time they spent on the study. The study was approved by the Central University Research Ethics Committee of the University of Oxford (*MSD-IDREC-C1-2014-003)*.

4.2.2 Handedness assessment

In addition to the self-report of handedness, two more measures of hand preference were obtained including a questionnaire (Edinburgh Handedness Inventory; Oldfield, 1971) and performance on a reaching task (Quantification of Hand Preference Task; Bishop et al., 1996).

Edinburgh Handedness Inventory (EHI). An abbreviated form of the Edinburgh Inventory (Oldfield, 1971) was used to assess the hand/foot used during the following 11 activities: (1) writing, (2) drawing, (3) throwing, (4) using scissors, (5) using a toothbrush, (6) using a knife [without fork], (7) using a spoon, (8) holding a broom [upper hand], (9) striking a match [hand holding the match], (10) opening a box [hand used to hold the lid] and, (11) kicking a ball. Using a rating scale ranging from one to five, participants were asked to indicate whether they always used the left hand (1), usually used the left hand (2), used both hands equally (3), usually used the right hand (4) or always used the right hand (5). For each participant, values across the first 10 items, which represent activities performed with one's hand, were summed and used as a quantitative measure for handedness. A score of 10 corresponds to extreme left-handedness and 50 to extreme right-handedness.

Quantification of Hand Preference Task (QHP). The QHP reaching task was included to obtain a behavioural measure of handedness preference. A cardboard template was used to mark seven positions along a semi-circle, at successive 30° intervals, each at a distance of 40cm from the mid-point of a baseline (*Figure 4.2*). Stacks of three playing cards were placed at each position and participants stood at the baseline with their arms resting down by their side. Participants were asked to pick up a named card and place it in the box positioned at the midline without time constraints. The card order was random, but the sequence of positions was the same for all participants. The hand that was used to pick up the card was recorded or each trial. The participant was not informed of the experimental interest in hand preference until the assessment was completed.

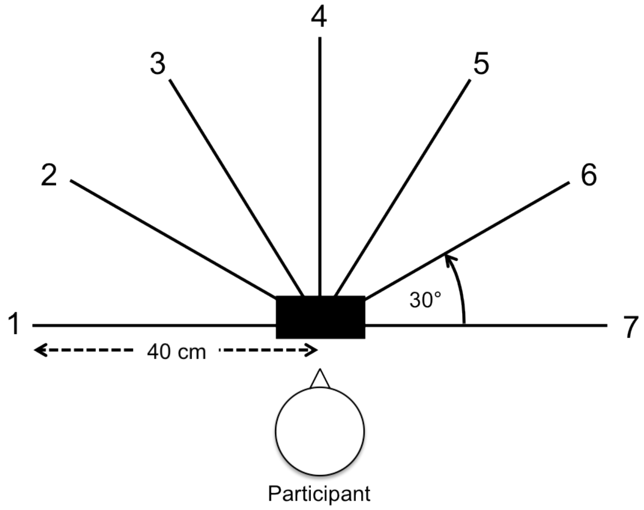


Figure 4.2. *Quantification of Hand Preference Task (QHP). The participant reaches for three cards at each of the numbered locations and places them in the central box. Adapted from "The measurement of hand preference: A validation study comparing three groups of right-handers" by D.V.M. Bishop et al., 1996, British Journal of Psychology, 87, p. 277. Copyright 1996 The British Psychological Society.*

A left-right hand bias was computed by subtracting 0.50 from the proportion of right-hand reaches (number of right hand reaches divided by the total number of reaches). This score ranges from +0.5 for participants who exclusively used their right hand through 0 for participants who did not show a preference to -0.5 for those who exclusively used their left hand.

4.2.3 Experimental procedure and paradigms

Participants were tested in a quiet laboratory and the entire procedure lasted approximately 1 hour and 20 minutes. At the beginning of each session, I obtained demographic information and instructed the participant. The understanding of the two language tasks was ensured by completing some practice test-trials before each experimental block. Across participants, the order of the tasks was kept the same starting with the word generation task followed by the semantic matching one. *Figure 4.3* gives a schematic summary of the two paradigms. Both tasks were programmed and visually presented on a standard monitor using Presentation Software (Neurobehavioural Systems), which sent marker pulses to the Doppler-Box^{TM}X system, too, to denote the onset of each trial.

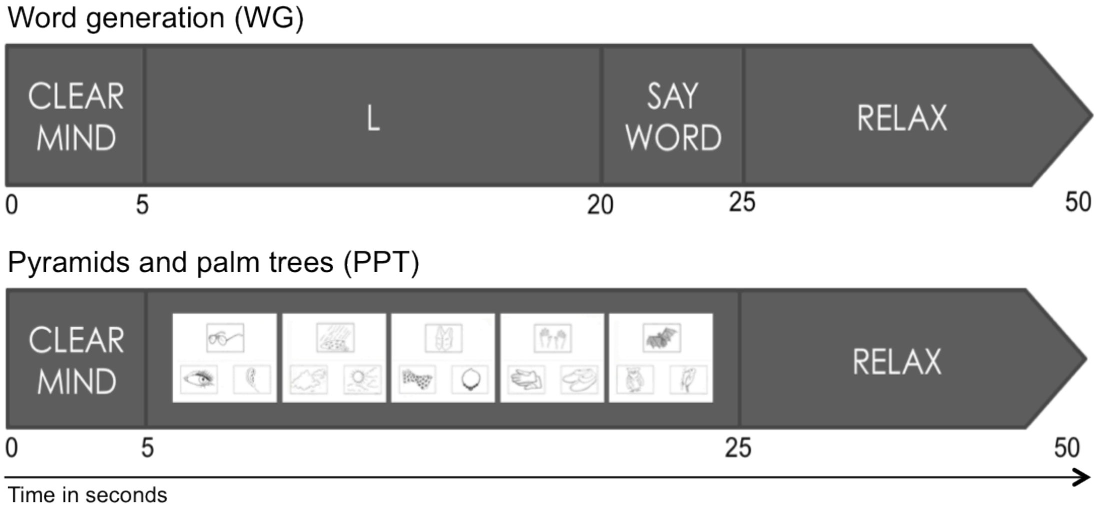


Figure 4.3. *Schematic diagram of timing events during FTCD activation tasks. Both task 'word generation' (WG, top) and 'pyramids and palm trees' (PPT, bottom) were matched in their time line as closely as possible.*

Word generation. The word generation task (WG) was based on the paradigm that was previously described by Knecht et al. (1996, 1998). To ensure that participants attended to the screen at the beginning of each trial, a cue ('Clear Mind') was presented for 5 s. Then a letter appeared for 2.5 s followed by a black screen during which participants were required to silently generate as many words as possible starting with the displayed letter. A second cue ('Say Words'), which was presented 15 s after the initial letter presentation, prompted participants to verbally report the previously generated words for 5 s thus allowing me to control for task performance. Each trial ended with 25 s of relaxation before the next letter was displayed in the same way. All participants completed a total of 23 trials - one for almost each letter of the alphabet; given that only very few words in the English language start with Q, X and Z these letters were not included. The order of letters presented was random and each letter was displayed only once.

Pyramids and palm trees task. A picture version of the pyramids and palm trees test (PPT; Howard & Patterson, 1992) was included to obtain a second laterality measure based on semantic association. During the task, participants were shown a triad of black and white line drawings - one picture above two others - and asked to indicate which of the bottom pictures corresponds best to the top one. To match the PPT paradigm as closely as possible to the timing of the WG task, I replaced the 20 s of word generation (i.e. 15 s silent and 5 s overt) with eight picture presentations - each displayed for 2.5 s. The two cues and relaxation period remained the same. All participants were instructed to indicate their answers by pressing the left and right ‘shift-keys’ with their left and right index fingers as quickly and accurately as possible. The whole task comprised 15 blocks of eight picture presentations including a total of 120 stimuli. To minimise possible effects of functional activation caused by finger movements (Hodgson, Richardson, & Hudson, 2015), I counter-balanced the side of the target pictures so that 50% of the correct answers required a left and the other 50% a right button press.

4.2.4 FTCD recording and data processing

Using a Doppler ultrasonography device (Doppler-Box^{TM} X, DWL Elektronische Systeme, Singen, Germany) changes in cerebral blood flow velocities (CBFV) of the middle cerebral arteries (MCA) arteries were measured as an indicator of brain activity during two language tasks. Participants were comfortably seated roughly 80 cm in front of the testing computer and fitted with a flexible headset. The insonation technique and how to correctly identify MCAs has been described in detail by Ringelstein et al., (1990). Briefly, two 2-MHz transducer probes were mounted on the headset and placed at the temporal skull window bilaterally. Each MCA was insonated at a depth of 50 mm and spectral envelopes of the Doppler signal were recorded with a sampling rate of 100 Hz and saved for subsequent off-line analyses.

Data analysis was carried out with dopOSCCI, a custom MATLAB (Mathworks Inc., Sherborn, MA, USA) program written for the automated assessment of functional lateralization of cognitive functions (Badcock, Holt, Holden, & Bishop, 2012). Similar to the analysis of evoked potentials, event-related CBFV changes were extracted (epochs) from a continuous signal and averaged time-locked to the corresponding stimulus presentation. In both paradigms, the trial-onset trigger was sent by the first cue (‘Clear Mind’) and epochs were defined as the window 15 s before till 25 s after stimulus presentation. Using dopOSCCI, which is based on the basic analysis paradigm developed by Deppe et al. (1997), the following processing steps were performed:

Down-sampling and data trim. FTCD recordings have excellent temporal resolution and provide continuous information about CBFV. Using the Doppler-Box^{TM} X, I was able to record velocities 100 times per second (100 Hz) resulting in one sample every 10 ms. However, since metabolic changes occur in the range of 5-10 s (Rune Aaslid, 1987), recordings were down-sampled from 100 Hz to 25 Hz to reduce computational costs. In addition, epochs were trimmed at the beginning and the end of each task in order to remove spurious activity caused by excessive motion typically occurring during these times.

Data transformation. To control for differences in the left and right signal that were unrelated to the task, such as measurement artefacts caused by different insonation angles (Deppe, Knecht, Lohmann, & Ringelstein, 2004), the spectral envelopes were transformed to relative units. DopOSCCI supplies automatic data normalization using the equation: (100 x data) / mean (data), where data refers to CBFV measured during freely selectable time periods of the left and right recording. Normalizing velocity values to a mean of 100% on a trial-by-trial basis, allowed me to account for possible signal changes due to participants' movement or subtle, but gradual shifts of the probe. These drifts are difficult to monitor online, but can bias LI calculation.

Heart cycle integration. By inducing changes in arterial blood pressure, the cardiac cycle is the major physiological activity that interferes with the examination of task-related changes in CBFV. In order to reduce these involuntary modulations, dopOSCCI employs a heart cycle integration algorithm that replaces the pulsating envelope curve by a step-like function. Because the width of the steps corresponds to the cardiac intervals, and the height represents the mean blood flow velocity within these intervals, the algorithm affected neither the phase of the CBFV changes nor introduced artificial correlation beyond the boundaries of cardiac cycles (Deppe et al., 1997).

Artefact rejection. After normalization, the data within each epoch were screened for unusually high or low levels of activity. Epochs that included velocity values outside the range of 60 to 140 (i.e. ±40% of the averaged blood flow velocity) were automatically detected and excluded from further analyses as measurement artefacts.

Baseline correction and averaging epochs. While the heart cycle integration was employed to remove the highest frequency effects, baseline correction was used to account for influences of slow spontaneous fluctuations or shifts. These can be related to breathing, less understood variations in sympathetic activity and states of arousal (Deppe, Ringelstein, & Knecht, 2004). Here, the baseline interval was defined relative to the trial onset marker (‘Clear Mind’) within each epoch ranging from -10 to 0 s for both language paradigms. For left and right recordings, mean activation of this pre-trigger interval was subtracted from all other activity within the corresponding epoch, so that deviations from zero represented an activity increase or decrease relative to baseline. Finally, the average of all non-rejected epochs was calculated for each participant and plotted across the specified epoch period (CBFV curves).

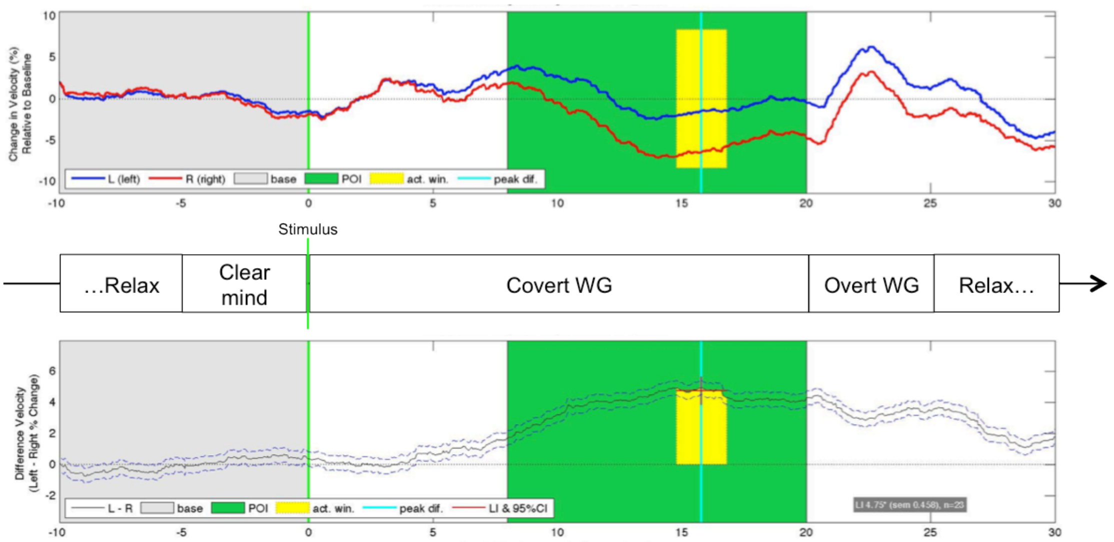


Figure 4.4 *Example of an average graph produced by dopOSCCI. Graphs are shown for word generation data from a single participant, averaged across 23 trials. The upper panel displays the left and right baseline corrected percentage change in blood flow velocity and the lower panel displays the difference between the left and right baseline corrected blood flow velocities. The baseline (grey) runs from -10 to 0 s relative to the visual letter presentation, and the period of interest (POI, green) runs from 8 to 20 s following the visual letter presentation. The time point of the peak difference is displayed in both panels, surrounded by a 2-s activation window (yellow) across which the laterality index (LI) is calculated. In the lower panel, the 95% confidence interval of the LI calculations is also displayed along with the LI value, the LI standard error of the mean, and the number of epochs averaged within the graph.*

LI calculation and categorization of functional laterality. Individual LIs were calculated as the maximum difference of the left and right CBFV curves within a defined period of interest (POI). To make this measure less sensitive to spikes, each LI was computed as the mean velocity difference of a 2-s window centred on the peak difference (*Figure 4.4*). POI values were task-specific and defined in relation to the trial onset trigger. For the WG task, the POI interval ranged from 8 to 20 s after the presentation of the initial cue (‘Clear Mind’). Because articulatory movements can induce additional noise, I did not include the 5 s of overt word generation. As a result, the POI for the PPT task was slightly longer than the one for WG ranging from 8 to 25 s. For each participant, the standard error of the LI across all suitable epochs was used to determine the 95% confidence interval (CI). Participants were categorized as left- or right lateralized if the range of the CIs remained positive or negative respectively. In cases in which the CI crossed zero, individuals were considered as being ‘low lateralized’ - in this study referred to as ‘bilateral’ (as in Badcock, Nye, & Bishop, 2012 or Bishop, Watt, & Papadatou-Pastou, 2009).

Goodness of recording. A data quality variable, which is available in dopOSCCI, was used to assess the ‘goodness of recording’. This statistic was first introduced by Knecht et al. (2001) and provides an estimate of variability by calculating the root mean square of the averaged CBFV fluctuations during rest. As suggested by Knecht and colleagues (2001), recordings with signal variation greater than 2% of the averaged CBFV were excluded from further analysis due to insufficient quality. This applied to nine recordings during WG (4.19%) and four during PPT (2.56%).

4.2.5 Statistical analysis

The following statistical analyses were conducted using SPSS (www.ibm.com/software/analytics/spss):

Internal reliability. Cronbach’s α (Cronbach, 1957) was used to assess the reliability of my FTCD results. I calculated Cronbach’s α based on LIs from all accepted epochs, which were provided by an optional dopOSCCI output (as used in Whitehouse et al., 2009). These estimates were interpreted as a correlation coefficients ranging from 0 to 1, with higher values indicating higher reliability.

Test-retest reliability. I evaluated test-retest reliability in a subsample of my participants, who were randomly selected and agreed to repeat the WG (N = 30) and PPT (N = 19) tasks. The interval between the two examinations, which were identical in protocol, recording procedure, and data analysis, ranged from 7 to 434 days ($M = 168$, $SD = 149$). A coefficient of stability was calculated using both Pearson's product moment correlation (Knecht et al., 1998) and intra-class correlation (Whitehouse et al., 2009) to allow for comparison with previous findings. Coefficients between 0.8 and 0.9 are thought to indicate a good test-retest reliability, and values greater than 0.9 an excellent one. In addition, the difference in mean LIs for the first and second session was examined for each paradigm using paired-samples t-tests. By subtracting the LI of the re-test from the LI of the initial test I calculated a 'stability index' for each participant to assess the level of agreement (as in Whitehouse et al., 2009). For each task, a one-sample t-test was performed to determine whether the mean reliability index differed significantly from zero.

LI comparisons. Given that only a few people show a right hemisphere bias for language, the distribution of LI data was skewed, thus violating the assumption of normality as assessed by Shapiro-Wilk test ($p < .0005$). To account for the skewness of distribution and minimize the effect of outliers, non-parametric tests were used for statistical analyses. First, I calculated the number/percentage of participants with left-lateralized, right-lateralized or bilateral activation for each paradigm. McNemar's test was used to determine whether the number of people showing typical (left) or atypical (non-left) language lateralization differed between the two tasks. Next, median LIs for WG and PPT were computed and compared within participants using related-samples Wilcoxon signed ranks test. I then conducted Spearman's correlation between individual LI values from the WG and PPT task. In order to assess the relationship between language lateralization and handedness, I divided the sample into left- and right-handers based on participant's self-report. Differences in count of LI categories and median LIs between the two groups were examined separately for each task using the Fisher's Exact test and the Mann-Whitney test respectively. Lastly, I used Spearman's correlations to explore associations between individual LIs and handedness measures.

4.3 Results

For some participants, FTCD data of the PPT task were not available due to the following reasons: i) the timing of the PPT paradigm was adjusted shortly after the start of the study to better match the WG task, therefore the first participants did not complete the final version of this paradigm (N = 26); ii) finding a suitable FTCD signal can be time consuming and in some volunteers the insonation of both arteries took longer than anticipated, thus leaving no time to complete both language tasks (N = 9); iii) in some people who wore glasses the signal was severely affected when putting them back on after the probes were fitted - while in most cases the letters presented during the WG task were large enough to complete the task without glasses, the pictures of the PPT were not (N = 8); and iv) due to technical problems some of the PPT data were recorded without sending trial onset markers and could not be used for off-line analyses (N = 16). Taken together, 215 participants completed the WG task and in 156 of these I also obtained data on the PPT task. While all available recordings were used to assess data quality and reliability as well as the relation between LIs and handedness for each task, only data of participants who completed both tasks were used in order to examine differences in LIs between the WG and PPT task (N=156).

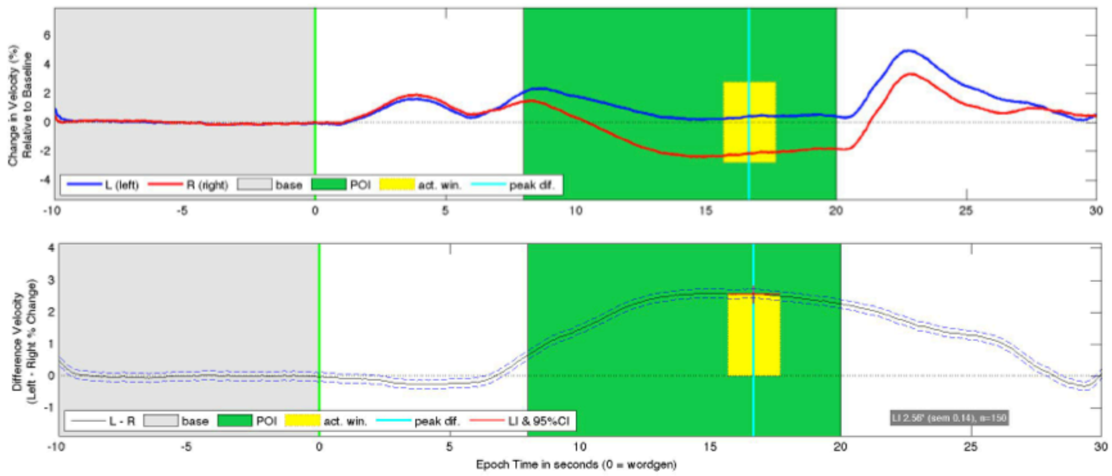
4.3.1 FTCD data quality and reliability

To assess whether overt speech during the WG task led to more measurement artefacts I inspected the number of accepted trials for each participant. For both paradigms, the number of included epochs suggested a low rate of artefact rejection. All participants had at least 20 out of 23 suitable epochs for the WG (87%) and 14 out of 15 for the PPT (93%) task. For participants with data on both paradigms, the proportion of excluded epochs did not significantly differ between the two tasks as assessed by a paired t test between percentages (p = .53). Moreover, Cronbach's α (WG: r = .82; PPT: r = .82) indicated a good level of internal consistency. Next, I examined test-retest reliabilities for the two paradigms based on LI values from the same participants tested on two different days. A paired-samples t test found no difference between the mean LI for the first ($M \pm SD$: WG 2.27 ± 2.19, PPT 1.57 ± 2.95) and second session ($M \pm SD$: WG 2.28 ± 2.01 PPT 1.73 ± 2.81) of the WG (p = .95) or PPT task (p = .59). Analyses revealed that mean stability indices of the WG (M = -0.08, SD = 0.33) or PPT (M = -0.16, SD = 1.20) task were not significantly different from zero (WG: p = .74; PPT: p = .59) suggesting no effect of practice between the first and second testing. Lastly, Pearson's correlation coefficient (WG: r = .80, $p < .0005$; PPT: r = .92, $p < .0005$) as well as ICC (WG: r = .89, $p < .0005$; PPT: r = .92, $p < .0005$) indicated a high degree of test-retest reliability for both paradigms.

4.3.2 LI differences between tasks

A total of 150 participants completed both language paradigms and were therefore included in this analysis. *Figure 4.5* illustrates baseline corrected CBFV for the left and right hemisphere as well as the left minus right difference averaged over all suitable epochs for the two paradigms.

A. Word generation (WG)



B. Pyramids and palm trees (PPT)

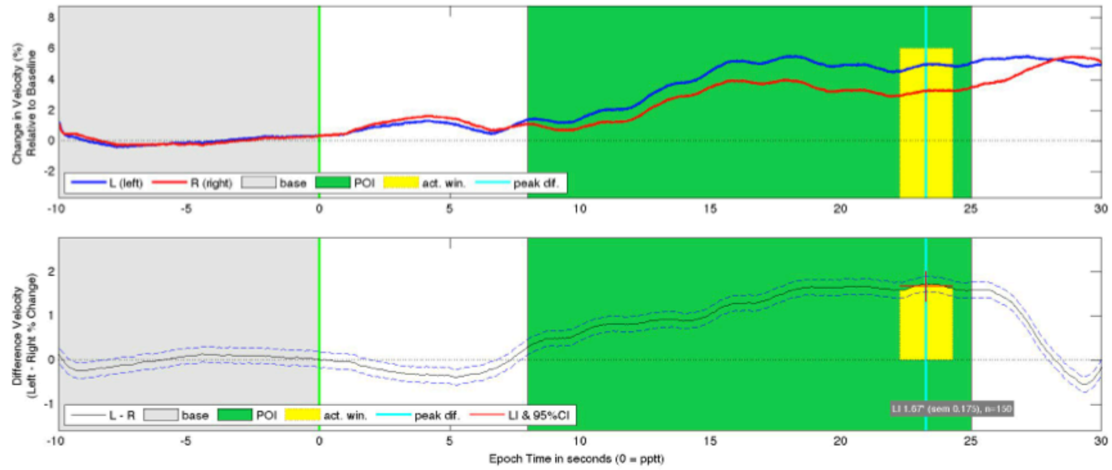


Figure 4.5 *Average of participant's baseline-corrected cerebral blood flow velocity for the left (blue line) and right (red line) hemisphere during 'word generation ' (A) and 'pyramids and palm trees' (B). The difference between left-right hemispheres is shown below each paradigm.*

At the group level, median LIs of the WG (z = 10.0, p < .0005) and PPT task (z = 7.38, p < .0005) were significantly different from zero indicating a left lateralization of activation for the group for both paradigms. For each task, I categorized participants as having a left, right or no hemispheric bias for language using the CI of individual LIs across epochs. The count of left-lateralized participants was numerically higher for the WG task, which classified 133 (88.7%) individuals as left, 9 (6.0%) as right, and 8 (5.3%) as bilateral; while the PPT revealed left-lateralized, right-lateralized and bilateral activation in 95 (63.3%), 19 (12.7%), and 36 (24.0%)

participants, respectively. McNemar's test, confirmed that the two paradigms significantly differed in the number of people with typical (left) and atypical (non-left) language lateralization ($\chi^2 = 29.76$, $p < .0005$).

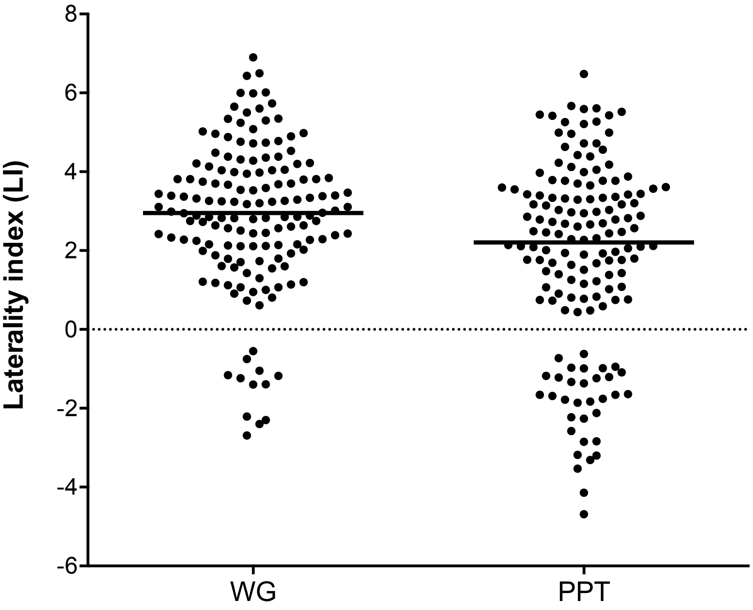


Figure 4.6 *Individual laterality indices (LI) are plotted for all participants (N =150) who completed both the word generation task (WG, left) and pyramids and palm trees task (PPT, right). Positive LIs indicate left- and negatives ones right language lateralization. Median LIs are depicted as a black line within each distribution.*

Individual LIs are plotted in *Figure 4.6* indicating a higher median for the WG (*Mdn* = 2.96, *IQR* = 1.98-4.04) relative to the PPT task (*Mdn* = 2.21, *IQR* = 0.70-3.47). To determine whether the observed difference was statistically meaningful, Wilcoxon signed ranks test was run. Analyses revealed that LIs for the WG task were significantly more strongly left lateralized than for the PPT ($z = -5.59$, $p < .0005$). As expected, the majority of participants were concordant for LIs based on WG and PPT tasks (N (%): total 103 (68.6%), left 91 (60.7%), right 8 (5.3%), and bilateral 4 (2.6%). LI categories of the remaining 47 (31.3%) participants, however, differed showing that most of these participants were classified as left-lateralized for WG and bilateral for the PPT task (N (%): 32 (21.3%)). Spearman's correlation coefficient was calculated to further assess the agreement of individual LIs. Analysis revealed a significant correlation indicating a moderately positive association between the LIs from WG and PPT task ($r_S = .47, p < .0005$), which is illustrated in *Figure 4.7.*

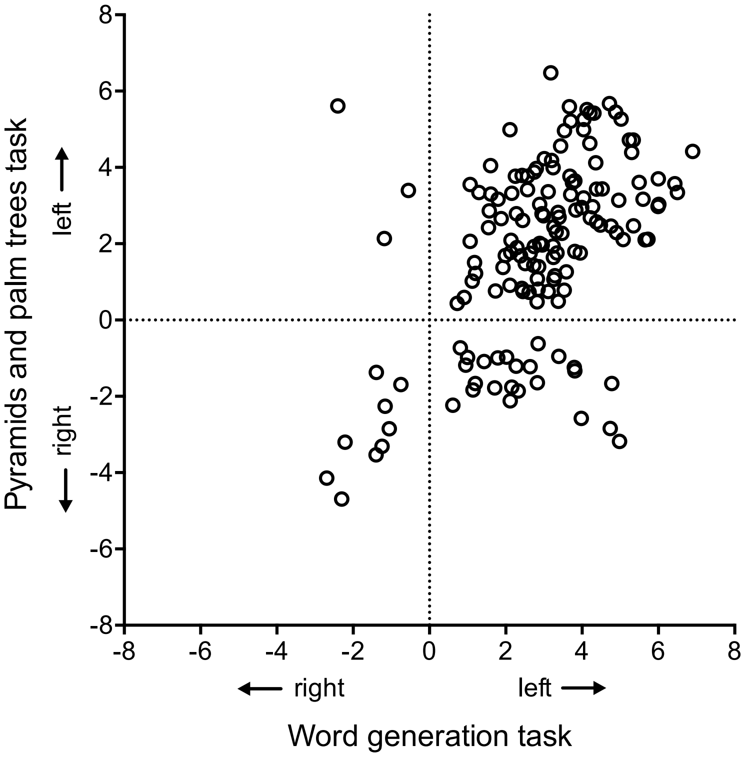


Figure 4.7 *Scatterplot of laterality indices (LIs) for the language production (word generation task) and semantic matching (pyramids and palm trees task) paradigm. Positive LIs indicate left- and negatives ones right language lateralization.*

It is worth noting that the way in which LIs are computed will make the data look bimodal (*Figure 4.6)*. This is because dopOSCCI calculates LI values based on the maximum peak value, regardless of left- or right-lateralized CBFV changes. It is therefore unusual to obtain LIs around zero and the question arises as to whether the positive correlation is driven solely by variability in the direction (left vs. right) or is there consistency in the degrees of laterality as well? To address this question, I re-calculated Spearman's rho excluding 12 participants who had LI values lower than zero in the WG task. In this case, the positive correlation remained significant ($r_S = .42, p < .0005$) revealing some consistency in the degree of lateralization, even when direction is held constant.

4.3.3 Relationship between LI and handedness

Descriptive statistics for left- and right-handed participants are presented in *Table 4.1.* As assessed by Mann-Whitney test, the two groups did not differ in age, neither for the WG (p = .20) nor PPT (p = .36). For both paradigms, the number of accepted epochs (WG: p = .93, PPT: p = .75) and the 'goodness of recordings' (WG: p = .36, PPT: p = .43) were also similar for left- and right-handed participants.

Table 4.1. *Descriptive statistics for left-handers and right-handers. Groups were defined based on their hand preference for writing (self-report). Data are shown for the word generation (WG) and pyramids and palm trees (PPT), separately.*

		WG (N = 206)		**PPT (N = 152)**	
		LH	RH	LH	RH
Demographic data	Age (*M* ± *SD*)	23.7 ± 4.5	22.9 ± 4.3	23.3 ± 4.2	22.7 ± 4.1
	Gender (M:F)	10:16	63:117	10:11	43:88
Language laterality	Left	19	166	6	91
	Non-left	7 (2)	14 (9)	15 (7)	40 (29)
	LI (*Mdn*)	2.41	3.10	-1.18	2.49
	LI (*IQR*)	0.27 - 3.35	2.16 - 4.11	-2.72 - 1.72	1.07 - 3.61
Handedness	Writing hand	26	180	21	131
	EHI (*M* ± *SD*)	23.8	48.1	23.7	48.1
	QHP (*M* ± *SD*)	-0.10	0.23	-0.13	0.22

Note: Values in brackets denote the number of participants with bilateral language representation. Statistics are Mean (*M*), standard deviation (*SD*), median (*Mdn*), and interquartile range (IQR).

By comparing the number of right-handers with the number of left-handers across lateralization groups (left vs. non-left), I examined whether a higher incidence of atypical language laterality (non-left) was observed in my left-handed participants. *Table 4.1* shows that atypical lateralization of language was observed in 26.9% of left-handed, but only 7.8% of right-handed participants based on WG. These percentages were elevated for the PPT task, in which 71.4% of left- and 30.5% of right-handers showed atypical language lateralization. Fisher's Exact test confirmed that there was a significant association between handedness and hemispheric lateralization for both language paradigms (WG: p_{corr} = .015 PPT: p_{corr} < .001). In addition, the two groups showed a significant difference in median LIs for WG (U =

3029, $z = 2.42$, $p_{corr} = .030$) and PPT ($U = 2176$, $z = 4.72$, $p_{corr} < .001$); LI values were significantly higher in right-handed relative to left-handed participants (Figure 4.8). When I classified participants as left- and right-handed based on the EHI score (a score of 40 or above on the abbreviated version), similar results in terms of association between handedness and count of LI categories as well as median LIs were obtained for the WG and PPT task.

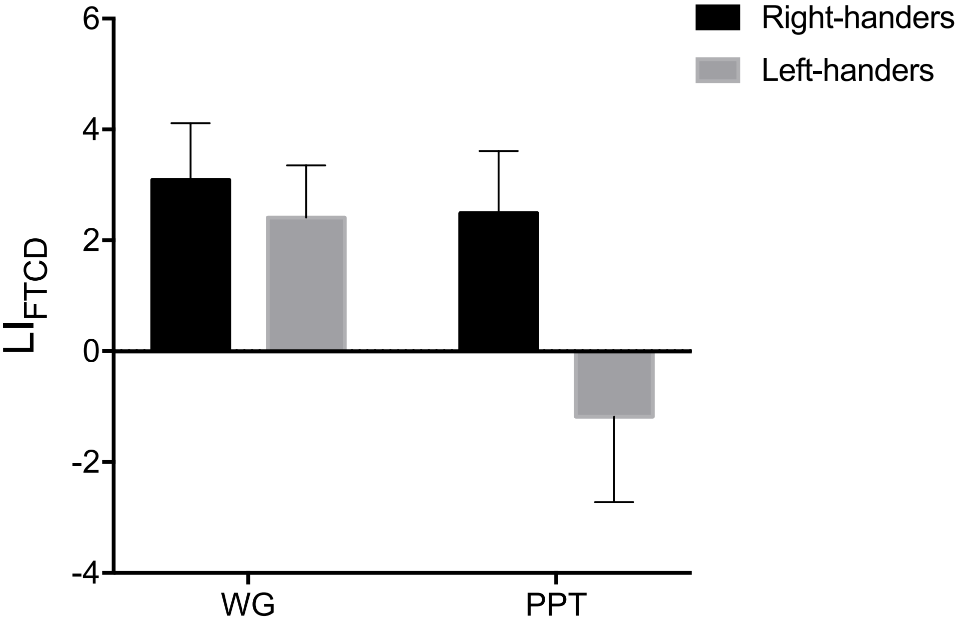


Figure 4.8 *Language laterality in left-handed and right-handed participants as assessed by FTCD. Bars represent median laterality index (LI) values associated with word generation (WG) and pyramids and palm trees (PPT) for right-handed (black bars) and left-handed (grey bars) participants. Error bars indicate the interquartile range (IRQ).*

Some researchers have argued that handedness is a quantitative rather than dichotomous trait (Annett, 1970; Bishop, 1990). Thus, Spearman's correlation coefficients were calculated to investigate the relationship between individual LI values and manual preference. Across participants a significant, but weak correlation was observed between the two handedness measures ($r_S = .32$, $p < .0005$). While indices of language lateralization based on the WG task correlated significantly with handedness as measured by the QHP task ($r_S = .16$, $p = .013$), LIs for the PPT showed significant association with EHI measures ($r_S = .23$, $p = .003$). These associations remained significant after correcting for the number of correlations (p_{corr} = .025). Spearman's rho, however, indicated only a very weak to weak association for the WG and PPT respectively (*Figure 4.9*).

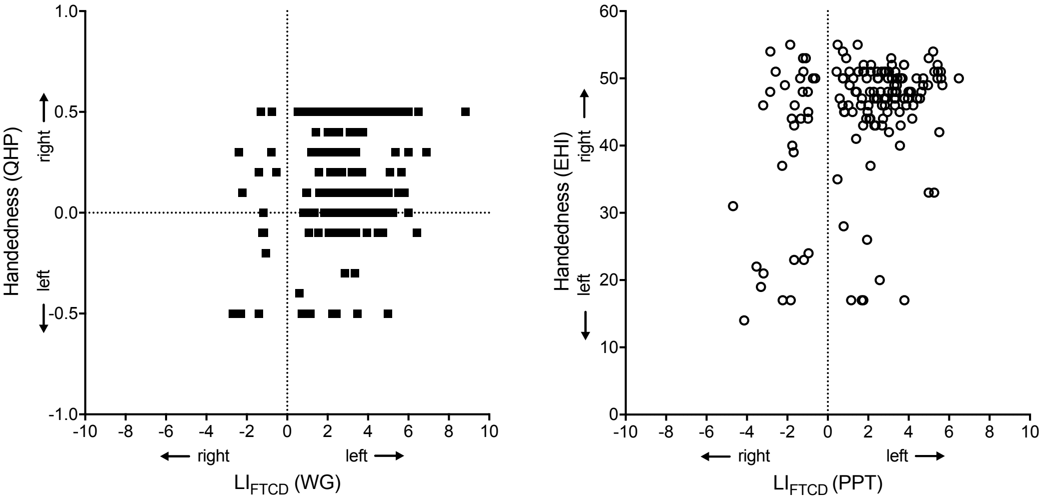


Figure 4.9 *Association between language laterality during word generation (WG) or pyramids and palm trees (PPT) and handedness.* *Scatterplots show laterality indices (LIs) on the x-axis and quantitative measures of handedness on the y-axis, including scores from the reaching task (QHP, left) and the Edinburgh handedness inventory (EHI, right).*

Again, the bimodal distribution of LI values raises the question whether direction or degree is driving this correlation. I therefore recalculated correlation coefficients when only including right-handers and found that the relationship between degree of (right) handedness and LI was no longer significant for either task.

4.4 Discussion

Using FTCD, I examined cerebral lateralization of perfusion during language production and semantic matching in a large number of neurotypical adults. Language production was assessed using a word generation paradigm (WG), which required participants to silently generate words to a visually presented letter. A receptive language paradigm based on the pyramids and palm trees test (PPT) required participants to select which one of two pictures was semantically related to a target picture. Indices of lateralization obtained during language production as well as semantic matching showed a good level of internal consistency and high test-retest reliability. As expected, both paradigms revealed significant left hemisphere lateralization at the group level, but the WG showed stronger left lateralization than PPT with respect to the number of left-lateralized individuals as well as strength of lateralization. When categorizing participants as left- or right-handed a significant association between manual preference and laterality group was found for both paradigms: atypical lateralization for language production and semantic matching occurred more frequently in left handers compared with right handers. When the magnitudes of lateralization and handedness were considered, however, only very weak correlations were observed between indices of language lateralization and handedness measures; these disappeared when only the right-handed participants were considered.

4.4.1 Reliability of FTCD data

Both paradigms used in this study showed good internal as well as test-retest reliability indicating that FTCD provided accurate and reproducible information on functional lateralization for language production and semantic matching. These findings are consistent with previous evaluations of FTCD (Knecht et al., 1998b; Whitehouse et al., 2009). For instance, WG in combination with FTCD is commonly used to determine language lateralisation and has been validated by direct comparison with the Wada technique (Knake et al., 2003; Knecht et al., 1998a) and FMRI (Deppe et al., 2000; Somers et al., 2011). Deppe and colleagues (2000) found that LIs obtained in 13 healthy adults using both FTCD and FMRI were not only concordant in all participants, but also highly correlated ($r = .95$, $p < .0001$; Deppe et al., 2000). More importantly, the same group of researchers demonstrated that individual indices of language lateralization as measured by FTCD were highly reproducible when reassessed 1 hour to 14 months after the initial testing ($r = .95$, $p < .0001$; (Knecht et al., 1998b). The authors therefore concluded that FTCD is a reliable method for investigating and determining functional language laterality (Knecht et al., 1998b). Another FTCD study, however, reported much lower test-retest reliability with a slightly modified version of the WG paradigm ($r = .53$, $p < .05$; Stroobant & Vingerhoets, 2001).

The reproducibility of FTCD measurements can be influenced by a number of factors (Knecht et al., 1998b). Firstly, CBFV values as measured by FTCD depend on the angle of insonation (Bartels & Flügel, 1994). A change in this angle during repeated FTCD assessments may thus affect reproducibility of laterality indices. Aaslid and colleagues (1982) demonstrated that changes of the insonation angle from 0° to 30° due to variability of probe position or arterial anatomy can render differences in the calculated absolute CBFV up to 13% between examinations or sides. Yet, an exact measurement of the angle is not possible as the arteries wind and branch out (Deppe, Ringelstein, et al., 2004). In fact, inter-individual differences in angles of insonation of 0° to 51° have been found for the MCA using transcranial color-coded Doppler sonography (TCCD, (Martin, Evans, & Naylor, 1995). My data are unlikely to be affected by this source of variability, however, as I used relative rather than absolute changes in CBFV in my statistical analyses. Specifically, flow velocities at rest were defined as baseline values, and task-induced changes in CBFV were expressed as percentages relative to baseline (Rihs et al., 1995).

Secondly, the FTCD signal is affected by spontaneous fluctuations in CBFV related to heartbeat and breathing that substantially contribute to the variability in blood flow data (Diehl, Diehl, Stodieck, & Ringelstein, 1997). These cardiovascular changes are typically of much greater amplitude than the changes related to neural activation, e.g.

they represent approximately 50% of the mean signal compared to 3% signal change during WG (Knecht et al., 1998). By integrating the heart cycle into the analysis, however, physiological modulations of CBFV can be effectively reduced (Deppe et al., 1997). To further improve the sensitivity of FTCD, the relative side-to-side difference in CBFV increase is evaluated for each individual, thus eliminating effects of systematic cardiovascular fluctuations (Deppe et al., 1997). Other factors that have been shown to influence the cerebral haemodynamic response include neurostimulants such as caffeine or nicotine (Kodaira et al., 1993) and circadian rhythms (Ameriso, Mohler, Suarez, & Fisher, 1994). These aspects, however, are thought to affect the entire cardiovascular system resulting in bilateral changes in CBFV, which would be cancelled out when subtracting the relative CBFV increase in the right from the left MCA (Knecht et al., 1998b).

Lastly, more general psychological and situational factors can affect measures of test-retest reliability, too. For example, repeating the exact same task could result in reduced cognitive demands or improved performance during the second assessment, which in turn could systematically influence CBFV (Knecht et al., 1998b). When examining lateralized cognitive functions such as language, practice effects might predominantly appear within one hemisphere, and therefore not be eliminated by the side-to-side subtraction algorithm used in FTCD analysis. Using the WG paradigm, Knecht and colleagues (1998b), however, evaluated LIs from ten successive FTCD sessions in a single participant and found no trend in lateralization over time. Moreover, all ten mean LIs were within the limits of the standard error indicating no significant variation in hemispheric perfusion differences across examinations (Knecht et al., 1998b). The analysis of stability indices in this study, however, indicated no practice effects in my data. Factors like motivation, ability to concentrate or a participant's cooperation to sit still during FTCD assessment also play an important role. While the former two aspects could be estimated through task performance, which was monitored during overt language production for WG and via recorded button presses for PPT, the latter was ensured by excluding datasets that did not pass the 'goodness of recording' criterion (see methods).

It should be noted that although WG ($r = .80$, $p < .0005$) as well as PPT ($r = .92$, $p < .0005$) showed a good to excellent reliability between the two sessions, test-retest agreement was not perfect. For the WG, two participants had right-greater-than-left hemisphere activation on the first assessment (Participant 4 = -0.55, Participant 12 = -0.75), but the reverse pattern on the second (Participant 4 = 2.16, Participant 12 = 1.63), while for the PPT, one participant exhibited left-greater-than-right hemisphere activation in the first (Participant 14 = 0.82) and the opposite in the second session (Participant 14 = -1.82). Strikingly, in these three cases the CI of the LIs based on the initial assessment crossed zero indicating "bilateral" or very weakly lateralized activation in that session. Neuroimaging studies with large samples have often found individuals with weak language lateralization (Binder et al., 1996; Knecht et al., 2000a; Knecht et al., 2000b). Yet, it remains unclear whether bilateral increases in blood flow reflect a truly bihemispheric language organization or rather artefacts of methodology (George et al., 1996; Just, Carpenter, Keller, Eddy, & Thulborn, 1996).

4.4.2 Lateralization of language production versus semantic matching

The assessment of functional language lateralization based on a single activation task results in a limited view of cerebral specialization and language processing. Therefore, I used two paradigms in this study which were chosen to encompass expressive as well as more receptive language functions thought to involve frontal as well as temporal areas: word generation (WG) and semantic matching (PPT). Both tasks revealed an overall left-hemispheric lateralization, which was more pronounced in the WG paradigm. This finding is consistent with previous studies that have reported variability in lateralization among different language tasks including picture description, auditory naming, sentence construction, reading, semantic decision, and story listening (Badcock, Nye, et al., 2012; Buchinger et al., 2000; Haag et al., 2010; Stroobant et al., 2009; Stroobant, Van Boxstael, & Vingerhoets, 2011). Buchinger and colleagues (2000) found that changes in CBFV measured by FCTD were more strongly lateralized for generating words than listening to sentences in 16 healthy adults. Other FTCD studies revealed similar results demonstrating that compared with receptive language tasks, expressive language tasks elicited a left hemisphere bias in a larger number of participants (Badcock, Nye, et al., 2012; Stroobant et al., 2011). All these studies, including the current one, are in line with the hypothesis that language comprehension is represented more bilaterally than language production (Boatman et al., 1998, 1999; Buchinger et al., 2000). Receptive language functions, for instance, have been shown to be less susceptible to unilateral brain damage as they recover more quickly and thoroughly than expressive ones in most patients (Boatman et al., 1999; Huber et al., 1997). In addition, indices of lateralization based on receptive language tasks and associated activation of brain regions are less concordant with the Wada test (Kim & Chung, 2008; Lesser, 2003; McDonald et al., 2009).

Other possible explanations for the observed differences between the two paradigms may relate to task difficulty, task design, or demands on cognitive processing more generally. For example, the pace of stimulus presentation, as one aspect of task difficulty, has been suggested to influence the strength of lateralisation (Payne, Gutierrez-Sigut, Subik, Woll, & MacSweeney, 2015; Shergill et al., 2002). Using

FMRI, Shergill et al. (2002) found that the strength of activation in the left IFG and left STG increased with greater rate of covert articulation. This finding is consistent with a recent FTCD study that demonstrated significantly greater cerebral lateralisation when linguistic (rhyme) or non-linguistic (line) judgements were presented at fast compared to slow pace (Payne et al., 2015). Assuming that for most neurotypical individuals the processes involved in word generation (e.g. lexical search and retrieval) per se is more demanding than choosing between alternatives provided (as in the PPT), reduced lateralization for the PPT may be explained by task difficulty. However, not all neuroimaging studies found differences in the strength of lateralization between varying levels of difficulty (Badcock, Nye, et al., 2012; Dräger et al., 2004; Dräger & Knecht, 2002). By presenting word stems of high and low frequency, Dräger and colleagues manipulated word-finding difficulty during WG using FMRI (Dräger et al., 2004) and FTCD (Dräger & Knecht, 2002). Although participants' performance decreased in a linear fashion from easy to difficult, indices of language lateralization remained constant in both studies (Dräger et al., 2004; Dräger & Knecht, 2002). Similar results were reported by Badcock et al. (2012) who demonstrated that behavioural responses were unrelated to physiological responses despite significant variation in task performance during WG and auditory naming. The absence of a clear association between behaviour and LI values (e.g. Badcock, Nye, & Bishop, 2012; Dräger et al., 2004; Stroobant, Buijs, & Vingerhoets, 2009; Stroobant, Van Boxstael, & Vingerhoets, 2011) suggests that there are also inherent lateralization differences between receptive and expressive language tasks which cannot be explained by task difficulty.

One of these inherent lateralization differences may relate to the distinct linguistic and cognitive processes involved in the two paradigms. While WG taxes predominantly phonological fluency as well as planning, coordination and execution of articulation, PPT involves the retrieval of semantic information from pictures. It has been suggested that semantic processing involves a number of systems, which are not related to language and located in both hemispheres such as memory encoding, visual perception and mental imagery (Deblaere et al., 2002). The PPT task may have drawn on non-linguistic domains to a greater extent than the WG task, which in turn reduced language-specific lateralization. Because FTCD has a poor spatial resolution, it cannot be used to differentiate between activation of language-related and other brain areas that lie within the MCA territory. Using other brain-imaging techniques like FMRI, it would be interesting and necessary to determine whether the observed differences in the magnitude of lateralization between the two paradigms reflect differences within the cerebral language network.

Lastly, differences in the strength of lateralization between the two paradigms could also relate to differences in task design. More specifically, the PPT task (N = 15) included fewer epochs than the WG task (N = 23) in order to be able to complete both tasks in a reasonable amount of time. A larger number of trials, however, potentially results in less noisy measurements and appears to improve test-rest reliability. In a study by Knecht et al. (1998b), for example, indices of lateralization were calculated for WG based on 23 letter presentations and showed a high test-retest reliability of $r = .95$. By contrast, Stroobant and Vingerhoets (2001) obtained LIs for WG based on only four letters and reported a much lower reliability of $r = .53$. Comparing the two studies suggests that the longer WG paradigm measured changes in CBFV more reliably. Differences in the number of trials could therefore underpin reduced functional lateralization for the PPT task. Prolonged testing times, on the other hand, limit the number of paradigms that can be assessed in a single participant and might affect a participant’s attention.

4.4.3 Handedness and language laterality

It is widely reported that over 90% of the right-handed population predominantly engages the left hemisphere during language processing (Knecht et al., 2000a). Although the relationship between handedness and language laterality is weak and imperfect, manual preference has long been used as an indicator of cerebral lateralization. To explore this relationship I included two handedness measures in this study: an abbreviated version of the Edinburgh Handedness Inventory (EHI) and a reaching task (QHP). When analysing the data categorically (right-handers vs. left-handers) I found a significant association between handedness and language laterality, which was similar to those described in previous studies (Groen et al., 2013; Knecht et al., 2000a; Whitehouse & Bishop, 2009). For both paradigms, a higher incidence of atypical language lateralization (non-left) was observed in left-handers compared to right-handers. Within the group of non-dextral participants, the occurrence of atypical lateralization for word generation (27%) agrees well with findings from the Wada test reported by Rasmussen and Milner (1977; 30% atypical) as well as FMRI reported by Pujol and colleagues (1999; 24% atypical) or Szaflarski and colleagues (2002; 22%). For the PPT, however, the number of atypical lateralization in left-handers (71%) was much higher showing the reverse pattern in comparison to WG. Given that atypical lateralization included individuals who showed weak lateralization of CBFV and that the PPT task was overall less lateralized than WG, the large number of atypical participants appears less surprising. Indeed, there were only two left-handers, who were classified as bilateral using WG, but seven left-handers who showed weak lateralization during PPT.

Although manual preference is often described as a dichotomy (left vs. non-left), there are two major problems associated with the categorical analysis of handedness data. Firstly, there is no agreement as to where cut-offs should be placed in order to classify people as dextral or non-dextral. Secondly, in order to avoid the loss of important information on variation within groups of right- or left-handers most researcher prefer to treat handedness as a continuum (Annett, 1970; Bishop, 1990). Hence, I calculated correlations between handedness quotients based on the short version of the EHI or handedness bias based on QHP and LI values for word generation and semantic matching. Despite being statistically significant, both associations of QHP scores with LIs of WG ($r_S = .16$) and EHI scores with LIs of PPT ($r_S = .34$) were rather weak suggesting that handedness in not a reliable indicator of cerebral language lateralization. None of these correlations remained significant when only dextral participants were considered.

It has long been known that the relation between handedness and language lateralization is far from perfect. It has also been shown that different handedness measures are often imperfectly intercorrelated (Rasmussen & Millner, 1975). What remains to be elucidated is whether manual preference provides a good indicator of cerebral lateralization for language and if so, which aspect of manual preference. Groen and colleagues (2013) used FTCD to determine the validity of three different handedness assessments as an indirect measure of language laterality in 57 left- and right-handed children (aged 6 to 16 years). As in the current study, manual preference was quantified using an abbreviated version of the EHI, the QHP task, plus a peg-moving task, and indices of lateralization were obtained for an animation description paradigm (language production). The authors found that LI values significantly correlated with handedness for the short version of the EHI (.29) and for performance on the QHP task (.40). At a first glance, the positive relation between QHP scores and lateralization for language production seems to be consistent with my findings; however, the strength of correlation was much weaker and almost negligible in the current study. Despite the significant association reported by Groen et al. (2013), scores of EHI and QHP only explained 8% to 16% of the variance in functional lateralization indicating that none of the handedness measures included was a reliable indicator of language laterality. Contrary to these findings, Knecht and colleagues (2000b) demonstrated a linear relationship between degree of handedness measured by EHI and the incidence of right-lateralized activation during word generation in a large sample of 326 neurotypical adults: the more left-handed the participants were, the higher was the incidence of atypical language laterality. This study extended previous FMRI results, which showed that in left- and right-handed individual the incidence of atypical language laterality depends not only on the direction but also on the degree of handedness (Pujol et al., 1999). Both findings suggest that left-handedness increases the likelihood of right-hemispheric language lateralization without being a precondition or a necessary consequence of atypical language laterality (Knecht et al., 2000b; Pujol et al., 1999).

Yet, for every study that has found a significant relation between handedness and functional language lateralization (e.g. Groen et al., 2013; Knecht et al., 2000b; Pujol et al., 1999; Szaflarski et al., 2002), there is one that has not (Badcock, Nye, & Bishop, 2012; Bishop, Watt, & Papadatou-Pastou, 2009; Springer et al., 1999; Stroobant, Buijs, & Vingerhoets, 2009; Stroobant, Van Boxstael, & Vingerhoets, 2011; Whitehouse & Bishop, 2009). Discrepancies between these studies may relate not only to differences in the studied samples, used imaging techniques or employed activation tasks, but also to the question of how to measure handedness. The validity of commonly used inventories, for instance, is questionable as they have no theoretical basis and lack empirical validation (Bishop, Ross, et al., 1996). In addition, inventories cannot be regarded as a good measure of biologically determined handedness due to the arbitrary nature of the items, which are often affected by cultural and training effects (Calvert & Bishop, 1998). Hence, assessing handedness is not as straightforward as it may seem and other quantifications such as relative hand skill (i.e. peg-moving, finger tapping or dotting) or behavioural measures of hand preference (i.e. long pegboard, long dots, QHP) may be better suited to examine laterality. For example, in the study by Groen et al. (Groen et al., 2013) the QHP showed the strongest association with cerebral language lateralization and was a better predictor than scores based on the EHI.

It is important to note that most of the studies that did not find an association between manual preference and indices of language lateralization included no or only very few left-handers. The latter is also true for the current study, which assessed 26 and 21 nondextral participants for the WG and PPT task respectively. Although these numbers reflect the distribution of handedness in the population, it may have affected the ability to detect valid associations due the skewed distribution of handedness scores. Future studies should therefore oversample left-handed participants in order to determine whether the weak correlations observed in this study reflect meaningful associations. In addition, actively seeking nondextral participants may also increase the likelihood of atypical language lateralisation (see Knecht et al., 2000b) resulting in greater within sample variability.

4.4.4 Limitations and future directions

As briefly mentioned in the previous paragraph, one limitation of this study is related to the poor spatial resolution of FTCD. In order to obtain indices of lateralization, FTCD measures event-related CBFV changes in the left and right MCA. The MCA is the largest branch of the internal carotid and supplies a portion of the frontal lobe as well as the lateral surface of the temporal and parietal lobes. Although relatively well defined, the wide territory of the MCA includes not only language related cortices, but also motor, sensory and auditory ones (van der Zwan et al., 1993). Because each task involves distinct linguistic and cognitive processes, different areas within the MCA territory will be engaged during word generation compared to semantic matching; it seems feasible that the reduced lateralization for PPT may reflect task-specific variation (Bishop, Watt, & Papadatou-Pastou, 2009). FTCD, however, does not provide useful information about localization within a hemisphere and can therefore not be used to examine effects at the neuroanatomical level. To determine whether the observed differences in lateralization were related to increased bilateral activation of language-related areas or to a greater engagement of other right-hemispheric cortices, future studies will need to employ imaging techniques with higher spatial resolution such as FMRI. In this context, FTCD is a valuable research tool as it can be used to predict individual differences in task-specific lateralization that could be examined using FMRI (Bishop, Watt, & Papadatou-Pastou, 2009).

4.5 Conclusion

Although it is well known that most people show a left hemisphere bias for language processing, the extent to which individuals are consistent in their functional lateralization across various domains of language remains unclear. In this study, I demonstrated that cerebral lateralization for both expressive and more receptive language functions can be assessed reliably with FTCD. In conclusion, the strength of language lateralisation varied between tasks indicating that changes in CBFV were more strongly left-lateralized during word generation than semantic matching. Because previous studies have found no effect of task difficulty on language lateralization, differences in LIs may reflect differences in expressive and receptive task demands. These findings improve our understanding with respect to the sensitivity of FTCD for evaluating functional lateralisation of more receptive language tasks.

5

Comparing different methods of measurement of language lateralization.

Abstract

Language is the most commonly investigated lateralized functions. Yet, there is no consensus on how best to measure cerebral language lateralization and whether its strength or direction is relevant for language functions. I compared different measures of language laterality obtained in a well-matched sample of typically (left) and atypically (right or bilateral) lateralized participants, as previously assessed by FTCD. All participants completed three language paradigms, namely word generation (WG), pyramids and palm trees (PPT), and auditory naming (AN) during FMRI in order to map language areas. In addition, a visual half-field task was used to obtain a behavioural measure of language lateralization. Standardized tests of intelligence, reading, and vocabulary were administered to examine the relation between functional lateralization and behaviour. The imaging data showed that all three tasks robustly activated the fronto-temporal language system. As expected the typical and atypical groups differed significantly on the FMRI tasks. The typical group robustly activated a left-lateralized language network on each task. However, the pattern obtained in the atypical group was not a mirror image of that obtained in the typical group. Rather, a pattern of bilateral activation, with significantly lower left-hemisphere activation and significantly higher right-hemisphere activation in the atypical group compared to the typical group. There was considerable inter-individual variability in the pattern of

activation obtained in the atypical group across both hemispheres. The group of typically lateralized participants showed varying degrees of leftward lateralization for language on the three FMRI tasks but were most likely to be categorized as left lateralized on these measures. With one exception, the same results were obtained using FTCD and the visual-half field test for that typical group. In contrast, the pattern obtained in the atypical group was more varied/unstable. The atypical individuals classified as atypical using FTCD, were most likely to be classified as left lateralised on the FMRI and behavioural measures. A couple of the right-lateralized individuals were also classified as right lateralized on these other measures. Across the two groups, however, LI values were well correlated between FTCD and FMRI measurements suggesting a positive association between the two methods. Importantly, the two groups did not differ on any behavioural measurement indicating that atypical language lateralization does not confer any disadvantage or advantage in cognitive tasks

5.1 Introduction

Functional neuroimaging has provided a wealth of information on the variability of the language system and its lateralization. A right hemisphere bias for language is only observed in about 1 out of 13 right-handed adults and is therefore described as atypical lateralization (Knecht et al., 2000a). When categorizing people as typical (left) and atypical, however, the latter often refers to both right-lateralized individuals and those who show bi-hemispheric activation (or weak lateralization) during language tasks (Binder et al., 1996; Knecht et al., 2000b; Pujol et al., 1999). The likelihood of atypical language laterality has been found to increase with the degree of left-handedness and has been estimated to occur in about 22-27% of left-handed individuals (Knecht et al., 2000b; Pujol et al., 1999; Szaflarski et al., 2002). Using the Wada technique, Rasmussen and Milner (1977) examined the incidence of left, right and bilateral language processing in relation to handedness and history of early damage to the left hemisphere in 396 patients. An increased occurrence of atypical lateralization was found in left- as well as right-handed patients with a clinical record of early compared to late brain injury indicating a shift of language from the left to the right hemisphere (Rasmussen & Milner, 1977). While substantial lesions can result in a complete shift of function, partial shifts are likely to occur with smaller ones (Loring et al., 1990; Woods, Dodrill, & Ojemann, 1988). Clinical studies, however, cannot ascertain the degree to which right-lateralized or bilateral patients reflect reorganisation of function rather than a normal variant that may be present in the general population (Risse, Gates, & Fangman, 1997). As a consequence, the concept of atypical language organization in neurotypical individuals remains poorly understood and more research is needed to determine how best to conceptualize functional lateralization in the healthy brain.

5.1.1 Assessment of functional language lateralization in the healthy brain

Although the Wada test (Wellmer et al., 2008) and intra-operative brain mapping (Roux et al., 2003) remain the standard assessments of hemispheric specialization for language, these procedures are invasive and therefore restricted to patients undergoing neurosurgery. FMRI and FTCD are used as non-invasive alternatives in most studies that examined functional lateralization of language in neurotypical individuals over the last 20 years. Both methods have been independently validated by direct comparison with the Wada test and demonstrate a high overall correlation (Binder et al., 1996; Knake et al., 2003; Knecht et al., 1998a). In addition, Deppe and colleagues (2000) directly examined the relation between cerebral blood flow velocity (CBFV) changes in the cerebral arteries measured by FTCD and brain tissue oxygenation changes measured by FMRI. Despite inherent methodological differences, indices of functional lateralization during language production based on FTCD were closely related to those based on FMRI (Deppe et al., 2000b). The authors suggest that both techniques can be used interchangeably to evaluate language laterality on a subject-by-subject basis (Deppe et al., 2000b). Because FTCD is relatively cheap, easy to apply, and mobile it can be used to examine larger groups within the healthy population. FMRI on the other hand provides information on localization of activity within each hemisphere due to its high spatial resolution; hence, the two methods should complement each other in the non-invasive and valid assessment of language laterality (Deppe et al., 2000b).

A behavioural method for determining cerebral lateralization, which has widely been used in traditional neuropsychology, is the visual half-field (VHF) task. This task is based on the idea that a stimulus presented to one visual field is processed by the contralateral hemisphere due to the crossing of the optic fibres from the nasal hemiretinae in the optic chiasm (Beaumont, 1983). In other words, if a picture is tachistoscopically presented to the left parafovea, visual information is initially projected to the right hemisphere and vice versa. Any visual field effects on task performance are therefore thought to reflect early differences in hemispheric functioning; i.e. projecting information to the non-dominant hemisphere will lead to an efficiency loss either because a transfer to the specialized hemisphere is required or because the non-specialized hemisphere processes it more slowly (Hunter & Brysbaert, 2008). Hence, the VHF task predicts that an individual with left-lateralized language function will show a RVF advantage marked by faster and more accurate recognition of verbal stimuli displayed in the RVF. Although this behavioural measure of functional lateralization has been deemed effective and efficient (Mondor & Bryden, 1992; Lindell & Nicholls, 2003), strict methodological controls are necessary in order to attain reliable and valid results (for a review see Bourne, 2006; Hunter & Brysbaert, 2008). Hunter and Brysbaert (2008) therefore carefully designed a VHF task by taking various considerations into account (e.g. bilateral stimulus presentation, matched stimulus sets for left and right visual field, and fixation control) and validated it against an FMRI study. A high correlation between LI values based on the VHF task and those measured by FMRI during word generation was found suggesting that this paradigm can be used as a reliable predictor of cerebral language laterality (Hunter & Brysbaert, 2008).

5.1.2 Relationship between functional lateralization and language abilities

Despite this extensive research on functional language lateralization, it remains unclear whether language abilities actually relate to the degree of cerebral specialization. Because intra-hemispheric transition times are shorter than inter-hemispheric ones, it has been speculated that increased hemispheric specialization during development is beneficial for language processing (Kupferman, 1995; Miller, 1996). Hence, a quantitative relationship between the strength of functional lateralization and language skills should exist (Gotts et al., 2013). Consistent with this notion, studies using functional neuroimaging have shown that language lateralization was weaker in both children and adults with language or literacy impairments compared to typically developing controls (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012; de Guibert et al., 2011; Illingworth & Bishop, 2009; Whitehouse & Bishop, 2008). Guibert and colleagues (2011), for example, acquired FMRI data during four different language tasks including two auditory lexico-semantic and two visual phonological paradigms and reported a significant lack of left lateralization in all core language regions in children with SLI. A study by Badcock et al. (2012) also showed that activity in language-related areas during a covert auditory naming task was reduced in SLI children relative to typically developing peers as well as unaffected siblings. While the pattern of language-related activity was clearly left lateralized in controls and siblings, language-impaired children showed reduced left-hemispheric lateralization and greater variability in their laterality measures (Badcock, Bishop, et al., 2012). Not all children diagnosed with SLI, however, show a deviation from the normal pattern of left-hemispheric language lateralization. This heterogeneity in functional brain organization of individuals with developmental language disorders, can therefore contribute to equivocal findings when comparing affected with unaffected populations. A better understanding of typical and atypical language lateralization in healthy individuals is needed in order to determine whether deviations seen in patients are normal or abnormal; which in turn can help to identify sensitive biomarkers.

In typical development, neuroimaging studies have shown that functional lateralization of language not only increases with age, but also correlates with language abilities (e.g. Everts et al., 2009; Holland et al., 2001; Mellet et al., 2014; Szaflarski et al., 2008). A positive relationship between verbal IQ and the strength of functional lateralization for vowel detection as measured by FMRI was observed in healthy children aged 8 to 20 years (Everts et al., 2009). Strikingly, this FMRI data indicated that age and performance, independently, account for increases of left-hemispheric lateralization for language with age (Everts et al., 2009). An FTCD study by Groen and colleagues (2012) demonstrated that children with left-lateralized language production performed better on tests of vocabulary and nonword reading, too, indicating a link between language function and left-hemisphere specialization. Similar findings have been reported by Mellet et al. (2014) in neurotypical adults using FMRI. Participants with bilateral activation during sentence generation had lower scores on verbal and non-verbal tests relative to those with strongly left- or right-lateralized activation. Other studies, however, found no association between performance and functional language lateralization (Gaillard et al., 2003; Knecht et al., 2001; Wood et al., 2004). One research group looked at developmental differences in FMRI activation maps between 29 adults and 16 children while completing a semantic fluency task in the scanner (Gaillard et al., 2003). Although children generated significantly fewer words than adults during a post MRI assessment, indices of functional lateralization based on the same task did not correlate with performance (Gaillard et al., 2003). Another study measured functional lateralization for word generation in over 300 neurotypical adults using FTCD and found no association between language lateralization and verbal fluency, number of fluently spoken foreign languages, academic achievements, or artistic talents (Knecht et al., 2001). In the same study, Knecht and colleagues (2001) assessed general intelligence as measured by the WAIS and speed of linguistic processing based on a picture-word verification task in a subgroup of 21 adults; but again, neither of the two measurements correlated significantly with language laterality. Whether or not a strongly lateralized language network is truly beneficial therefore remains to be elucidated. Discrepancies in the reported findings could conceivably be due to any of several differences in methodology such as the studied population, applied image acquisition technique, language task used or data analysis methods.

5.1.3 Aims of this study

In this study, I aimed to address this issue by assessing language lateralization in neurotypical adults using three different non-invasive methods including VHF task, FTCD, and FMRI. The latter two were acquired while participants separately completed a verbal fluency task and a receptive semantic matching task. In addition, standardized tests of language abilities and intelligence were administered to each participant to elucidate the behavioural relevance of hemispheric specialization. Two groups of well-matched healthy volunteers with either typical (left) or atypical (right or bilateral) language lateralization as determined by FTCD were included in this study. My specific aims were i) to investigate differences in brain activity between typically and atypically lateralized individuals ii) to compare patterns of functional lateralization associated with expressive and more receptive language tasks between typical and atypical participants; iii) to test whether FTCD, FMRI and VHF measure language lateralization concordantly; iv) to examine the relationship between different measures of functional language lateralization and behaviour.

5.2 Methods

Two hundred and fifteen neurotypical adults initially completed an assessment of functional language lateralization using FTCD (see chapter 4). A subset of 32 volunteers participated in this study, which comprised two sessions: an FMRI scan (60 minutes) and a follow-up assessment (150 minutes). The latter took place one to 31 days (*M* = 11.8, *SD* = 9.12) after the scan and included a neuropsychological assessment and the completion of the visual half-field task (VHF).

5.2.1 Participants

All participants who showed right-lateralized or bilateral activation during word generation, as previously assessed by FTCD, were asked to take part in this study. Out of the 21 atypically lateralized volunteers, 16 individuals agreed to take part and fulfilled all MRI safety criteria (7 women and 9 men, M_{age} = 25 years, SD_{age} = 5 years). In addition, 16 individuals with typical language lateralization based on the same FTCD assessment were recruited (7 women and 9 men, M_{age} = 25 years, SD_{age} = 5 years). Typically and atypically lateralized participants were matched for age, gender and handedness. All participants were native speakers of English with normal or corrected-to-normal vision and no reported history of neurodevelopmental, neurological or psychiatric disorders. Based on participants' self-reports the sample included 20 right-handers (10 atypical) and 12 left-handers (6 atypical). Written informed consent was obtained from all volunteers, who were compensated for their participation according to the time they spent on the study. The study was approved by the Medical Sciences Inter Divisional Research Ethics Committee of the University of Oxford (*MSD-IDREC-C1-2014-109)*.

5.2.2 Neuropsychological assessment

All participants underwent a neuropsychological evaluation during which verbal and non-verbal IQ, receptive vocabulary, reading speed, and relative hand skill was assessed. Each session lasted about 2 hours and included the following tests:

Intelligence (IQ). All four subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler & Chen, 1999) were administered to assess verbal and nonverbal cognitive functions. As 'vocabulary' and 'similarities' are thought to measure word knowledge, verbal concept formation, and reasoning, the two subtests were used to obtain an index of verbal IQ (VIQ). 'Block design' and 'matrix reasoning', which are designed to capture the ability to analyse and synthesise abstract visual stimuli, were used to estimate performance IQ (PIQ). The combination of all four subtests yielded a full-scale IQ (FIQ). One participant was familiar with the administration of the WASI. Thus, the four subtests were substituted with their equivalent subtests from the Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1981), namely the vocabulary and similarities to approximate VIQ as well as block design and picture completion for PIQ.

Language. The Test Of Word Reading Efficiency (TOWRE; Torgesen, Wagner, & Rashotte, 1999) was used to assess word-level reading skills in all participants quickly and reliably. An individual's ability to pronounce printed words (Sight Word Efficiency) and phonemically regular nonwords (Phonemic Decoding Efficiency) was measured using two forms of each subtest (Form A and B). In this test, the each participant was asked to read aloud as many words as possible within 45 seconds.

Words increased in difficulty from simple single-syllable to multisyllabic words progressively. Raw scores, which represent the number of correctly read words or nonwords within the given time limit, were converted into standard scores. In addition, receptive vocabulary was examined using the British Picture Vocabulary Scale II (BPVS-II; Dunn et al., 1997). Participants were presented with a choice of four pictures on an easel, and asked to indicate the picture of the word spoken by the examiner. Raw scores were calculated by subtracting the number of errors from the ceiling item, which is the last item in the ceiling set (i.e. eight or more responses were wrong per set of items). Because no norms were available for individuals older than 16 years raw scores (X) were converted into standard scores ($z = (X - M_{\text{data}}) / SD_{\text{data}}$) based on the group tested; with a mean of 100 and a standard deviation of 15 ($z_{100} = 100 + 15 * z$).

Handedness. Peg-moving was used as a test of relative hand skill. The set-up and dimensions of the pegboard were identical to those described by Annett (1985). Briefly, participants stood in front of the pegboard, which was placed on a table of convenient height, and were asked to move ten dowelling pegs from the back row of the pegboard to the front row. For each trial, pegs were picked up and placed one by one as fast as possible using one hand. If a peg was dropped, the trial was restarted. All participants completed five trials with their right hand (moving pegs from right to left) and five trials with their left hand (moving pegs from left to right) - alternating between hands. Time was measured from touching the first peg till releasing the last one; it was used to calculate quotients of relative hand skill ($(L-R)/(L+R)*100$), with negative numbers indicating a faster performance (indicating higher skill) on left-hand trials and positive numbers a faster performance on right-hand trials. In addition, handedness scores based on an abbreviated version of the Edinburgh Handedness

Inventory (EHI; Oldfield, 1971) as well as a left-right hand bias obtained during a reaching task (QHP) were available for each participant (see Chapter 4 for details).

5.2.3 *Visual half-field task*

Stimuli and procedure of the visual half-field (VHF) picture naming task was adopted from Hunter and Brysbaert (2008) and is illustrated in *Figure 5.1*. Before the start of the experimental blocks, each participant completed eight practice trials. The whole experiment took about 20 minutes from setting up and explaining the task to presenting all practice and test trials.

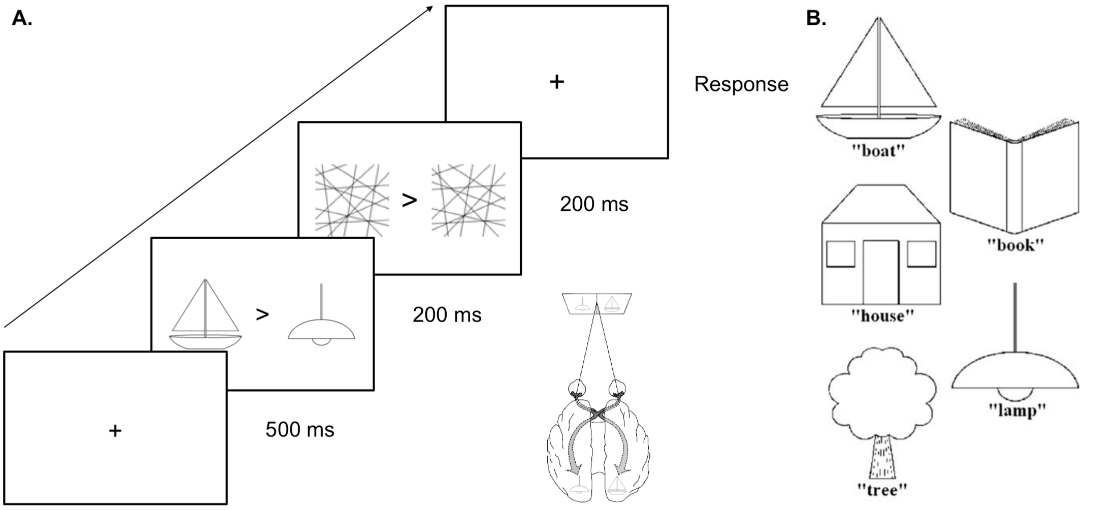


Figure 5.1. *Stimuli and procedure of the visual half-field (VHF) picture naming task. An example sequence of the VHF task (A) and the used stimuli (B) are presented. The latter consisted of five symmetrical line drawings, which had to be named repeatedly in the task. Adapted from "Visual half-field experiments are a good measure of cerebral language dominance if used properly: evidence from fMRI" by Z. R. Hunter and M. Brysbaert, 2008, Neuropsychologia, 46, p. 320. Copyright 2007 by Elsevier Ltd.*

Experimental design. In a quiet testing room, participants were seated comfortably in front of a computer monitor at a viewing distance of ~60 cm. A cross was presented in the centre of the screen and participants were instructed to fixate the cross at the beginning of each trial. After 500 ms the cross was replaced by an arrow pointing to the left or right side and two pictures appeared simultaneously for 200 ms at a visual angle of 1.91° from fixation. The pictures were presented in a bilateral fashion, meaning that one line drawing occurred in the left VHF and the other one occurred simultaneously in the right VHF. While the arrow stayed on the screen, both pictures were masked with a cluster of randomly oriented lines to avoid after-images. Masks matched the pictures in sizes and were presented for 200ms. Participants were asked to name aloud the picture indicated by the arrow as quickly and accurately as possible. A voice key was used to record the onset of speech as reaction time and to trigger the next trial.

Stimuli. Five symmetrical line drawings including a boat, a book, a house, a lamp, and a tree, were presented repeatedly in a randomized order. Each picture represented a monosyllabic word and was shown 16 times within the left and 16 times within the right VHF leaving the participant with a total of 160 images to name.

LI calculation. Before calculating LI_{VHF}, the following trials were excluded: naming correction or errors (3.22%), voice key failures (0.33%) and trials with RTs less than 200ms or greater than 1500ms (5.55%). Thus, mean RTs for the left and right VHF were based on 90.9% of all trials and used for calculating individual LI_{VHF} as described by Hunter & Brysbaert (2008): $LI_{VHF} = (\text{left VHF}) - (\text{right VHF})$. Resulting LI_{VHF} values were used to determine each participants' VHF advantage, with LI_{VHF} of more than 10 ms indicating a right VHF advantage (i.e. typical) and those less than -10 ms indicating a left VHF advantage (i.e. atypical). Values in between were classified as 'no advantage' or bilateral.

5.2.4 FMRI tasks

During their functional brain scan, participants completed three different tasks that are known to robustly activate cortical language areas, namely auditory naming, word generation, and semantic matching based on the pyramids and palm tree test. The latter two tasks were designed to be as comparable as possible to the ones used with FTCD. Participants were briefed about the imaging protocol 90 minutes prior to his/her session, during which they practiced a short versions of each task outside the scanner.

Auditory naming. The auditory naming paradigm (AN) was based it on the Auditory Responsive Naming task (Bookheimer et al., 1998) and identical to the one used by Badcock and colleagues (2012), who adapted this task for the use in FMRI. Through MRI compatible in-ear headphones (model S14, Sensimetrics) participants heard short definitions of a high frequency noun and were required to silently generate the described word (e.g. the participant heard ‘shines in the sky’ and thinks of ‘sun’). A reversed speech condition was included to control for auditory stimulation. For this, digitally reversed recordings of the short definitions were used to create meaningless strings of auditory stimulation while maintaining the spectrotemporal complexity. Participants were instructed to passively listen to reversed speech stimuli. During baseline, no auditory stimuli were presented. Speech, reversed speech, and baseline condition were presented in blocks of 30 seconds and repeated four times in a pseudo-randomized order. Thus, no condition occurred consecutively. Within each block of speech or reversed speech, six stimuli were presented - one every 5 seconds.

Word generation. For the word generation task (WG), participants were required to generate as many words as possible beginning with a letter that was displayed in the middle of the screen. To minimize motion artefacts associated with speaking, participants were instructed not to overtly generate target words, but instead to ‘think of them inside their heads’. Twelve different letters were selected according to their associative frequencies (Borkowski, Benton, & Spreen, 1967; high = A, S, M, B; medium = E, G, N, O; low = U, K, V, J;) and presented in a randomized order. Each word generation block lasted 15 s and was followed by a 15 s rest interval during which a plus sign was displayed at screen centre. Participants were asked to relax and keep their gaze fixed in the middle of the screen. Stimuli were in white over a black background and projected on a screen that was placed behind the scanner and visible to all participants through a mirror mounted on the head-coil.

Pyramids and palm trees task. The picture version of the pyramids and palm trees test (PPT) was employed as a more receptive semantic matching task. Each stimulus comprised three black and white pictures, one above the central fixation point and two below. Participants were asked to indicate with a button press which of the bottom pictures was related to the top one. Responses were made with the left and right thumbs using an MRI compatible button box, which was held by the subject like a gamepad (i.e. in both hands) throughout the scan.

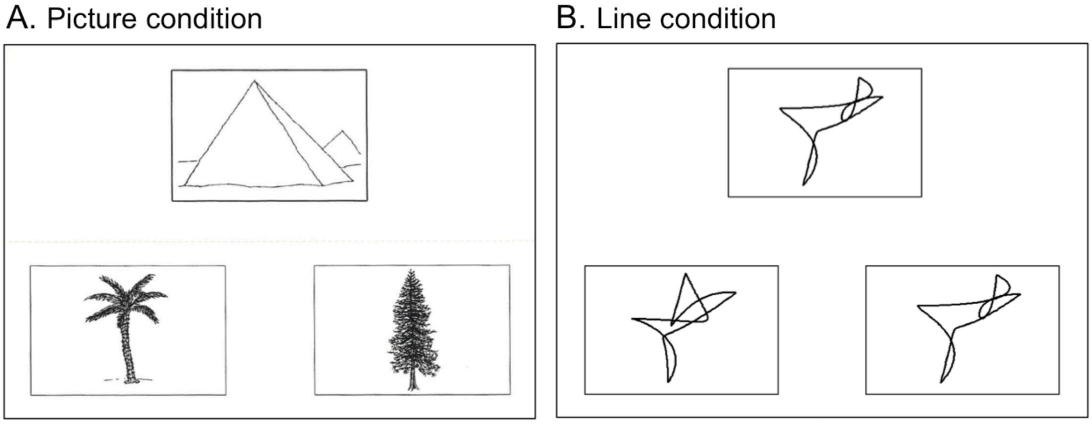


Figure 5.2. *Examples of stimuli used in the activation task (A) and control condition (B) of the pyramids and palm trees (PPT) paradigm. A. Picture condition: semantic decision on pictures of familiar objects. B. Line condition: perceptual matching of unfamiliar drawings of lines.*

A perceptual condition was included as a control for the visual stimulation. In this condition, each stimulus comprised three drawings of lines in a random array. Participants had to indicate whether the drawing on the left or right was perceptually identical to the one above. The picture and line conditions and a baseline condition during which no visual stimulus occurred were presented in 20 s blocks and repeated six times (counterbalanced). The order was pseudo-randomized so that no condition was shown twice in a row. Each block of the picture and line conditions comprised eight stimuli that were displayed every 2.5 s.

All three experiments were performed using Presentation® software (Version 16.3, Neurobehavioral Systems, Inc., Berkley, CA, www.neurobs.com) and for each activation block, the stimulus onset was synchronised with the scanner.

5.2.5 FMRI acquisition and analysis

Data were collected at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR, University of Oxford) using a 3-T Siemens Trio scanner with a 32-channel head coil. A high-resolution T1-weighted MPRAGE was acquired in each participant for image registration (TR = 2040 ms, TE = 4.7 ms, flip angle = 8°, 192 transverse slices, 1-mm isotropic voxels). During each language task, blood oxygen-level dependent changes were measured using whole-head T2*-weighted echo-planar images (EPI; TE = 30 ms, flip angle = 90°) that were acquired every 3 s for 6 min (120 volumes). Each volume comprised 48 3-mm axial slices with an in-plane resolution of 3 x 3 mm. The order of the tasks was counter-balanced across participants.

First-level analysis. Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) as part of FSL (FMRIB Software Library: http://www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Preprocessing of all functional data followed standard procedures and consisted of head motion correction through realignment to the middle volume of the 4D data set, skull stripping using BET (Brain Extraction Tool), spatial smoothing applying a 6 mm full-width-half-maximum Gaussian kernel, and high-pass temporal filtering equivalent to 90 s to remove low-frequency fluctuations. To improve image registration, fieldmaps were first used to unwarp the functional data employing PRELUDE (Phase Region Expanding Labeller for Unwrapping Discrete Estimates) and FUGUE (FMRIB's Utility for Geometrically Unwarping EPI; Jenkinson, 2003). EPIs were then non-linearly registered via the subject’s T1-weighted structural scan to the MNI-152 template using FNIRT (FMRIB’s Non-linear Image Registration Tool). Next, task-based statistical parametric maps were computed for each experiment and its conditions using a general linear model (GLM) based on the experimental time course, convolved with a double-gamma function and its temporal derivatives. Six motion correction parameters (translations and rotations in x, y and z) were included as covariates of no interest in the analyses. For WG, PPT, and AN the main contrast of interest was word generation compared to rest, semantic matching compared to perceptual matching (pictures > lines), and responsive naming compared to passive listening (speech > reversed speech), respectively.

Higher-level analysis. For each of these contrasts, group averages and differences between typically and atypically lateralized participants were calculated using FMRIB’s Local Analysis of Mixed Effects (FLAME, Woolrich et al., 2004). Statistical maps were cluster-thresholded at $Z > 3.1$, and clusters were reported that survived a statistical test for extent ($p = .05$, fully corrected for multiple comparisons). Standard group analyses (i.e. mean group effects) were complemented with measures of inter-subject variability by generating probabilistic overlap maps. Overlap maps were used to visualise consistency in patterns of activation and can be considered as a measures of reliability across participants (Specht, Willmes, Shah, & Jäncke, 2003). For each task and each participant, z-statistics were thresholded voxel-wise at $Z > 4.5$ ($p < .000005$ uncorrected for WG (word generation > rest) or at $Z > 3.1$ ($p < .001$ uncorrected) for PPT (pictures > lines) and AN (speech > reversed speech), and registered to MNI standard space. Resulting images were then binarized by assigning each voxel a 1 or 0 depending on whether the voxel exceeded the statistical voxel-wise threshold or not. These binary maps were summed up across typically or atypically lateralized participants, to obtain an image showing the spatial consistency in activation across participants.

LI calculation. The degree of hemispheric specialization for word generation, semantic matching, and auditory naming was assesses by calculating laterality indices (LI_{FMRI}) using the LI toolbox (Wilke & Lidzba, 2007) in SPM8. This toolbox employs a weighted-bootstrapping algorithm to generate threshold-free LI values. The approach is based on the concept of laterality curves that iteratively explore LIs at increasing thresholds, and has been described in detail by Wilke and Schmithorst (2006). Briefly, the contrast image of interest was thresholded and masked to obtain voxel values for the left and right side. These values were stored in a vector that was used to generate n bootstrapped resamples (default: 100). LI values were calculated for all possible combination and plotted in a histogram showing LIs on the x- and frequency of occurrence on the y-axis. The central 50% were averaged to compute the overall LI at the given threshold. This process was repeated for each threshold (default: 20; equally sized intervals from 0 to the maximum value in the masked image) and the resulting distribution of overall LIs was displayed in a histogram. To account for the 'meaningfulness' of values obtained from different thresholds, a weighted mean was calculated by using the corresponding threshold as a weighting factor for each data point. Weighted LIs were calculated for individual z-statistic images of the following contrasts: word generation > rest (WG), pictures > lines (PPT), and speech > reversed speech (AN). Based on the area of interest, a frontal, temporal, or combined frontal-temporal mask was applied to extract the voxel values used for LI calculation. Masks were based on the standard LI toolbox templates that covered the corresponding lobules bilaterally while excluding the medial wall 5 mm from the centre of the image. As for my previous study (Chapter 3), the FMRI laterality index was defined as: $LI_{FMRI} = (L - R)/(L + R)$, corresponding to LIs based on FTCD (LI_{FTCD}), positive values reflected left lateralisation and negative ones right lateralization. Values of $-0.2 \leq LI \leq 0.2$ were considered indicative of bilateral representations (Wilke et al., 2006).

5.2.6 Statistical analysis

All statistical analyses were conducted using SPSS (www.ibm.com/software/analytics/spss). Unless otherwise stated, Shapiro-Wilk's test was used to determine whether dependent variables were normally distributed, outliers were identified by visual inspection of boxplots (± 3 box-lengths) and Bonferroni correction was applied for multiple post-hoc comparisons. If applicable, Levene's test, Box's M test, and Mauchly's test were used to assess homogeneity of variances, homogeneity of covariances, and sphericity, respectively. Violations of the latter were addressed by applying Greenhouse-Geisser correction. If there were only two levels of repeated measures, sphericity was not taken into account.

Comparison of FMRI laterality indices for typical and atypical participants. A three-way mixed ANOVA with group (typical vs. atypical) as a between-subjects factor and brain area (frontal vs. temporal) as well as task (WG vs. PPT vs. AN) as within-subjects factors was run to examine differences in mean LI_{FMRI}. Based on the assumption that WG, PPT, and AN involve different parts of the cortical language network more strongly, this analysis aimed to address the following questions: i) Do typical and atypical participants differ in their pattern of functional lateralization? ii) Does functional lateralization differ between frontal and temporal areas? iii) Does functional lateralization differ among the three activation tasks? iv) Are group differences more evident in one brain area than the other, or in one task more than the others? v) Do the tasks differ in their lateralization for frontal and temporal lobe activation? vi) Are group differences evident in one task more than the others in different brain areas? To further investigate the relationship between LI_{FMRI} values associated with the three language paradigms bivariate correlations were performed. To account for the skewness in LI_{FMRI} data, Spearman's rho was calculated.

Comparison of laterality indices obtained by FTCD, FMRI, or VHF. To examine differences in mean LI_{FMRI} values associated with each method, a two-way mixed ANOVA with group (typical vs. atypical) as between-subjects factor and method (FTCD vs. FMRI vs. VHF) as within-subjects factor. Because WG was used to determine language lateralization using FTCD, I chose to include LI_{FMRI} associated with WG, too. LI_{FMRI} values were calculated based on activation within both frontal and temporal lobes corresponding roughly to the MCA vascular territory. Next, non-parametric correlations were run to explore the relationship between LI values obtained by FTCD, FMRI, and VHF. Significant associations were further examined using a multiple regression analysis with LI_{FTCD} and LI_{VHF} as predictors of LI_{FMRI}. Lastly, I calculated the number and percentage of typically (left) and atypically (non-left) lateralized participants for each method to assess whether FTCD, FMRI, and VHF provide concordant information. As WG is the gold standard for evaluating laterality with FTCD, I focussed my analysis on the following comparisons: i) $FTCD_{WG}$ versus $FMRI_{WG}$ versus VHF, ii) $FTCD_{WG}$ versus $FMRI_{PPT}$ versus VHF, and iii) $FTCD_{WG}$ versus $FMRI_{AN}$ versus VHF. Cochran's test was used to determine whether the number of participants with typical and atypical lateralization differed among the three methods.

Relationship between language laterality and language abilities. Mann-Whitney U tests were used to investigate differences between typical and atypical participants in behavioural test scores obtained during neuropsychological testing. Non-parametric correlations between LIs obtained by FTCD, FMRI, or VHF and scores of standardized language tests including verbal IQ (WASI), sight word reading (TOWRE-sw), phonetic decoding (TOWRE-pd) and receptive vocabulary (BPVS-II) were computed to determine whether functional lateralization was associated with language abilities.

To detect differences between 16 typically and 16 atypically lateralized participants at 80% power and 5% alpha (one-tailed assuming lower values in the atypical group), the effect size required, needed to exceed 0.88. In other words, statistical comparisons would be sensitive only to large effect sizes.

5.3 Results

All participants were initially classified as typically (left) or atypically (non-left) lateralized based on FTCD measurements during WG. The two groups were well matched for age (*M* ± *SD*: TYP 24.6 ± 5.18 years, ATYP 25.3 ± 5.20 years; independent t-test, *p* = .736), gender (9 men and 7 women in each group), and handedness based on self-report (i.e. writing hand; 10 right and 6 left handers in each group). For each participant, demographic data and LIs associated with the different methods and tasks are displayed in *Table 5.1,* which revealed some interesting data. Firstly, members of the typical group, who were classified as left-lateralized using FTCD in combination with WG, were reliably left-lateralized across the three MRI paradigms and the VHF task - with the exception of a couple of participants who were classified as bilateral based on FMRI activation during PPT or on the VHF task, and one participant who was classified as right-lateralized on the latter. Secondly, the members of the atypical group who were classified as bilateral by FTCD were most frequently classified as left-lateralized using FMRI or the VHF task.

Table 5.1. *Demographic data and laterality indices (LI) based on functional transcranial Doppler ultrasound (FTCD), functional magnetic resonance imaging (FMRI), and visual half-field task (VHF) for typically and atypically lateralized participants*[a].

Group	**ID**	**Age**	**Sex**	**Hand**	**FTCD**		**FMRI**[b]						**VHF**	
							WG		PPT		AN			
					LI	Cat	LI	Cat	LI	Cat	LI	Cat	LI	Cat
ATPY	01	20	M	Left	-2.69	R	-0.20	R	-0.72	R	-0.66	R	-33.6	R
ATPY	02	28	M	Right	-2.40	R	0.27	L	0.86	L	0.80	L	33.1	L
ATPY	03	28	M	Right	-2.30	R	-0.13	Bi	-0.75	R	-0.73	R	-10.3	R
ATPY	04	20	F	Right	-2.21	R	0.51	L	-0.71	R	-0.70	R	4.60	Bi
ATPY	05	33	M	Left	-1.40	R	0.48	L	-0.62	R	-0.50	R	21.9	L
ATPY	06	20	F	Right	-1.39	R	0.67	L	-0.24	R	0.28	L	36.6	L
ATPY	07	27	F	Left	-1.24	R	-0.22	R	-0.58	R	-0.33	R	-14.0	R
ATPY	08	34	M	Left	-1.16	R	0.55	L	0.15	Bi	0.39	L	20.0	L
ATPY	09	20	F	Right	-1.05	R	-0.23	R	-0.11	Bi	0.02	Bi	-86.1	R
ATPY	10	20	M	Right	-1.18	Bi	0.15	Bi	0.42	L	0.46	L	91.9	L
ATPY	11	26	M	Left	-0.75	Bi	0.56	L	0.24	L	0.12	Bi	5.70	Bi
ATPY	12	23	F	Right	-0.55	Bi	0.76	L	0.32	L	0.54	L	14.5	L
ATPY	13	23	M	Left	0.61	Bi	0.81	L	0.63	L	0.87	L	20.6	L
ATPY	14	35	M	Right	0.73	Bi	0.28	L	0.23	L	0.31	L	21.0	L
ATPY	15	24	F	Right	0.81	Bi	0.81	L	0.56	L	0.78	L	2.52	Bi
ATPY	16	23	F	Right	1.34	Bi	0.71	L	0.79	L	0.62	L	3.90	Bi
		25.3	**7F**	**6 Left**	**-0.93**		**0.36**		**0.03**		**0.14**		**8.27**	
TYP	17	23	F	Right	1.18	L	0.89	L	0.02	Bi	0.54	L	20.9	L
TYP	18	30	M	Right	1.43	L	0.65	L	0.30	L	0.66	L	76.4	L
TYP	19	29	M	Right	2.11	L	0.21	L	0.41	L	0.76	L	26.4	L
TYP	20	20	F	Left	2.39	L	0.75	L	0.47	L	0.68	L	21.0	L
TYP	21	22	M	Left	2.43	L	0.45	L	0.49	L	0.71	L	61.9	L
TYP	22	19	F	Left	2.82	L	0.55	L	0.18	Bi	0.77	L	37.4	L
TYP	23	34	M	Right	2.89	L	0.76	L	0.78	L	0.77	L	60.4	L
TYP	24	23	F	Left	3.24	L	0.74	L	0.03	Bi	0.75	L	26.1	L
TYP	25	34	M	Right	3.26	L	0.85	L	0.70	L	0.65	L	39.8	L
TYP	26	23	M	Left	3.53	L	0.90	L	0.71	L	0.83	L	3.20	Bi
TYP	27	31	M	Right	3.80	L	0.76	L	0.41	L	0.30	L	-5.80	Bi
TYP	28	20	F	Right	3.95	L	0.33	L	0.48	L	0.56	L	36.7	L
TYP	29	23	F	Right	4.38	L	0.74	L	0.23	L	0.62	L	106.8	L
TYP	30	23	M	Left	4.78	L	0.70	L	0.38	L	0.75	L	35.5	L
TYP	31	20	M	Right	5.50	L	0.74	L	0.31	L	0.68	L	40.1	L
TYP	32	20	F	Right	6.43	L	0.49	L	0.35	L	0.90	L	-48.0	R
		24.6	**7F**	**6 Left**	**3.38**		**0.66**		**0.39**		**0.68**		**33.7**	
P value		0.74	1.00	1.00	0.000		0.010		0.024		0.001		0.056	

Note: Data are shown for individuals and the mean scores were calculated for the group of typically (TYP) and atypically (ATYP) lateralized participants separately. The order of participants is from most right-lateralized to most left-lateralized based on their LIFTCD values.

[a] Participants were initially classified as left-lateralized (L), right-lateralized (R), or bilateral (Bi) based on LI values obtained by FTCD during word generation (note that the 95% confidence interval (CI) around each individual's LI was used to determine the corresponding LI category (L, R, Bi). It is therefore possible that the magnitude of the LI value for a person classified as Bi would be greater than one classified as L or R because the range of CIs crossed zero).

[b] LI_{FMRI} values were calculated based on activity within frontal and temporal lobes during word generation (word generation > rest, WG), pyramids and palm trees (pictures > lines, PPT), and auditory naming (speech > reversed speech, AN).

Thirdly, only the atypical group members originally classified as right-lateralized using FTCD (WG) were classified as right-lateralized based on one or more of the other laterality measures (with the aforementioned exception in the typical group). However, the classification among measurements in participants who show right-lateralized language function was quite variable. In the remainder of the result section, I will address some of these observations using statistical analyses that were chosen to answer a number of different questions related to the aims of this study

5.3.1 Do people with typical and atypical language lateralization show different patterns of brain activity?

Group averages of activation based on WG (word generation > rest), PPT (pictures > lines), and AN (speech > reversed speech) for participants with typical and atypical language lateralization are presented in *Figure 5.3*.

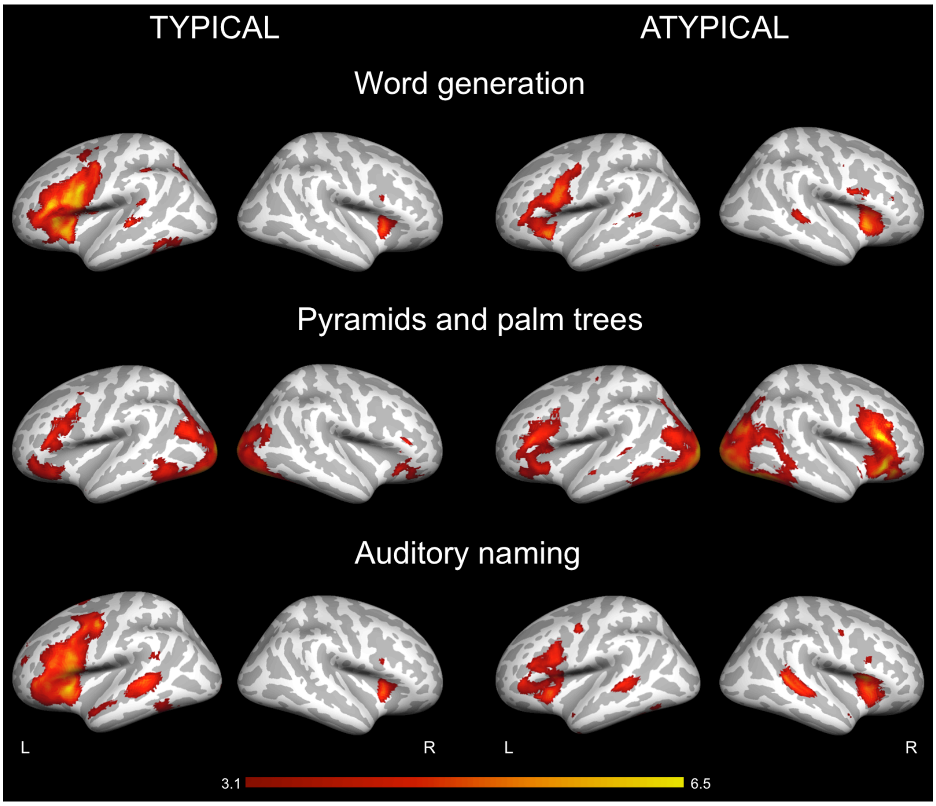


***Figure 5.3**. Areas of significant group activity are shown for the contrast word generation > rest, pictures > lines), and speech > reversed speech for word generation (top), pyramids and palm trees (middle), and auditory naming (bottom), respectively. Statistical maps (cluster threshold at Z > 3.1; p < 0.05, corrected for multiple comparisons at the whole-brain level) are superimposed on to the MNI standard brain for typically and atypically lateralized participants.*

Table 5.2. *Peak coordinates and extent of significant clusters of activity during word generation (WG), pyramids and palm trees (PTT), and auditory naming (AN).*

	Clusters of activation based on Z > 3.1 (*p* = .05)							
	#	*X*	*Y*	*Z*	*Max Z*	*Cluster size*	*Hemisphere*	*Description*
WG: Word generation > Rest								
ATYP	1	-32	24	0	5.76	4390	L	Inferior frontal cortex
	2	34	18	2	5.71	2153	R	Inferior frontal cortex
	3	-6	18	42	5.33	3511	L	Superior frontal cortex (pre SMA) extending bilaterally)
	4	24	-66	-48	4.86	532	R	Cerebellum
TYP	1	-44	26	14	6.41	32432	L	Inferior frontal cortex (extended)
PPT: Picture > Lines								
ATYP	1	4	-90	0	6.96	34451	R	Occipital cortex extending to posterior temporal cortex
	2	48	28	14	6.71	4061	R	Inferior frontal cortex
	3	-56	32	24	5.16	3029	L	Inferior frontal cortex
	4	2	24	50	5.00	816	R	Superior frontal cortex (pre SMA) extending bilaterally
TYP	1	-36	-42	-22	6.13	23279	L	Inferior temporal cortex extending to occipital lobe bilaterally
	2	-36	10	34	4.78	2829	L	Inferior frontal cortex
	3	32	30	-10	4.29	337	R	Orbitofrontal cortex
A > T	1	48	26	16	4.81	533	R	Inferior frontal cortex
AN: Speech > Reversed speech								
ATYP	1	42	16	10	5.58	5608	R	Inferior frontal cortex (extended)
	2	-30	22	4	5.17	3551	L	Inferior frontal cortex
	3	-56	-36	6	5.24	2126	L	Superior temporal cortex
	4	44	-42	8	5.30	893	R	Superior temporal cortex
	5	-6	-78	-24	4.08	448	L	Cerebellum extending bilaterally
TYP	1	-42	-22	14	5.95	13117	L	Inferior frontal cortex (extended)
	2	36	-58	-28	5.16	3425	R	Cerebellum
	3	-8	4	62	5.48	2685	L	Superior frontal cortex (pre SMA) extending bilaterally
	4	30	20	8	5.23	826	R	Inferior frontal cortex
	5	-30	52	28	4.41	336	L	Frontal pole

Note: Clusters for the contrasts *word generation > rest (WG), pictures > lines (PPT)* and *speech > reversed speech (AN)* were formed by thresholding at Z > 3.1, p = .05 (corrected). There were no significant differences between typical and atypical participants in activation based on WG and AN.

In the group of typically lateralized participants, the expected network of brain regions involved in language processing was activated for each task (*Table 5.2*). This included large portions of the left IFG extending to the anterior insula, the pre-supplementary motor area (preSMA), the dorsal striatum and the anterior cerebellum bilaterally. In addition, WG and AN significantly activated portions of posterior temporal lobe (superior and inferior), while PPT evoked activity in the occipital cortex bilaterally. Smaller portions of the right IFG, in particular the anterior insular and frontal opercular cortex, were significantly activated in each task. Across tasks, the atypical group revealed similar patterns of brain activity to the typical group comprising IFG, STG and occipital cortex bilaterally. Visual inspection of the contrasts, however, suggested that compared to the typical group, activation in the left IFG was less extensive, and activation in the right homologue was more extensive (*Figure 5.3*). To examine these differences between groups, I calculated statistical contrasts within the GLM. Using a threshold of Z > 3.1 (p = .05, cluster-corrected), significant differences were only found for patterns of activation associated with PPT. Relative to participants with typical language lateralization, the atypical group showed significantly increased activity in a confined cluster centred on the right IFG, pars opercularis (*Figure 5.4*). There were no areas of reduced activation in atypically compared to typically lateralized participants.

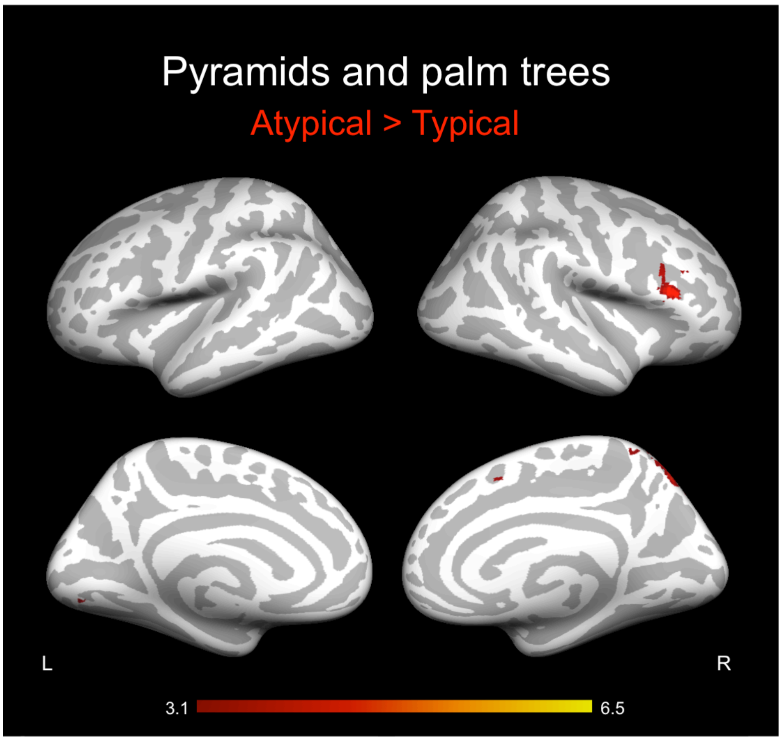


Figure 5.4. *Group differences in brain activity associated with the pyramids and palm trees task (PPT) for the contrasts pictures > lines. Statistical maps are thresholded at Z > 3.1 (p = .05, cluster-corrected) and superimposed on to the MNI standard brain. Areas in blue show significantly reduced and areas in red significantly increased activation in atypical compared to typical participants.*

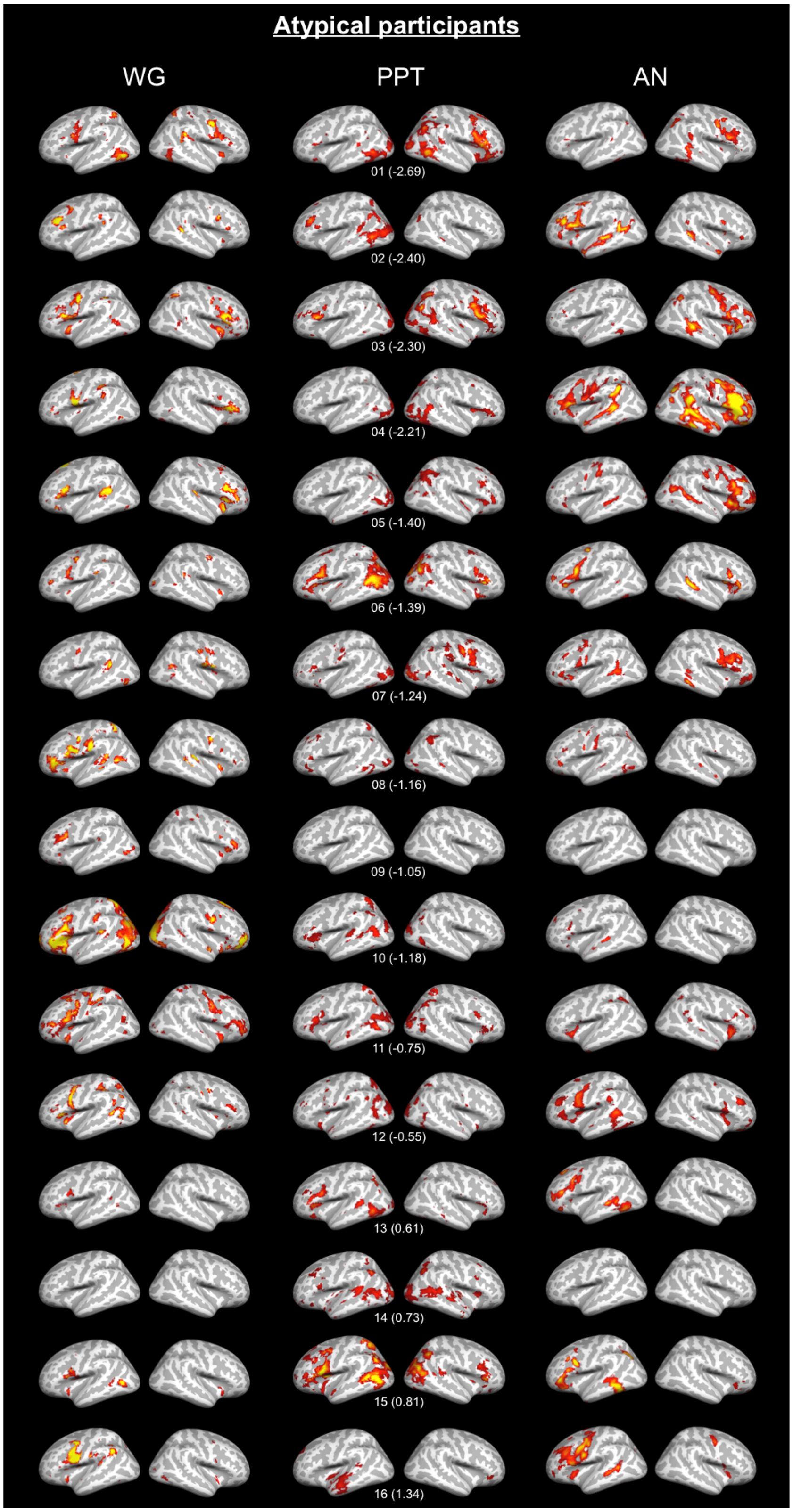


Figure 5.5*. Individual activation patterns associated with word generation (WG) semantic matching (PPT) and auditory naming (AN) for the atypical group (N = 16). Statistical maps (superimposed on to the MNI standard brain) are shown for the contrasts word generation > rest (left), pictures > lines (middle) and speech > reversed speech (right) thresholded at Z > 4.5 for WG and at Z > 3.1 for PPT as well as AN. Participants are ordered according to their degree of language lateralization, as assessed by FTCD (WG), i.e. from the most strongly right lateralized (lowest* LI_{FTCD}*) to the most bilateral (*LI_{FTCD} *closest to zero) participant. Displayed subject IDs and* LI_{FTCD} *values correspond to the ones shown in Table 5.1 (page 168).*

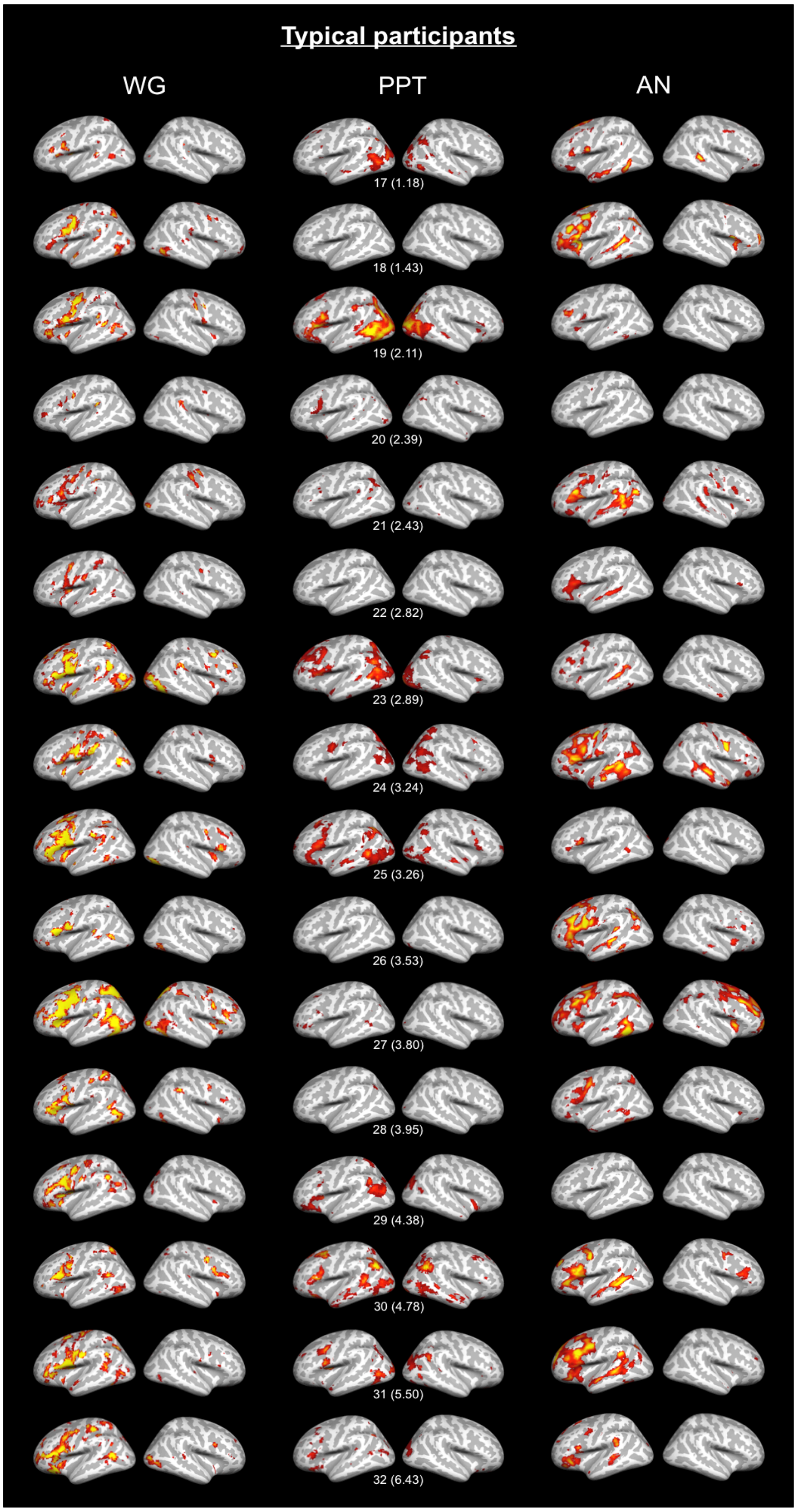


Figure 5.6. *Individual activation patterns associated with word generation (WG) semantic matching (PPT) and auditory naming (AN) for the typical group (N = 16). Statistical maps (superimposed on to the MNI standard brain) are shown for the contrasts word generation > rest (left), pictures > lines (middle) and speech > reversed speech (right) thresholded at Z > 4.5 for WG and at Z > 3.1 for PPT as well as AN. Participants are ordered according to their degree of language lateralization, as assessed by FTCD (WG), i.e. from the least strongly left lateralized (lowest* LI_{FTCD}*) to the most strongly left lateralized (highest* LI_{FTCD}*) participant. Displayed subject IDs and* LI_{FTCD} *values correspond to the ones shown in Table 5.1 (page 168).*

Because group analyses compare the averages of neural activity that is spatially coincident across participants, I also examined individual activation maps to investigate inter-subject variability. As shown in *Figure 5.5* and *Figure 5.6*, significant clusters of activation varied across participants in in spatial extent, location and height of statistic indicating considerable heterogeneity for each task. A number of interesting observations can be made regarding these images. Firstly, across participants the pattern of activity was more variable in terms of spatial location in the right hemisphere than in the left hemisphere; this was true even in the atypical group. Secondly, in participants with strongly left-lateralized language function the extent and reliability (statistical height) of the evoked response was consistently seen in the left IFG. Lastly, the variability within subjects across tasks was considerable - although these are tasks with different language requirements, one might have expected a set of common areas across tasks to be evident in the same participants.

Probabilistic overlap maps, which display for each voxel the number of individuals who showed a significant (see methods) word generation > rest (WG), pictures > lines (PPT), or speech > reversed speech (AN) response at that voxel, were generated to quantify and visualize this inter-subject variability (*Figure* 5.7).

In the typical group, WG revealed the voxels with the highest overlap across individuals: 15 out of 16 participants (93.8%) significantly activated the left IFG (pars opercularis) and preSMA bilaterally. A similar, but less consistent pattern was observed for AN, during which inferior frontal and medial frontal areas were significantly activated in 13 out of 16 participants (81.3%). The overlap of activation in the left IFG was further reduced for the PPT showing that only 9 out of 16 individuals (56.3%) with typical language lateralization recruited this brain region consistently. Instead, the highest coincidence of activity was detected in the left occipital pole, which was activated in 11 out of 16 participants (68.8%).

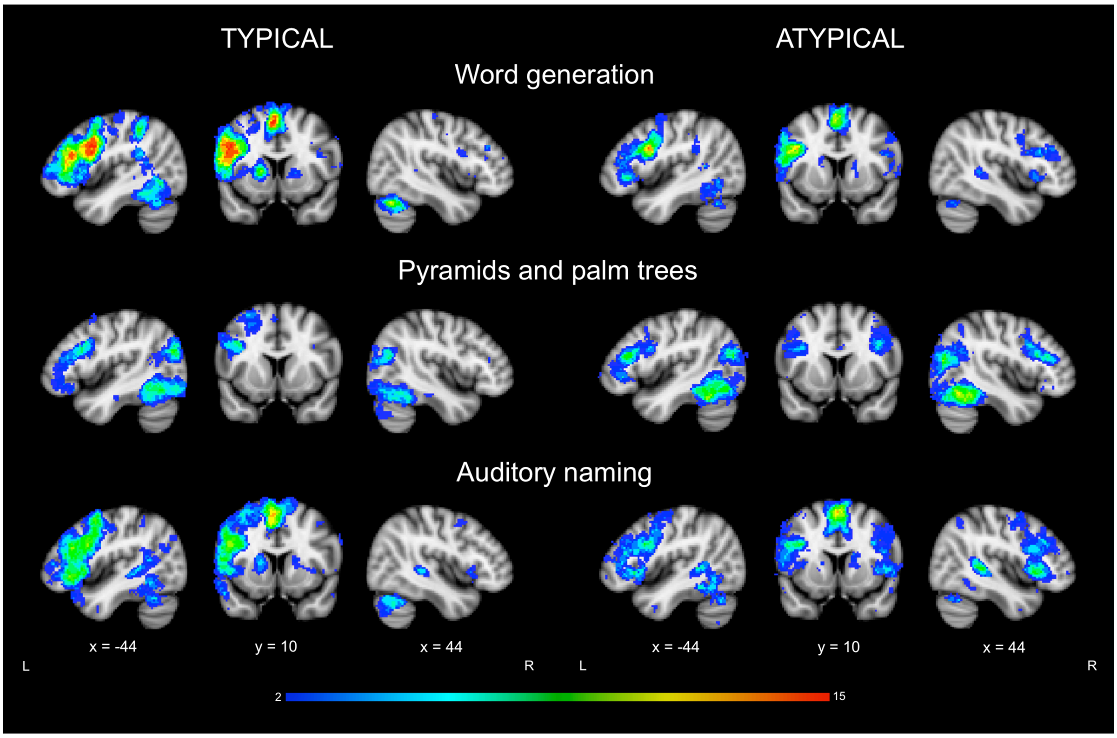


***Figure* 5.7**. *Probabilistic overlap maps for typically and atypically lateralized participants. Colours indicate the number of participants showing significant activation at Z > 4.5 for word generation (word generation > rest, top) or Z > 3.1 for pyramids and palm trees (pictures > lines, middle) and auditory naming (speech > reversed speech, bottom) in each voxel. The warmer the colour the more participants activated the area ranging from a minimum of 2 individuals (blue) to a maximum of 15 individuals (red). Maps are superimposed on to the MNI standard brain on a sagittal slice through the left and right hemisphere 44 mm from the midline and on an axial slice 10 mm above the bicommissural plane.*

In the atypical group, voxels with the greatest consistency were activated in 13 (81.3%), 10 (62.5%), and 9 (56.3%) out of 16 individuals for WG (left IFG), PPT (left occipital pole), and AN (preSMA) respectively. The pattern seen across task for the atypical group is one of bilateral activation and is consistent with the individual data shown in *Figure 5.6* indicating that this group contains individuals in whom activity was evoked during tasks in the left and the right hemispheres and often in both. Accordingly, the number of individuals who reliably activated the left hemisphere is reduced relative to the typical group and the number of individuals who activated the right hemisphere is increased. In the right hemisphere, the task on which fewest individuals showed evoked activity was the WG task, which is consistent with this task showing the least number of right-lateralized individuals according to MRI (see *Table 5.1*). This is interesting because this was the same task used to select the group using FTCD. Based on these data, this task is the least likely to show right IFG activation.

In summary, people who are typically and atypically lateralized for language showed apparent differences in their patterns of activation across tasks used in FMRI. However, there was considerable variation among individuals in the regions activated, the extent and the significance of activation. Data were more reliable in the typical group, especially in those strongly left-lateralized. The atypical group were considerably more mixed with respect to both the brain areas activated by language tasks within and between hemispheres. Furthermore, the brain areas activated by different tasks were surprisingly varied within individuals, lacking a common network or hub.

5.3.2 Do typically and atypically lateralized individuals show different patterns of activation on FMRI tasks?

The significance and degree of hemispheric lateralization for language, as assessed by FMRI, was further investigated by calculating LIs. To investigate differences in mean LI_{FMRI} values between typically and atypically lateralized participants, the three activation paradigms, and frontal versus temporal areas - as well as their possible interactions - I ran a three-way mixed ANOVA with group (typical vs. atypical) as a between-subjects factor and brain area (frontal vs. temporal) and task (WG vs. PPT vs. AN) as within-subjects factors. My main questions of interest were: do typical and atypical participants differ in their FMRI lateralization pattern? If so, are group differences more evident in one task or brain region than the other? And, does language lateralization differ within subjects for expressive and receptive language tasks?

Preliminary assumption testing revealed that there were no outliers in the LI data, as assessed by visual inspection of boxplots. With the exception of LI_{FMRI} values based on temporal lobe activation during WG in typically and atypically lateralized participants ($p > .05$) and those based on temporal activity during PPT and frontal activity during AN in the typical group ($p > .05$), data were not normally distributed. In addition, the assumption of homogeneity of variances ($p < .05$) was violated, as assessed by Levene's test. Because ANOVAs are considered fairly "robust" to deviations from normality and somewhat "robust" to heterogeneity of variance, if group sample sizes are equal, analysis was carried out regardless. Greenhouse-Geisser correction was applied to account for violations in sphericity of task ($\chi^2(2) = 12.8$, $p = .002$, $\varepsilon = .74$) and task x brain area ($\chi^2(2) = 17.2$, $p < .0005$, $\varepsilon = .69$).

The analysis revealed no statistically significant three-way interaction between group by task by brain area on language lateralization ($p = .46$). The two-way interaction between task and group approached, but did not reach statistical significance ($p = .071$). The remaining two-way interactions, brain area by group ($p = .25$) and task by brain area ($p = .46$) were non-significant, too. The main effect of group, however, showed significant differences between typically and atypically lateralized participants in mean LI_{FMRI} across frontal and temporal activation for the three paradigms ($F(1, 30) = 14.2$, $p = .001$, $\eta^2 = .32$). Consistent with my previous FTCD findings, LI_{FMRI} values were higher, thus indicating a more strongly left-lateralized pattern of activation, in typical ($M = 0.59$, $SEM = 0.079$) compared to atypical individuals ($M = 0.16$, $SEM = 0.079$), who were on average showing a LI classified as bilateral (*Figure 5.8*). In addition, the main effect of area ($F(2, 60) = 6.76$, $p = .014$,

$\eta^2 = .18$) and the main effect of task ($F(1.47, 44.2) = 11.2$, $p < .0005$, $\eta^2 = .27$) reached statistical significance, too. While the former demonstrated that across groups, LI_{FMRI} obtained during WG, PPT, and AN was more strongly lateralized in frontal ($M = 0.43$, $SEM = 0.068$) relative to temporal areas ($M = 0.32$, $SEM = 0.051$), the latter indicated that LI_{FMRI} based on fronto-temporal activation varied among the three tasks (*Figure 5.7*). Post-hoc analysis revealed that mean LI_{FMRI} was significantly lower for the PPT relative to both WG ($M_{diff} = 0.28$, 95% CI [0.10, 0.45], $p = .001$) and AN ($M_{diff} = 0.13$, 95% CI [0.037, 0.23], $p = .004$). There was no significant difference between the LIs for AN and WG ($M_{diff} = 0.14$, 95% CI [-0.019, 0.31], $p = .098$).

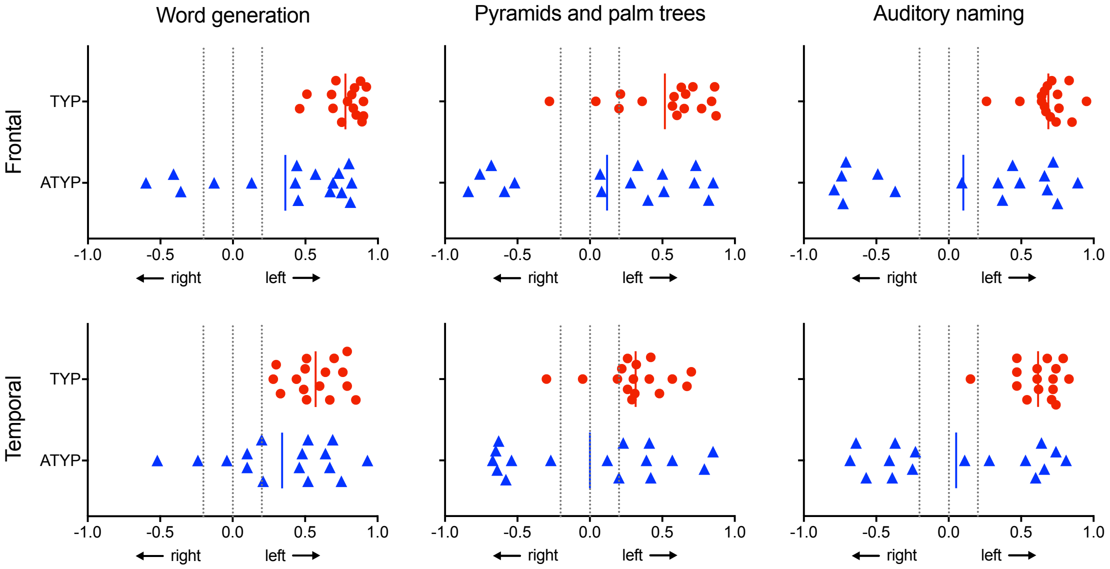


Figure 5.8. *Laterality indices (LI_{FMRI}) for functional activation in the frontal and temporal lobes. Individual LI_{FMRI} values are plotted for typically (TYP, red circles) and atypically (ATYP, blue triangles) lateralized participants, as assessed by FTCD. Data are shown for the word generation (word generation > rest, left), pyramids and palm trees (pictures > lines middle), and auditory naming (speech > reversed speech, right) paradigm for frontal (top row) and temporal lobe activation (bottom row). The mean of each group is marked with a line. Positive LI_{FMRI} values indicate left and negative ones right lateralization. Values falling within the range of ±0.2 as indicated by the dotted lines, were considered bilateral (not lateralized) activation.*

I repeated the analysis without a within-subjects factor of brain area to examine LI_{FMRI} based on whole-brain activation as well as activation in a more constrained language area, namely the IFG (pars triangularis and pars opercularis) and found similar results: While there were no significant interactions between group and task, typically lateralized individuals showed significantly higher mean LI_{FMRI} compared to atypically lateralized individuals, and across participants LI_{FMRI} values differed significantly among WG, PPT and AN.

Table 5.3. *Spearman's rho for correlations of* LI_{FMRI} *values based on frontal lobe or temporal lobe activation associated with word generation (WG), pyramids and palm trees (PPT), and auditory naming (AN) across all participants.*

		Frontal			**Temporal**		
		WG	PPT	AN	WG	PPT	AN
ALL							
Frontal	WG	1.000					
	PPT	$.484^{**}$	1.000				
	AN	$.653^{**}$	$.935^{**}$	1.000			
Temporal	WG	$.393^{*}$	.262	.199	1.000		
	PPT	$.478^{**}$	$.616^{**}$	$.558^{**}$	.147	1.000	
	AN	$.427^{*}$	$.462^{**}$	$.697^{**}$	$.418^{*}$	$.611^{**}$	1.000

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Next, Spearman's rho was calculated to assess the relationship between mean LI_{FMRI} based on frontal or temporal lobe activity during WG, PPT, and AN. Although my previous analysis demonstrated a significant effect of group on LI_{FMRI} values - as expected - there was no significant interaction between group and brain area or between group and task. Thus, correlations were performed across typically and atypically lateralized participants. For frontal lobe activation, LI_{FMRI} values correlated significantly among all three tasks (*Table 5.3,* top half). Analysis revealed moderate to strong positive correlations indicating that higher indices of functional lateralization for one language task were associated with higher LI_{FMRI} values for the other two language tasks. While there was no significant correlation between indices of lateralization based on temporal lobe activation for WG and PPT, LI_{FMRI} based on temporal activity during AN correlated significantly with those for WG and PPT (*Table 5.3,* bottom half). Again, Spearman's rho indicated moderate to strong positive correlations among LI_{FMRI} values associated with the three paradigms.

In addition, indices of lateralization derived from frontal lobe activation correlated positively with those based on temporal lobe activation within each paradigm (i.e. WG, PPT, AN). As shown in *Table 5.3*, Spearman's rho was numerically higher for $\mathrm{LI}_{\mathrm{FMRI}}$ values linked to AN or PPT relative to WG indicating that associations of lateralization between frontal and temporal lobe activation were stronger for more receptive language tasks. After correction for multiple comparisons ($p_{corr} < .003$), the relationship between $\mathrm{LI}_{\mathrm{FMRI}}$ based on frontal and temporal lobe activation remained significant for PPT and AN, but not WG.

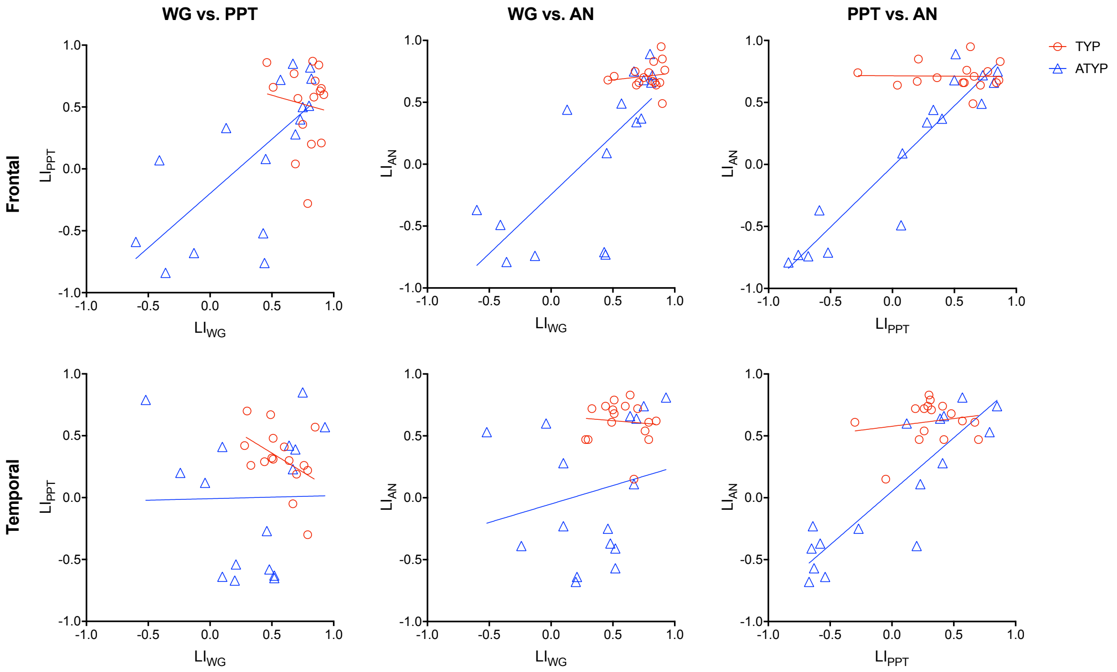


Figure 5.9*. Scatterplots of laterality indices (LI) obtained by FMRI during word generation (WG), pyramids and palm trees (PPT), and auditory naming (AN). Data are shown for LIs based on activation in the frontal (top row) and temporal lobes (bottom row). Positive LIs indicate left- and negatives ones right language lateralization.*

Visual inspection of the scatterplots in *Figure 5.9* suggested that positive associations were predominantly driven by participants with atypical language lateralization. To test this, I calculated regression lines separately for the two groups and examined whether the slopes of these lines were statistically significant. Although regression lines appear to be different based on visual inspection, statistical analysis revealed no differences in the regression coefficients between typically lateralized and atypically lateralized participants - neither for frontal or temporal activation.

5.3.3 Do FTCD, FMRI and VHF measure language lateralization concordantly?

First, I compared LIs for typical and atypical participants (between-subjects factor of group) obtained using FTCD, FMRI and VHF (within-subjects factor of method) using a two-way mixed ANOVA.

Visual inspection of boxplots indicated that there were no outliers. In addition, LI data were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$), with the exception of LI_{FMRI} values for the atypical group ($p = .041$). Leven's test and Box's M test confirmed that there was homogeneity of variances and covariance ($p > .05$) - again except for variances of LI_{FMRI} values ($p = .004$). Because sphericity was violated for the two-way interaction, as indicated by Mauchly's test ($\chi^2(2) = 164$, $p < .0005$), Greenhouse-Geisser correction was applied ($\varepsilon = .50$). Analysis revealed an interaction that approached, but did not reach statistical significance ($p = .077$). Consistent with my previous findings, there was a significant main effect of group ($F(1, 30) = 5.55$, $p = .025$, $\eta^2 = .16$). As illustrated in *Figure 5.10,* typical participants ($M = 12.6$, $SEM = 3.00$) had higher LI values, suggesting stronger left lateralization for language, than atypical participants ($M = 2.57$, $SEM = 3.00$) across the different assessments. In addition, the main effect of method ($F(1.00, 30.1) = 9.91$, $p = .004$, $\eta^2 = .25$) demonstrated that across the two groups mean LI values varied among FTCD, FMRI, and VHF.

To test whether these findings are robust across the different FMRI activation tasks, I repeated the analysis using i) LI_{FMRI} values based on activation during AN since this language paradigm revealed the most concordant results, ii) composite LI_{FMRI} values that were calculated by averaging indices of lateralization based on FMRI across all three language paradigms, and iii) LI_{FMRI} values based on activation during PPT for completeness. All three analysis revealed very similar, almost identical, results: There were no significant two-way interactions between group (TYP vs. ATYP) and method (FTCD vs. FMRI vs. VHF), but the main effect of group indicated that typically lateralized individuals showed significantly higher mean LIs compared to atypically lateralized individuals across assessments. Mean LI values across all participants also varied significantly among FTCD, FMRI, and VHF.

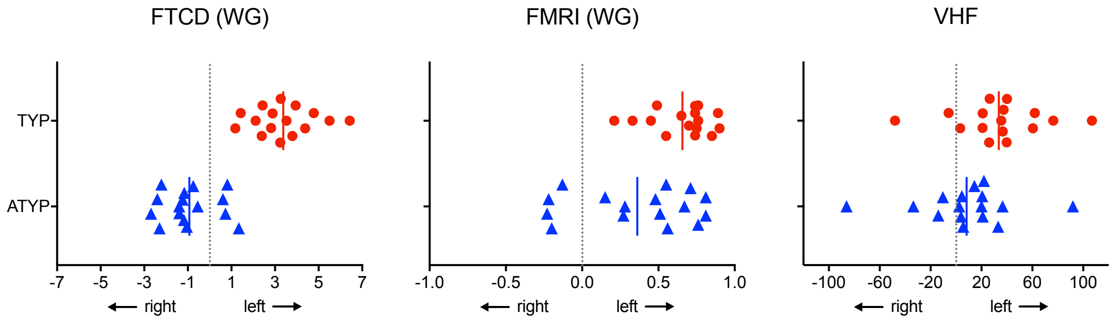
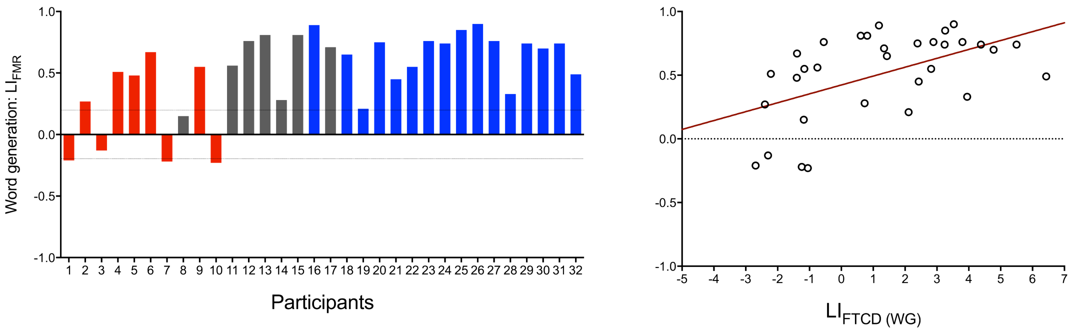


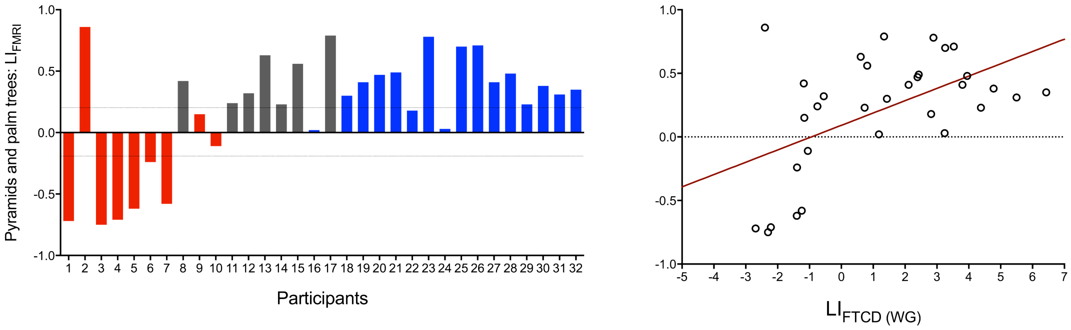
Figure 5.10. *Mean LIs obtained using FTCD, FMRI, or VHF task. Individual LI values are plotted for typically (TYP, red circles) and atypically (ATYP, blue triangles) lateralized participants. Data are shown for* LI_{FTCD} *based on WG (left),* LI_{FMRI} *based on combined frontal/temporal lobe activity during WG (word generation > rest, middle), and* LI_{VHF} *based on reaction time differences (in ms) during picture naming (right). The mean of each group is marked with a line. Positive* LI_{FMRI} *values indicate left and negative ones right lateralization. Values falling within the range of ±0.2 as indicated by the dotted lines, were considered bilateral (not lateralized) activation.*

Next, Spearman's correlations were conducted to assess the relationship between LI values obtained by FTCD, FMRI, and VHF. For all three language paradigms, LI_{FMRI} and LI_{FTCD} were positively correlated suggesting that both techniques correspond in the degree of lateralization (*Figure 5.7*). Overall, Spearman's rho revealed moderate associations between FMRI and FTCD with strongest correlation coefficients LIs based on AN (r_S (30) = .59, p < .0005), followed by WG (r_S (30) = .49, p = .005), and then PPT (r_S (30) = .44, p = .012). No significant correlations were found between LI_{VHF} and LI_{FTCD} (p = .070) or LI_{FMRI} for WG (p = .429), PPT (p = .118), or AN (p = .106).

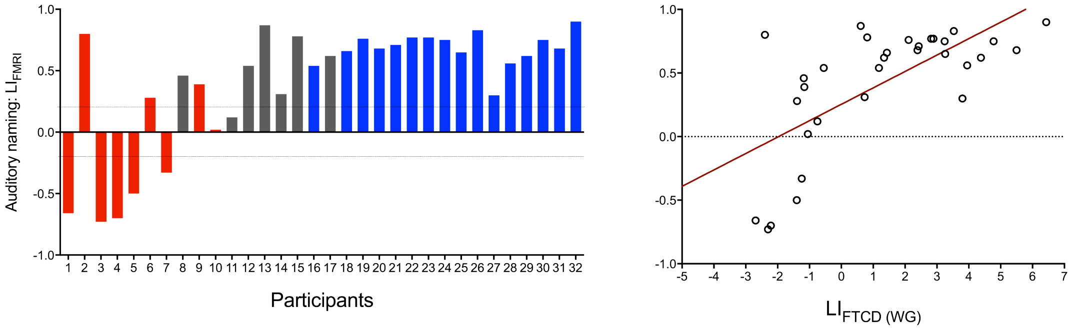
A. Word generation (WG)



B. Pyramids and palm trees (PPT)



C. Auditory naming (AN)



D. Visual half-field task (VHF)

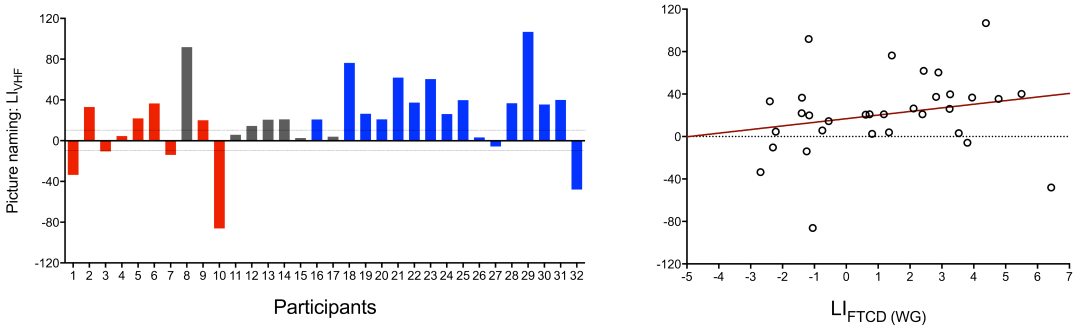


Figure 5.11. *Laterality indices (LI) obtained by functional magnetic resonance imaging (FMRI) and visual half-field (VHF) task.* LI_{FMRI} *are based on activation in the frontal and temporal lobes during word generation (A), pyramids and palm trees (B), and auditory naming (C).* LI_{VHF} *reflect differences in reaction time for target stimuli that were presented in the left or right visual field (D). Bar graphs show individual LIs plotted in ascending order based on participants'* LI_{FTCD} *(i.e. from the most atypical to the most typical one). Colours label participants as right-lateralized (red), bilateral (grey), or left-lateralized (red) as assessed by FTCD during WG. Scatterplots on the right, illustrate the relationship between* LI_{FTCD} *and* LI_{FMRI} *(A-C) or* LI_{VHF} *(D).*

Lastly, I calculated and compared the number of participants classified as typically (left) or atypically (non-left) lateralized between the three methods. *Table 5.4* shows the number of participants classified as left lateralized, bilateral and right lateralized based on FTCD, FMRI, and VHF. Using FMRI, three participants from the atypical group were identified as right lateralized during WG, four during PPT, and five during AN. This finding was concordant with their classification based on FTCD. The remaining six (WG), three (PPT), and four (AN) individuals, who were right lateralized on FTCD, showed either bilateral or left-lateralized activation in FMRI. In addition, all participants except one that were classified as bilateral based on FTCD revealed a clear left lateralization in FMRI. All participants with typical language lateralization, as classified by FTCD, also had left-lateralized activation as measured by FMRI, except for three individuals who showed bilateral activation during PPT. *Figure 5.11* illustrates these findings by plotting individual LI_{FMRI} that are displayed in ascending order based on participants' LI_{FTCD} (i.e. from the most right to most left lateralized participant). Overall, FTCD and FMRI assessed language lateralization concordantly in 20 (62.5%), 19 (59.4%), and 21 (65.6%) out of 32 participants for WG, PPT, and AN, respectively.

Table 5.4. *Number (%) of participants classified as left lateralized, bilateral, or right lateralized based on FTCD, FMRI, and VHF task.*

N = 32		**Left lateralized**	**Bilateral**	**Right lateralized**
FTCD		16 (50.0%)	7 (21.9%)	9 (28.1%)
FMRI	WG	27 (84.4%)	2 (6.25%)	3 (9.35%)
	PPT	21 (65.6%)	5 (15.6%)	6 (18.8%)
	AN	25 (78.1%)	2 (6.25%)	5 (15.6%)
VHF		21 (65.6%)	6 (18.8%)	5 (15.6%)

Note: For FTCD, participants were classified as left-lateralized, right-lateralized, or bilateral based on LI values obtained during word generation (WG).

The VHF task revealed a similar degree of concordance when compared with FTCD, namely 62.5%. Specifically, VHF identified four participants as right lateralized, three as bilateral, and thirteen as left lateralized, which was concordant with their classification based on FTCD (*Figure 5.11*). One right-lateralized participant, as assessed by FTCD, was classified as bilateral and the remaining four as left-lateralized using the VHF task. In addition, four participants, who showed bilateral activation during FTCD, were left lateralized based on VHF; and three participants with left lateralized activation during FTCD, were identified as bilateral (two) or right-lateralized (one) based on VHF. When compared with FMRI, VHF assessed language laterality in 23 (71.9%) participants for WG, 18 (56.3) participants for PPT, and 24 (75%) participants for AN concordantly. As confirmed by Cochran's Q test, the proportion of participants who were identified as typically (left) or atypically (non-left) lateralized for language differed significantly between FTCD, FMRI, and VHF ($\chi^2(4) = 16.7, p = .002$).

5.3.4 Does language lateralization relate to language ability?

For each participant, behavioural data related to general cognitive abilities (WASI), reading skills (TOWRE), receptive vocabulary (BPVS-II) and handedness (EHI, QHP, Pegboard) are displayed in *Table 5.5*. Across tasks, there were no statistically significant differences in test scores between individuals with typical or atypical language lateralization, as examined by Mann-Whitney U tests (*Table 5.5*).

Because the two groups did not differ in their performance on any standardized test of language, typically and atypically lateralized participants were combined for further analysis. Spearman's correlations were computed to assess the relationship between test scores and LI values based on FTCD, VHF, and FMRI. The latter were based on activation in the frontal and temporal lobes during WG, PPT, and AN. No significant correlations were found between IQ, reading skills, or receptive vocabulary and either LI_{FTCD}, $LI_{VHF,}$ or LI_{FMRI} based on the three language paradigms.

Table 5.5. *Behavioural test scores for typically and atypically lateralized participants.*

Group	**ID**	**EHI**[a]	**QHP**[b]	**PEG**[c]	**VIQ**	**PIQ**	**FIQ**	**TOWRE** sight word reading	**TOWRE** phonemic decoding	**TOWRE** total word reading	**BPVS-II** picture naming
ATPY	01	14	-0.5	-7.00	135	126	134	104	102	104	98
ATPY	02	50	0.3	6.35	135	127	135	113	106	111	108
ATPY	03	31	-0.5	-7.07	123	108	118	112	105	110	85
ATPY	04	46	0.1	2.55	131	129	134	114	121	121	85
ATPY	05	22	-0.5	-10.14	122	127	128	114	112	116	95
ATPY	06	50	0.2	11.36	125	121	126	91	90	89	83
ATPY	07	19	-0.1	2.58	132	125	132	114	118	119	113
ATPY	08	37	-0.1	-3.61	121	103	114	86	110	98	103
ATPY	09	48	-0.2	0.61	125	127	129	110	108	111	100
ATPY	10	52	0.0	2.12	135	125	134	110	116	116	98
ATPY	11	39	0.5	-0.06	127	110	121	114	109	114	100
ATPY	12	48	0.2	4.63	128	127	131	113	108	112	88
ATPY	13	17	-0.4	-8.12	128	127	131	114	121	121	85
ATPY	14	51	-0.5	-1.82	102	107	106	84	92	86	105
ATPY	15	50	0.0	7.45	116	109	114	114	105	111	105
ATPY	16	48	0.0	-1.30	133	128	134	109	111	111	105
		38.9	**-0.09**	**-0.09**	**126**	**120**	**126**	**107**	**108**	**109**	**97**
TYP	17	51	0.5	-0.64	144	121	138	109	106	109	100
TYP	18	53	0.4	4.07	138	129	139	114	115	117	120
TYP	19	53	-0.1	8.76	119	104	113	100	101	101	85
TYP	20	17	-0.1	-8.17	126	123	127	90	105	96	103
TYP	21	54	-0.5	-3.38	136	120	132	113	100	108	120
TYP	22	35	0.0	2.12	141	128	139	114	111	115	113
TYP	23	46	0.1	6.30	129	121	128	114	108	113	118
TYP	24	26	0.5	-0.40	131	126	132	104	121	115	110
TYP	25	51	0.3	2.09	98	120	109	97	96	96	72
TYP	26	28	0.0	-4.38	139	129	139	114	115	117	113
TYP	27	48	0.0	7.32	133	132	137	110	116	116	128
TYP	28	51	-0.1	7.27	134	120	131	111	105	110	98
TYP	29	50	0.0	5.17	141	127	139	114	117	119	103
TYP	30	23	0.1	-6.31	132	106	120	114	111	115	98
TYP	31	50	0.1	5.02	146	124	140	114	115	117	113
TYP	32	40	-0.1	5.16	113	108	112	95	95	94	55
		42.3	**0.07**	**1.88**	**131**	**121**	**130**	**108**	**109**	**110**	**103**
P value		0.47	0.12	0.33	0.19	0.81	0.34	0.84	0.95	0.88	0.28

Note: Data are shown for individuals and the mean scores were calculated for the group of adults with typical (TYP) and atypical (ATYP) language lateralization separately. Scores are standard scores (mean 100 ± 15) unless otherwise indicated.

[a] Edinburgh Handedness Inventory (EHI). Ratings across ten items representing activities performed with one's hand, were summed resulting in a minimum of 10 (extreme left-handedness) and a maximum of 50 (extreme right-handedness). Values of 35 or above indicate right-handedness, 25 or below left-handedness, and values in between denote ambidexterity.

[b] Quantification of Hand Preference (QHP). A hand bias score was calculated based on the performance on a reaching task. Scores range from +0.5 (exclusive use of right hand) through 0 (no preference) to -0.5 (exclusive use of left hand).

[c] Peg-moving (PEG). A relative hand skill quotient was calculated based on reaction times (i.e. moving ten pegs with the left or right hand). Negative values indicate a faster performance on left-hand trials and positive values a faster performance on right-hand trials.

5.4 Discussion

The current study investigated lateralization of language function in a well matched sample of typically (left) and atypically (right or bilateral) lateralized participants, as previously determined by FTCD. All participants completed three different language paradigms, namely word generation (WG), pyramids and palm trees (PPT), and auditory naming (AN) during FMRI to map language areas involved in language production and comprehension and examine functional lateralization. In addition, a visual half-field task to obtain a behavioural measure of language lateralization based on picture naming. A comprehensive neuro-psychological test battery assessing IQ, language abilities and handedness was administered to compare cognitive abilities between the two groups. The following were the main findings: i) WG, PPT, and AN robustly activated the fronto-temporal language system; yet, substantial inter-individual variability in location, size, and strength of activation was observed across participants; ii) activation in fronto-temporal areas was less left lateralized for all three language tasks in atypical compared to typical participants; iii) although concordance for categorically defined laterality was less good than previously reported (Deppe et al., 2000b), this study confirmed a positive relationship between laterality indices obtained by FTCD and FMRI, but not VHF; iv) No behavioural measure was related to language laterality as assessed by FTCD, FMRI, or VHF.

5.4.1 How atypical is atypical language lateralization in FMRI?

Qualitatively, the typical group showed clearly left lateralized activation during WG, PPT, and AN, while the atypical group revealed a more bilateral pattern, particularly in inferior frontal areas. The observed differences in functional lateralization were statistically significant as assessed by laterality indices, which were higher in typical compared to atypical participants indicating more strongly left lateralized activation. Indeed, mean LIs for the atypical group based on PPT and AN (but not WG) fall within the critical range of ±0.2 indicating a bilateral increase of activation.

To the best of my knowledge only one other study looked at differences in language activation between neurotypical adults with left-hemisphere and right-hemisphere language, who had initially been screened using FTCD (Knecht et al., 2003). Contrary to my findings, Knecht and colleagues (2003) found no evidence for increased bilaterality of FMRI activation during word generation in seven atypically lateralized participants relative to seven typically lateralized ones. Instead the atypical group showed a pattern of activation that was the mirror reverse of the pattern seen in the typical group (Knecht et al., 2003). Unlike the current study, Knecht et al. (2003) did not include bilateral participants, but rather individuals with strong left or right language lateralization as assessed by FTCD. Given that participants, who showed low lateralization during FTCD, were classified as atypical in this study; and that most of these participants revealed left lateralized activation in FMRI, in is reasonable to assume that bilateral participants drove the increase in symmetric activation seen in my atypical group.

5.4.2. Discordance between laterality measures based on FTCD, FMRI and VHF

Overall, FMRI laterality measures involving expressive language (WG and AN) showed a better agreement with both FTCD and VHF compared to those based on more receptive language (PPT). Studies using FMRI and FTCD have shown that language production is more strongly lateralized compared to language comprehension (Badcock, Nye, & Bishop, 2012; Bishop, Watt, & Papadatou-Pastou, 2009; Buchinger et al., 2000; Stroobant, Buijs, & Vingerhoets, 2009). In addition, low lateralization has been shown to be more difficult to measure reliably than strong lateralization (Arora et al., 2009; Andreas Jansen et al., 2006). Hence, reduced concordance for LIs based on PPT relative to WG and AN may be a consequence of less lateralized activation during semantic matching. Two findings from the current study support this assumption. Firstly, typical and atypical participants revealed a more bilateral pattern for PPT relative to WG and AN as indicated by lower mean LIs. Secondly, while ten out of 16 left lateralized (62.5%) and four out of nine right lateralized (44.4%) participants were classified consistently across all three tasks and methods, none of the seven participants with bilateral language revealed concordant results indicating that laterality assessment was more congruous in strongly lateralized compared to low lateralized participants.

The best agreement between methods was observed for FMRI activation during AN, which produced consistent laterality measures in 65.6% and 75.0% of participants when compared with FTCD and VHF, respectively. Given that WG is the gold standard method in assessing functional language lateralization and that it was completed during both FTCD and FMRI, this finding was somewhat unexpected. As indicated by group activation patterns, WG predominantly activated inferior frontal cortex, while AN involved frontal as well as temporal language areas. Activation during AN may therefore represent a more sensitive marker of lateralization. However, the difference in the proportion of concordantly classified participants between WG and AN was marginal, i.e. one participant.

Across language paradigms, the concordance for categorically defined language laterality was 62.5% for FMRI and FTCD, and 67.7% for FMRI and VHF. This was considerably lower than previously reported, namely 86 - 100% for FTCD (Deppe et al., 2000b; Somers et al., 2011) an about 90% for VHF (Hunter & Brysbaert, 2008). Discrepancies could arise from a number of factors that may lead to increased variability and individual measurement error. To begin with, Deppe and colleagues (2000), who demonstrated that FTCD and FMRI determined laterality in all participants concordantly, scanned adults with strong left lateralized or strong right lateralized language. Unlike my study they did not include bilateral subjects. As noted earlier, difficulties in reproducibility and thus interpretation of low lateralization have been demonstrated in FMRI (Adcock et al., 2003; Jansen et al., 2006). For example, Jansen and colleagues (2006) demonstrated that a neurotypical participant could be easily categorized as bilateral by one method of MRI analysis although this classification was neither supported by another analysis approach nor reproducible in a second FMRI assessment. Another FMRI study, which measured language laterality in patients with epilepsy also found that reproducibility of FMRI LI values was lowest for patients with bilateral activation (Adcock et al., 2003).Thus, the inclusion of low lateralized participants in this study may contribute the reduced concordance between FMRI and FTCD or VHF. It is important to note that low reproducibility of laterality measures in FMRI is not restricted to bilateral language activation. Fernández and colleagues (2003) evaluated test-retest reliability of FMRI language activation in patients with epilepsy and reported that maximal 48.9% of activated voxels overlapped between the first and second assessment. In neurotypical participants, a similar percentage of 41% was found for clusters of activation based on a combined task analysis of three language paradigms (Rutten et al.,2002). However, for each individual task this proportion was considerably lower, namely 24% for verb generation, 26% for picture naming, and 21% for an antonym task (Rutten et al., 2002).

Another factor relates to the dependency of LI measures, particularly those obtained by FMRI, on various methodological decisions concerning the quantification of activity, localizations of ROIs or choice of statistical thresholds (for review see Seghier, 2008). Since there is no consensus on how to best calculate indices of lateralization, a multitude of different approaches have been used. For instance, Deppe et al. (2000) computed LI values based on the number of activated voxels using a customized wedge-shaped mask that roughly corresponded to the vascular territory of the MCA, while Somers and colleagues (2011) used signal intensity changes (sum of β-values) in areas known to be involved in language processing including triangular part of IFG, insula, MTG, STG, supramarginal gyrus, and the angular gyrus. Then again, Hunter and Brysbaert (2008) employed an anatomical mask that only comprised inferior frontal language areas (BA44 and BA45) in order to compute LIs based on the number of activated voxels. These differences in LI calculation as well as more general ones in MRI analysis could partially account for discrepancies between my findings and earlier ones. Specifically, I used the technique involving a combination of bootstrapping procedure and histogram analysis proposed by Wilke and Schmithorst (2006) to calculate threshold-free LI values, while the studies described above, based their LIs calculation on active voxel count or total signal change of significant voxels at a single fixed statistical threshold. Use of a single threshold has been criticised and acknowledged to reveal no robust or reproducible LIs as values strongly vary with the threshold (Jansen et al., 2006). At a high threshold the number of significant voxels typically decreases because false positives as well as “truly” activated voxels are excluded; the opposite can be observed at a low threshold, which can results in a more bilateral pattern of activation due to the increase of false positive voxels in both hemispheres (Jansen et al., 2006).

Performing a bootstrap analysis at different statistical thresholds on the other hand, has been demonstrated to reveal more robust and stable LIs (Wilke & Schmithorst, 2006).

The analyses presented above have relied on the assumption the initial FTCD measurement was accurate. Unless further validation using an interference technique is implemented, we cannot be sure, which measurement is valid. It is possible that the FMRI and VHF measurements are more accurate and that atypical participants were classified inaccurately during the initial FTCD testing. The reliability of LI values obtained by FTCD can be evaluated by the confidence interval of a measurement (Knecht et al., 1998b). As suggested by Knecht and colleagues (1998b), the 95% confidence interval of LI can be deduced from the standard error ($LI \pm 1.96 * s_{LI}$), which therefore can be regarded as a statistical estimator for the uncertainty of LI. In the current study, the standard error of individual measurements varied between 0.26% and 0.79% ($M = 0.53\%$) indicating that the accuracy of the LI was better than 0.79% of the mean hemispheric difference for all 32 FTCD assessments. These values are very similar to those reported by Knecht and colleagues (1998b), which ranged from 0.3% - 1.0%, suggesting that FTCD detected relative CBFV differences between the left and right MCA accurately. There were no differences in accuracy between typically and atypically lateralized participants ($p > .05$), too. Moreover, LI based on WG during FTCD, showed a good level of internal consistency ($r = .82$, $p < .0005$) and high test-retest reliability ($r = .89$, $p < .0005$) as demonstrated in my previous study (Chapter 4). In sum, there is every indication that FTCD provided accurate and reproducible information about language lateralization.

Discordance between laterality assessments may therefore reflect technical and methodological differences between FTCD, FRMI, and VHF. It is reasonable to assume that a total agreement between different LIs may not be reached, given that the three methods examine distinct phenomena, namely CBFV changes in basal arteries during FTCD, cerebral oxyhemoglobin-deoxyhemoglobin ration in FMRI, and reaction times of verbal responses for VHF. A related confounding variable might be the different settings, in which participants performed each task. For FTCD and VHF, participants were seated in front of a computer in a quiet room – an environment that is familiar to most people. This was different for the FMRI assessment, during which participants were lying in the narrow tube of the MRI scanner exposed to its acoustic noise. This alien environment may have affected participants' attention, emotional state, and thus task performance more generally, while the presence of the examiner during FTCD might have enhanced activation and motivation. In addition, it has been reported that scanner noise can alter brain activation during the performance of a cognitive task (Tomasi, Caparelli, Chang, & Ernst, 2005). Whether or not any of these variables, alone or in combination, are sufficient to explain the observed rates of discordance remains unknown. It is worth noting that one study has demonstrated a near-perfect correlation (r = .95) and 100% concordance between LIs measured with FTCD and FMRI (Deppe et al., 2000a). However, this study was performed in a relatively small number of strong left- and right lateralized participants (N = 13), and therefore the findings might reflect an overestimation of the actual relationship between FTCD and FMRI. Somers et al. (2011), for instance, also examined the measurement of language lateralization with FTCD and FMRI and found significantly positive, but considerably lower correlations between LI_{FTCD} and LI_{FMRI} (r = .75). Similar values were reported for associations between FMRI and VHF, which ranged from r = .65 (Van der Haegen et al., 2011) to r = .77 (Hunter & Brysbaert, 2008).

Lastly, the discordance observed for some atypical participants may reflect true changes in lateralization indicating that language laterality in some people is more variable than others. Spatial heterogeneity in language lateralization, which has been demonstrated in a large sample of neurotypical adults (Seghier et al., 2011), may explain some cases of discordance. Indeed, one participant, who was classified as right lateralized with FTCD, showed left lateralized activation in frontal, but right-lateralized activation in temporal areas during all three language paradigms in FMRI. For WG, three more participants with right-hemisphere language, based on FTCD, demonstrated a reversal of language lateralization in different brain regions: one revealed right lateralized activation in frontal and left lateralized activation in temporal areas, while the remaining two showed the opposite pattern of interhemispheric dissociation. This is in good agreement with studies that found discordant results between Wada and FMRI assessments in epilepsy patients who also showed regional dissociation in language lateralization (Janecek et al., 2013; Lee et al., 2008).

Taken together, the discordance between different laterality measures observed in this study could arise from a number of factors such as dependency of LI values on different methodological decisions, individual measurement errors due to poor data quality, physiological differences in the recorded responses, or spatial heterogeneity of language lateralization. Although studies have reported higher rates of LI discordance in patients with epilepsy and neurotypical adults with bilateral language representation (Arora et al., 2009; Janecek et al., 2013; Jansen et al., 2006), not many have systematically examined methodological or subject factors that may predict discordant results among different assessments. One study investigated demographic, clinical, and methodological predictors of discordance in a large number of patients with epilepsy, but found neither differences between concordant and discordant group in subject variables (e.g. age, gender, handedness, education, IQ, age at seizure onset, location of seizure focus, and number of anticonvulsant medication), Wada quality indices, or FMRI quality indices, nor a systematic relationship between these measures and LI discordance (Janecek et al., 2013). Moreover, no data are yet available specifically comparing discordance between measures obtained by FMRI and FTCD or FMRI and VHF. Thus, the reasons for discordant laterality measures within one person remain poorly understood.

5.4.3 Behavioural relevance of language lateralization

One aim of this study was to investigate whether and how different indices of language lateralization relate to standardized measures of general cognitive ability and verbal skills. I found no significant differences between typically and atypically lateralized participants (as assessed by FTCD) in verbal/non-verbal IQ, sight word reading, phonetic decoding, or receptive vocabulary. Compared with participants, who showed strong left or right lateralization during FTCD, those with bilateral language representation scored equally well on all administered tests. In addition, language laterality measured by FTCD, FMRI, or VHF did not correlate with any behavioural measure. Thus, my data provide no evidence for a link between functional language lateralization and cognitive abilities or language skills.

Yet, from a theoretical point of view, there are a number of reasons why hemispheric specialization for language is likely to reflect evolutionary selection rather than a random phenomenon. During language development functional clustering in one hemisphere may allow accelerated linguistic processing as transmission between different language regions within one hemisphere is faster than crossing between hemispheres via the corpus callosum (Nowicka & Tacikowski, 2011). In addition, language lateralization may be advantageous because it prevents simultaneous initiation of incompatible responses (Crow et al., 1998). Developmental language disorders, for example, have long been associated with a poorly lateralized brain (e.g. de Guibert et al., 2011; Illingworth & Bishop, 2009; Whitehouse & Bishop, 2008) and neuroimaging studies with participants from the general population have also demonstrated a relation between atypical language lateralization and performance in verbal and non-verbal tasks (Everts et al., 2009; Groen et al., 2012; Mellet et al., 2014; van Ettinger-Veenstra et al., 2010). The latter, however, reveal no consistent pattern of association: while some authors reported better linguistic abilities for individuals with left-lateralized language (Everts et al., 2009; Groen et al., 2012), others found that increased bilateral activation was related to improved performance in behavioural language tasks (van Ettinger-Veenstra et al., 2010). Yet, in another study by Mellet et al. (2014), participants with weak language lateralization had significantly lower scores on standadized test of language, memory, and spatial abilities than those with strongly left or right lateralized language. Therefore, the evidence for a direct and behaiourally relevant link between language laterality and language function is far from compelling.

Discrepancies between these studies and my findings are likely to reflect differences in various aspects of the experimental designs. These include - but are not limited to - the paradigms employed for language mapping, methods used for LI calculation, or tests administered during neuropsychological assessment. The lack of sensitivity could be another reason for my negative findings. By including participants with right or bilateral language representation I aimed to increase variability in my sample. Atypical language lateralization in otherwise healthy participants is rare and therefore my sample size rather small. In addition, most participants that took part in this study were Oxford University students, who scored very high on all standardized tests of language and intelligence. Due to the low variance in my behavioural data, it is reasonable to assume that ceiling effects may have impaired the ability to detect a link between language laterality and language abilities.

Knecht and colleagues (2001), however, examined functional language laterality in a large sample of neurotypical adults (N = 326) using FTCD and found no significant differences in verbal fluency, mastery of foreign languages, academic achievement, or artistic talents between participants with left, right or bilateral language representation. Moreover, language laterality did not correlate with verbal, non-verbal, or combined IQ or speed of linguistic processing as assessed in a selected subgroup of 21 participants (Knecht et al., 2001). While this is consistent with my findings, it remains to be seen whether future research with larger samples of atypically lateralized participants can replicate this lack of association.

5.4.4 Limitations and future directions

Laterality indices are commonly used in neuroimaging studies because they facilitate the description of complex activation patterns associated with a specific cognitive function; in other words, it is easier to manipulate a single value per participant than thousands of voxels in a contrast image (Seghier, 2008). However, reducing the complexity of a brain activation map to a single measure comes with the cost of losing relevant information for interpreting functional lateralization. For example, if two participants obtain the same LI, does that indicate their functional lateralization is identical? Perhaps one participant activates large areas in both hemispheres, while the other shows very restricted activation in both hemispheres. Or the extent of activation may be the same, but the areas within each hemisphere differ. Such information is necessary for a comprehensive understanding of hemispheric functioning - especially in cases where discordant indices suggest a more complex pattern of laterality. While these cases are often dismissed as unreliable or invalid, they are potentially informative with respect to causes of discordance (Janecek et al., 2013). Furthermore, by categorizing individuals based on LI values (i.e. left vs. right vs. bilateral), some participants were placed confidently within a group, while others were placed on the threshold between categories. Thus, in some participants a small change in mean LI could result in a change of LI category, which in turn may unduly affect estimates of concordance. This seems particularly problematic because the thresholds for categorization are often defined arbitrarily or even data-driven. In general, the costs of creating artificial groups, namely the loss of data resulting in a loss of power and the neglect of within-group variability (Cohen, 1983; Naggara et al., 2011), should always be considered when assessing functional lateralization.

While these limitations pertain to most studies that examine cerebral lateralization, it is important to acknowledge some that are specific to the current investigations. First of all, this study did not directly assess reliability of FMRI or VHF, thus individual measurement errors cannot be excluded as a possible confounder. However, previous research has demonstrated that both methods can be used as an accurate and reliable predictor of language lateralization (Binder, 2011; Hunter & Brysbaert, 2008; Liégeois et al., 2002; Van der Haegen et al., 2011). Specifically, I used the same carefully designed VHF task described by Hunter and Brysbaert (2008), which has been validated by direct comparison with FMRI. According to the authors, this task provides a valid measure of language lateralization because it contained an acceptable number of observations (>150), used matched stimulus sets, comprised bilateral stimulus presentation with an adequate fixation control at the beginning of each trial, and clearly visible stimuli that were masked at the offset (see Hunter & Brysbaert, 2008 for details). For FMRI, both visual inspection of raw data and quantitative assessment of participants' motion (i.e. plotting motion for x, y and z-axis, detecting motion outliers and volumes that are affected by motion) indicated good-quality FMRI data across language paradigms and participants. Thus, there is only little - if any - indication, to assume that FMRI or VHF measured language lateralization inaccurately. Another limitation is that performance during FMRI was not assessed for WG or AN as participants were asked to generate responses covertly to reduce motion artefacts. During the initial FTCD assessment, however, participants performed WG in the presence of the experimenter and all showed good cooperation and adequate task performance. In addition, accuracy for semantic matching during the PPT was very high across participants (96.2%) indicating a similar degree of performance during FMRI. Because the same stimuli were used for WG and PPT during FTCD and FMRI, task-repetition may have affected task performance and brain activation (Lohmann et al., 2004). Lohmann and colleagues (2004) found that task repetition can lead to changes in task-related autonomic drive leading to an increase in the number of activated voxels within both hemispheres. This can mimic increased bilaterality of brain activation and potentially bias laterality measures obtained by FMRI. Although this effect was shown for word generation, the increase in activated voxels was observed over ten successive examinations with a systematic decline in FMRI lateralization index. Participants in this study repeated WG and PPT only once; therefore it is reasonable to assume that the task-repetition effect was negligible.

The current study brought attention to some limitations related to the interpretability of laterality indices - irrespective of whether lateralization was assessed by FMRI, FTCD, or VHF. When assessing and interpreting global LI values, it is vital to also consider inter-subject variability as well as the relative contribution of different cortical language areas. Further research is required to identify and elucidate causes of discordance as this will help to improve our understanding of how and why laterality changes. Given that high rates of discordance were repeatedly found for neurotypical participants and patients with bilateral language, future studies should focus rather than exclude bilateral individuals.

5.5 Conclusion

In conclusion, I have shown that functional lateralization for language may not be a highly stable characteristic of individuals. Although my data confirmed a positive relation between laterality indices obtained by FTCD and FMRI, the concordance for categorically defined laterality was less good than previously reported (Deppe et al., 2000b). In particular, most individuals classified as bilateral on FTCD had left lateralized language on FMRI. Because the accuracy of FTCD measurements, as assessed by the confidence interval, was better than 0.79% of the mean hemispheric difference, it is reasonable to assume that discordant LIs did not result from erroneous FTCD examinations. The change in category of participants with atypical language lateralization may therefore reflect instability in laterality for such individuals that could vary depending on task or other factors. Further research is required to evaluate the reproducibility of these assessments and thus determine the extent to which discordance reflects true changes in functional lateralization rather than individual measurement errors.

6

Correlates of language lateralization in the microstructure of white matter tracts

Abstract

A number of neuroimaging studies have examined whether structural asymmetries underlie functional lateralization of language, but the search for a direct and unequivocal structure-function relationship is enduring. I combined diffusion-weighted imaging with different measures of functional lateralization to study 32 healthy participants with typical and atypical language laterality closely matched for age, gender, and handedness. In addition to voxel-based analysis of white matter diffusion properties (TBSS), probabilistic tractography was used to reconstruct dorsal (arcuate fasciculus) and ventral (extreme capsule fasciculus) language pathways as well as inter-hemispheric connection via the corpus callosum to investigate changes in the integrity and/or asymmetry of white matter as a function of language lateralization. While typical and atypical participants did neither differ in their whole-brain white matter, nor in the integrity or size of the corpus callosum, I demonstrated that participants with left-lateralized language function also showed a significant and marginally significant leftward asymmetry of the ventral language and dorsal language tract respectively. Strikingly, the asymmetry of the extreme capsule fasciculus was absent in participants with atypical language lateralization. Indices of asymmetry for the ventral, but not dorsal language tract correlated significantly with verbal IQ and handedness indicating that increased leftward asymmetry was

associated with higher scores on language-related subtests of the WASI and increased right-handedness. Asymmetry of the extreme capsule fasciculus may therefore be a promising neuroanatomical marker of language laterality.

6.1 Introduction

Although many studies have investigated language laterality, its neuroanatomical basis is still not fully understood. A longstanding hypothesis suggests that structural asymmetries underlie functional language lateralization (Eberstaller, 1890; Geschwind & Levitsky, 1968). In agreement with this notion, Geschwind and Levitsky (1968) were the first to describe a leftward asymmetry of the planum temporale (PT) - an area of the temporal lobe that is thought to be involved in language processing. Because many neuroimaging studies have since replicated this finding, it has been argued that the PT asymmetry may represent the anatomical substrate for language lateralization (Foundas, Leonard, & Heilman, 1995; Geschwind & Levitsky, 1968; Moffat, 1998; Tzourio, Nkanga-Ngila, & Mazoyer, 1998). A leftward asymmetry, however, has also been reported in frontal language areas showing that the pars opercularis and pars triangularis of the inferior frontal gyrus (IFG) were larger in the left than right hemisphere (Falzi, Perrone, & Vignolo, 1982; Foundas et al., 1995, 1996, 1998, 2001; Keller et al., 2007). However, unlike the findings for the PT, subsequent research on inferior frontal lobe asymmetry revealed rather mixed results, with several studies reporting no hemispheric differences in volume, cortical thickness or surface area of the IFG pars opercularis and pars triangularis (Eckert et al., 2003; Good et al., 2001; Hervé et al., 2006; Knaus et al., 2006, 2007; Luders et al., 2004, 2006; Watkins et al., 2001). These conflicting findings have led to the assumption that if a structural asymmetry of the frontal language area exists, it is highly variable and therefore differs from functional language lateralization, which is more consistent (Keller, Crow, Foundas, Amunts, & Roberts, 2009).

6.1.1 Structure-function relationship of cortical language areas

To explore the relationship between cortical asymmetries and functional lateralization of language, later studies started to combine a variety of neuroimaging techniques (Chiarello, Vazquez, Felton, & Leonard, 2013; Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; S. Moffat, 1998; Tzourio-Mazoyer et al., 2015; Tzourio, Nkanga-Ngila, & Mazoyer, 1998; Warrier et al., 2009). Warrier and colleagues (2009), for instance, showed that the size of the left primary auditory cortex, relates to inter-individual differences in the processing of acoustic information. More specifically, in the left hemisphere, larger volumes of Heschl's gyrus were associated with greater extents of activation during temporal processing - which is thought to play an important role during language comprehension (Warrier et al., 2009). A similar relationship between leftward asymmetry of Heschl's gyrus and left-lateralized functional activation during speech listening in a large sample of neurotypical individuals was found by Tzourio-Mazoyer and colleagues (2015).

In terms of more frontal regions, a recent study by Chiarello et al. (2013) examined 200 young adults and revealed a robust leftward asymmetry of the insula, which was related to functional lateralization during word recognition. This finding is consistent with a previous study that demonstrated a relationship between volume asymmetry of the insula and functional lateralization for word generation (Keller et al., 2011). In their study, Keller et al. (2011) found that the structural asymmetry predicted not only language laterality in 88% of participants, who showed clear left or right lateralization as measured by FTCD, but also correlated positively with the degree of hemispheric specialization. Strikingly, hemispheric asymmetries of inferior frontal areas and the PT were not related to language lateralization (Keller et al., 2011).

In epileptic patients, a voxel-based morphometry (VBM) analysis not only revealed an asymmetry in grey matter volume in the posterior part of the inferior frontal gyrus (pars opercularis), but also showed that these differences were directly related to functional language lateralization as assessed by the Wada technique (Dorsaint-Pierre et al., 2006). This structural asymmetry favoured the left hemisphere in patients that were classified as left-lateralized for language and the right hemisphere in those classified as right-lateralized suggesting that it may reflect use-dependent plasticity in patients with language reorganization (Dorsaint-Pierre et al., 2006). The authors also confirmed a leftward asymmetry for the volume of the PT and Heschl's gyrus (HG; Dorsaint-Pierre et al., 2006). These asymmetries, however, were unrelated to functional language lateralization; for example only three out of eleven right-lateralized patients showed a greater volume of the right relative to the left HG, while the remaining eight and all bilateral patients revealed the same leftward asymmetry as the left-lateralized patients (Dorsaint-Pierre et al., 2006). Because anatomical asymmetries in HG and PT did not necessarily follow the direction of functional lateralization, Dorsaint-Pierre and colleagues (2006) concluded that these asymmetries may be predetermined and more resistant to change compared to those observed in the IFG.

Taken together, these studies indicate that no one individual cortical asymmetry underlies language lateralization (Keller et al., 2011). Instead it is more likely that multiple intra- and inter-hemispheric networks give rise to hemispheric specialization (Stephan, Fink, & Marshall, 2007). Thus, it has been suggested that underlying white matter fibre bundles may represent a better anatomical marker of language lateralization than cortical areas alone (Hagmann et al., 2006; Penhune et al., 1996).

6.1.2 Structure-function relationship of language-related white matter tracts

Diffusion MRI has been used to examine association fibres within the left hemisphere indicating that several white matter tracts connect Broca's area with Wernicke's area (Catani, Jones, & Ffytche, 2005; Dick, Bernal, & Tremblay, 2013; Friederici, 2009). At least one dorsal language pathway is thought to connect posterior temporal regions via the arcuate fasciculus (AF) with frontal areas including lateral parts of the superior temporal gyrus (STG) and middle temporal gyrus (MTG), whereas two ventrally located tracts, namely the extreme capsule (ECF) and the uncinate fasciculus, have been proposed to connect anterior inferior frontal cortex with the anterior STG, MTG and inferior temporal cortex (Frey et al., 2008; Parker et al., 2005).

Most diffusion MRI studies have focussed on the AF as a key anatomical substrate underlying functional language lateralization. Catani and colleagues (2007), for example, found a strong asymmetry of the AF favouring the left hemisphere; the left hemisphere bias of the AF was observed more frequently in their right-handed population (82.5%) than the one for the PT (65%). A leftward asymmetry of the AF associated with tract volume or fibre density has since been confirmed by several independent studies (e.g. Glasser & Rilling, 2008; Parker et al., 2005; Thiebaut de Schotten et al., 2011). Yet, only a handful of diffusion studies have examined the asymmetry of this white matter tract in relation to functional language lateralization and the results are split evenly: out of the four investigations, two demonstrated a significant correlation between laterality measures of structure and function (Powell et al., 2006; Vassal et al., 2016) and two did not (Propper et al., 2010; Vernooij et al., 2007).

6.1.3 Associations between dorsal and ventral language tracts and behaviour

Despite limited evidence of whether or not white matter asymmetries underlie functional ones, the dorsal pathway has been implicated in normal language processing (Glasser & Rilling, 2008). By comparing tractography results with peak activation coordinates from previous functional neuroimaging studies, Glasser and Rilling (2008) found that STG and MTG terminations of AF were strongly left lateralized and overlapped with phonological and lexical-semantic activations respectively. Functional relevance of language-related white matter tracts was further investigated by defining cortical network nodes based on FMRI activation that was associated with two different language tasks designed to functionally segregate the dorsal and ventral stream (Saur et al., 2008). While the dorsal pathway mediated sublexical repetition of speech, higher-level language comprehension was subserved by the ventral one (Saur et al., 2008).

These studies suggest that measures of the dorsal and ventral pathways may be correlated with language abilities in children and adults. Indeed, significant associations between the microstructural properties of white matter underlying the language network and language skills have been reported using diffusion MRI (e.g. Deutsch et al., 2005; Klingberg et al., 2000; Yeatman et al., 2011). For example, measures of FA in the left temporo-parietal region correlated positively with reading scores in neurotypical children and adults as well as reading impaired adults (Deutsch et al., 2005; Klingberg et al., 2000). Although Yeatman and colleagues (2011) found a significant association between diffusivity measures in the left AF and phonological awareness, too, FA values were negatively correlated with behaviour. Further analysis revealed that this correlation arose because children with better phonological abilities showed greater radial diffusivity in the left AF than children with poor phonological abilities (Yeatman et al., 2011). The authors also reported that indices of AF asymmetry based on volume measures correlated negatively with phonological memory and reading skills (Yeatman et al., 2011). Two other studies demonstrated a significant relation between AF asymmetry and language abilities (Catani et al., 2007; Catherine Lebel & Beaulieu, 2009). In a sample of 68 children, Lebel and Beaulieu (2009) showed that individuals with a stronger leftward asymmetry of AF volume scored higher on standardized test of receptive vocabulary. A positive correlation was also found between the asymmetry indices of the AF and verbal recall based on semantic association in neurotypical adults (Catani et al., 2007). Yet, the total number of correctly recalled words was lower for individuals with an extreme leftward asymmetry compared to those with bilateral patterns indicating that adults with more symmetric AF connections were better overall at remembering words (Catani et al., 2007).

This brief review of neuroimaging studies illustrates that the association between language-related brain asymmetries and their behavioural relevance is still not fully understood. Although much is known about diffusion properties of white matter tracts, there is limited data available to relate asymmetry measures of dorsal and ventral language tracts to measures of functional language lateralization and language abilities.

6.1.4 Aims of this study

In this study, I used diffusion MRI to investigate changes in the white matter microstructure of language-related fibre bundles and their functional relevance in the same group of typically and atypically lateralized adults who took part in my previous study. My primary aims were i) to determine whether typically and atypically lateralized participants, as identified by FTCD, show differences in the microstructure of white matter underlying the cortical language network; ii) to investigate whether the direction and degree of functional lateralization is related to structural asymmetries of language-related white matter pathways or strength of inter-hemispheric connections; iii) to assess whether integrity and asymmetry of language-related white matter tracts are related to language abilities.

6.2 Methods

Demographics and behavioural test-scores for all participants as well as the analysis pipeline for diffusion MRI data have been described previously and are briefly summarized here. For a detailed explanation of the neuropsychological assessment and calculation of functional laterality indices or the analysis of diffusion imaging data, in particular probabilistic tractography, please see Chapter 5 and Chapter 2 respectively.

6.2.1 Participants

Participants were the same as those who took part in my previous study: 32 neurotypical adults (14 women and 18 men, M_{age} = 25 years, SD_{age} = 5 years, left-handed = 12) with typical (left, N = 16) and atypical (right or bilateral, N = 16) language lateralization, as assessed by FTCD. The two groups were closely matched for age, gender and handedness. All participants had English as their first language and no history of developmental or psychiatric disorder. Functional laterality measures based on FTCD, FMRI and VHF task as well as neuropsychological data including standardized scores of IQ, language abilities (sight word reading, phonetic decoding, receptive vocabulary), and handedness were obtained in all individuals and are displayed in *Table 5.1* (page 168) and *Table 5.5* (page 186) of my previous study

(Chapter 5). The study was approved by the Medical Sciences Inter Divisional Research Ethics Committee of the University of Oxford (*MSD-IDREC-C1-2014-109)* and written informed consent was obtained from all volunteers.

6.2.2 MRI data acquisition

All images were obtained using a 3-T Siemens Trio scanner with a 32-channel head coil. At the beginning of each scan, a high-resolution T1-weighted MPRAGE (TR = 2040 ms, TE = 4.7 ms, flip angle = 8°, 192 transverse slices, 1-mm isotropic voxels) was acquired for registration and anatomical localization of the fibre tracts. Diffusion data were acquired using an echo-planar imaging sequence (TR = 8900 ms, TE = 94.8 ms, 64 transverse slices, 2-mm isotropic voxels) with b-value of 1500 s/mm^2 uniformly distributed across 60 gradient directions. Four non-diffusion-weighted images (b0) were collected every 16 volumes. Another b0 image was acquired after this sequence with reversed phase-encoding blips resulting in a pair of images with distortions going in opposite directions. From these pairs the susceptibility-induced off-resonance field was estimated using a method similar to that described by Andersson, Skare, and Ashburner (2003) as implemented in FSL (TOPUP, Smith et al., 2004) and the two images were combined into a single corrected one. The acquisition of diffusion-weighted images lasted about ten minutes and participants were asked to lie as still as possible with eyes open or closed - whichever made them feel more comfortable.

6.2.3 MRI data analysis

Diffusion data were analysed using FDT (FMRIB Diffusion Toolbox), part of the FMRIB Software Library (FSL: http://www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). First, two non-diffusion weighted images (b0) with opposed phase-encoding direction were used to estimate susceptibility induced distortion with the TOPUP tool in FSL (Andersson et al., 2003; Smith et al., 2004). The resulting distortion field was fed into EDDY (Andersson & Sotiropoulos, 2016), which employs a Gaussian Process predictor that additionally estimates eddy-current and head motion distortions before correcting all image distortions in a single resampling step. To account for partial or complete signal loss (dropout) caused by motion that coincides in time with the diffusions encoding part of the sequence, EDDY was run with outlier replacement (Andersson, Graham, Zsoldos, & Sotiropoulos, 2016). The dtifit function in FDT was used to fit the diffusion tensor model at each voxel in order to create images of fractional anisotropy (FA), mean diffusivity within a voxel (MD), axial diffusivity along the primary diffusion direction (L1), and radial diffusivity (RD) across the two axes perpendicular to L1.

Tract-based spatial statistics. To compare FA values between typically and atypically lateralized participants, TBSS (Tract-Based Spatial Statistics, Smith et al., 2006) was run including the standard analysis steps: i) aligning of all FA images to the FMRIB58_FA 1 x 1 x 1 mm standard-space image using nonlinear registration; ii) averaging and thinning all aligned FA images to generate an "FA skeleton" that represents the centre of white matter tracts common to all participants in the study; iii) thresholding the "FA skeleton" at 0.2 before projecting each participant's FA onto the mean skeleton by filling it with the highest FA values from the nearest relevant tract centre; iv) performing voxelwise statistics on the "FA skeleton" using t-tests to identify voxels that were significantly different between the two groups. Statistical inference was carried out using Threshold-Free Cluster Enhancement (TFCE) in randomise (exhaustive permutations) and changes were considered significant at $p < .05$ (fully corrected for multiple comparisons across space).

Probabilistic tractography. Probabilistic tractography was run using the BedpostX and ProbtrackX functions in FDT (Behrens et al., 2003). A multiple region-of-interest (ROI) approach (see Giorgio et al., 2010) was used to reconstruct white matter fibres bundles comprising the genu, body and splenium of the corpus callosum (CC) as well as those thought to represent the dorsal (AF) and ventral language tract (ECF) in each hemisphere of each participant. Four types of masks were applied to constrain probabilistic tracking including a seed mask (all voxels from which probabilistic tractography proceeded), target mask (only those tracts passing through it were retained), termination mask (used to terminate paths beyond seed and target regions), and exclusion mask (used to remove any paths entering this region). For the CC, AF, and ECF the exact placement of each mask has been described in Chapter 2.

All masks were defined in standard space and registered to the native diffusion space of each participant via nonlinear registration using FNIRT (FMRIB's Non-linear Image Registration Tool, Andersson, Jenkinson & Smith, 2007). Probabilistic maps were thresholded, binarized, and used to mask individual FA imaged to extract mean FA and tract volume for further analysis. There is no straightforward method to define a threshold and often an arbitrary cut-off is chosen. Here, I used the robust maximum intensity of each normalized tract (i.e. the probabilistic map was first divided by the total number of streamlines) as an image-specific threshold.

6.2.4 Statistical analysis

SPSS (www.ibm.com/software/analytics/spss) was used for all statistical analyses. Unless otherwise stated, the assumption of normal distribution was assessed using Shapiro-Wilk test and Bonferroni correction was applied for multiple post-hoc comparisons. If applicable, Levene's and Box's M tests were used to determine homogeneity of variances and covariances. The assumption of sphericity was examined by Mauchly's test, and Greenhouse-Geisser correction was applied when violated. Because there were only two levels of repeated measures for the AF and ECF (left vs. right), sphericity was not taken into account.

Between-group comparison of tract measures. A two-way mixed analysis of variance (ANOVA), with a between-subjects factor of group (typical vs. atypical) and a within-subjects factor of either hemisphere (left vs. right) or portion of the CC (genu vs. body vs. splenium) was used to compare mean FA and total volume for each tract.

Asymmetry assessment. To examine hemispheric differences in the dorsal and ventral language pathway indices of asymmetry were calculated based on mean FA and total tract volume using the formula: $AI = (T_L - T_R) / (T_L + T_R)$, described in Chapter 2. Positive indices ($AI_{max} = 1$) indicated leftward asymmetry of white matter tracts, whereas negative indices ($AI_{min} = -1$) indicated rightward asymmetry. One-sample t-tests were used to determine whether mean AI values for typical and atypical participants were significantly different from zero. Another mixed ANOVA was performed to assess differences in the asymmetry of dorsal and ventral language pathways between typical and atypical participants. For this analysis, group (typical vs. atypical) was used as a between-subjects factor and tract (AF vs. ECF) as a within-subjects factor.

Structure-function relationships. Spearman's correlations between LIs obtained by FTCD, FMRI, or VHF and AIs of the AF or ECF were computed to determine whether functional lateralization was associated with asymmetries of language-related white matter pathways. LI_{FMRI} were calculated for word generation (WG), pyramids and palm trees (PPT), and auditory naming (AN) based on activation within frontal and temporal lobes.

Tract measures and neuropsychological assessment. The relationship between tract measures (mean FA, volume) or asymmetry (AI) of white matter pathways and individual scores on standardized test of IQ, language, and relative hand skill were explored by calculating Spearman's rho. Because typical and atypical participants did not differ in any behavioural measure (see Chapter 5), the two groups were collapsed for this analysis.

Just as for my analyses described in Chapter 5, power calculations showed that the sample size of 16 for each group was adequate to detect differences significant at 5% (one-tailed, 80% power) if the effect size of this difference was large.

6.3 Results

6.3.1 Comparison of tract-based spatial statistics (TBSS) in typically versus atypically lateralized participants

Mean FA derived from all cerebral voxels did not differ between typical (*M* = 0.25, *SD* = 0.010) and atypical participants (*M* = 0.26, *SD* = 0.006).

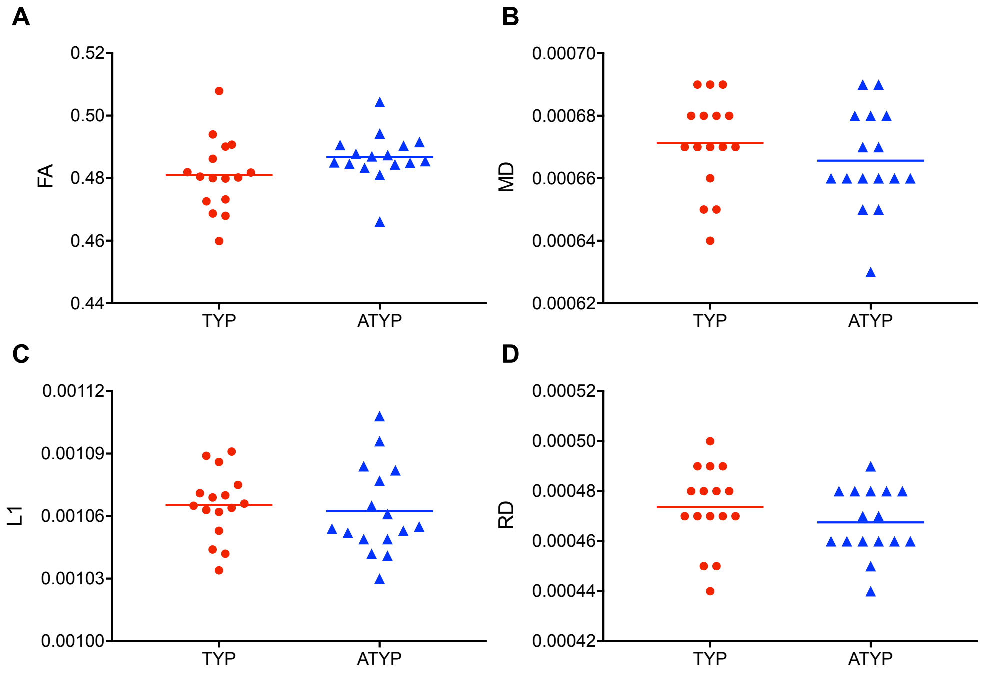


Figure 6.1 *White matter diffusion properties for participants with typical and atypical language lateralization, as assessed by FTCD. Individual values of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1), and radial diffusivity (RD) extracted from the TBSS skeleton for typical are plotted in graph (A), (B), (C), and (D), respectively. Lines represent the mean of each group.*

TBSS analysis revealed no significant group differences in FA, MD, L1, or RD following correction for multiple comparison using threshold-free cluster enhancement (TFCE). Further, no trends were identified when examining white matter diffusion properties at an uncorrected threshold of $p < 0.005$. There were also no significant differences in mean FA ($p = .36$), MD ($p = .77$), L1 ($p = .98$) and RD values ($p = .67$) between typically and atypically lateralized participants when only the TBSS skeleton voxels were considered (*Figure 6.1*).

6.3.2 Comparison of tract measures in typically versus atypically lateralized participants

Using probabilistic tractography, the genu, body, and splenium of the CC as well as the AF, as part of the dorsal, and the ECF, as part of the ventral language pathway were successfully reconstructed in all participants (*Figure 6.2*). Total volume and mean FA were extracted for each tract and, if applicable, used to calculated AIs. Mixed ANOVAs were run to determine whether mean FA or volume for the left and right hemisphere (or part of the CC) differed between typically and atypically lateralized participants. Preliminary assumption testing demonstrated that the assumption of homogeneity of variances ($p > .05$) and covariances ($p > .05$) was met for all tract measures.

For the CC, both groups showed similar values of mean FA and volume for the genu, body and splenium of the CC (*Table 6.1*). Statistical analysis revealed neither a significant interaction between groups and CC portion for mean FA ($p = .904$) or volume ($p = .800$), nor a significant main effect of group ($p = .076$) confirming that typical and atypical participants did not differ in white matter integrity or size of the CC. As expected, mean FA ($F(1,60) = 486$, $p < .0005$, $\eta_p^2 = .94$) and volume ($F(2,60)$

= 1312, $p < .0005$, $\eta_p^2 = .98$) differed significantly among all three parts of the CC - except the volume of the genu and splenium which were similar.

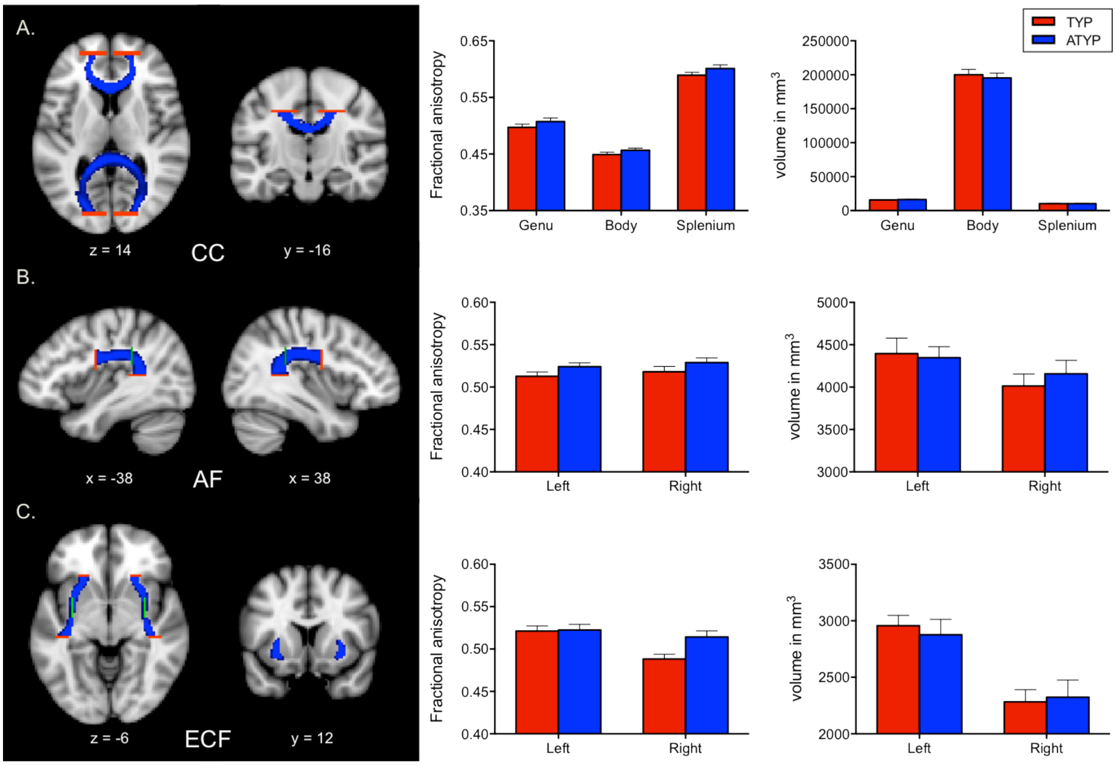


Figure 6.2 *Post-imaging_reconstruction of white matter pathways. Underlying brain image is the MNI152 template T1-weighted image in standard space. Blue areas are the average of the thresholded tracts across all participants between the seed masks (green) and the target masks (red). (A) The genu and splenium of the corpus callosum (CC) are displayed on an axial slice 14mm above the bicommissural plane and the callosal body on a coronal slice at 16 mm posterior to the anterior commissure. (B) The arcuate fasciculus (AF) is shown on sagittal slice through the left and right hemisphere 38 mm from the midline. (C) Extreme capsule fasciculus is shown for both hemispheres on an axial slice at 6 mm below the bicommissural plane. Adjacent bargraphs display mean FA (left) and tract volume (right) for participants with typical (red) and atypical language lateralization (blue). Error bars indicate the standard error of the mean (SEM).*

As shown in *Table 6.1*, mean FA values obtained from the left and right AF, were very similar for typically and atypically lateralized participants, too. No significant interaction between group and hemisphere ($p = .934$) was found, and the main effects of group ($p = .121$) and hemisphere ($p = .114$) were also not significant. Thus, white matter integrity of the left and right AF did not differ between the two groups. The volume of the left AF was numerically higher than the volume of the right AF for typical as well as atypical participants (*Table 6.1*). Mixed ANOVA analysis, however, revealed no significant interaction between group and hemisphere ($p = .516$), nor a significant main effect of group ($p = .774$) or hemisphere ($p = .059$) indicating that the size of AF was similar for the left and right hemisphere as well as for typically and atypically lateralized participants.

Table 6.1. *Fractional anisotropy (FA) and tract volume for white matter pathways. Group statistics (M ± SD) are shown for typically lateralized (left) and atypically lateralized (non-left) participants*

		Mean FA		**Volume in mm3**	
		Atypical	Typical	Atypical	Typical
Corpus callosum	Genu	0.51 ± 0.025	0.50 ± 0.023	16250 ± 2151	15804 ± 1667
	Body	0.56 ± 0.015	0.45 ± 0.016	195535 ± 27530	200148 ± 31227
	Splenium	0.60 ± 0.026	0.59 ± 0.020	10299 ± 1750	10357 ± 1743
Dorsal tract (AF)	Left	0.52 ± 0.018	0.51 ± 0.020,	4347 ± 525	4395 ± 735
	Right	0.53 ± 0.022	0.52 ± 0.025	4158 ± 636	4015 ± 562
Ventral tract (ECF)	Left	0.52 ± 0.027	0.52 ± 0.024	2877 ± 547	2957 ± 363
	Right	0.51 ± 0.029	0.49 ± 0.023	2325 ± 606	2283 ± 432

In participants with typical language lateralization, mean FA of the left ECF was higher than mean FA of the right ECF, as indicated by visual inspection of *Figure 6.2*. This hemispheric difference appeared to be less evident in atypical participants. Statistical analysis confirmed a significant interaction between group and hemisphere on mean FA ($F(1,30) = 11.0$, $p = .002$, $\eta_p^2 = .27$). Mean FA of the right, but not left ECF differed significantly between the two groups ($F(1,15) = 7.90$, $p = .009$, $\eta_p^2 = .21$). In addition, typical participants showed significantly higher FA values for the left compared to the right ECF ($F(1,15) = 32.9$, $p < .0005$, $\eta_p^2 = .69$), while atypical participants did not ($p = .098$). The volume of the ECF was numerically higher for the left relative to the right ECF for both groups (*Table 6.1*). Consistent with this observation, the mixed ANOVA revealed no significant interaction between group and hemisphere ($p = .525$), but a significant main effect of hemisphere on volume ($F(1,30) = 41.8$, $p < .0005$, $\eta_p^2 = .58$) indicating that the left ECF was larger than the right ECF across typically and atypically lateralized participants. There was no significant main effect of group ($p = .896$) on ECF volume.

6.3.3 *Asymmetry of language-related fibre tracts in typically and atypically lateralized participants*

Consistent with these results, AIs based on mean FA for the AF (*M* ± *SD*: TYP -0.005 ± 0.017, ATY -0.004 ± 0.017) appeared to be similar for participants with typical and atypical language lateralization, while those based on mean FA for the ECF (*M* ± *SD*: TYP 0.033 ± 0.023, ATY 0.008 ± 0.018) were numerically higher for typical relative to atypical participants (*Figure 6.3*).

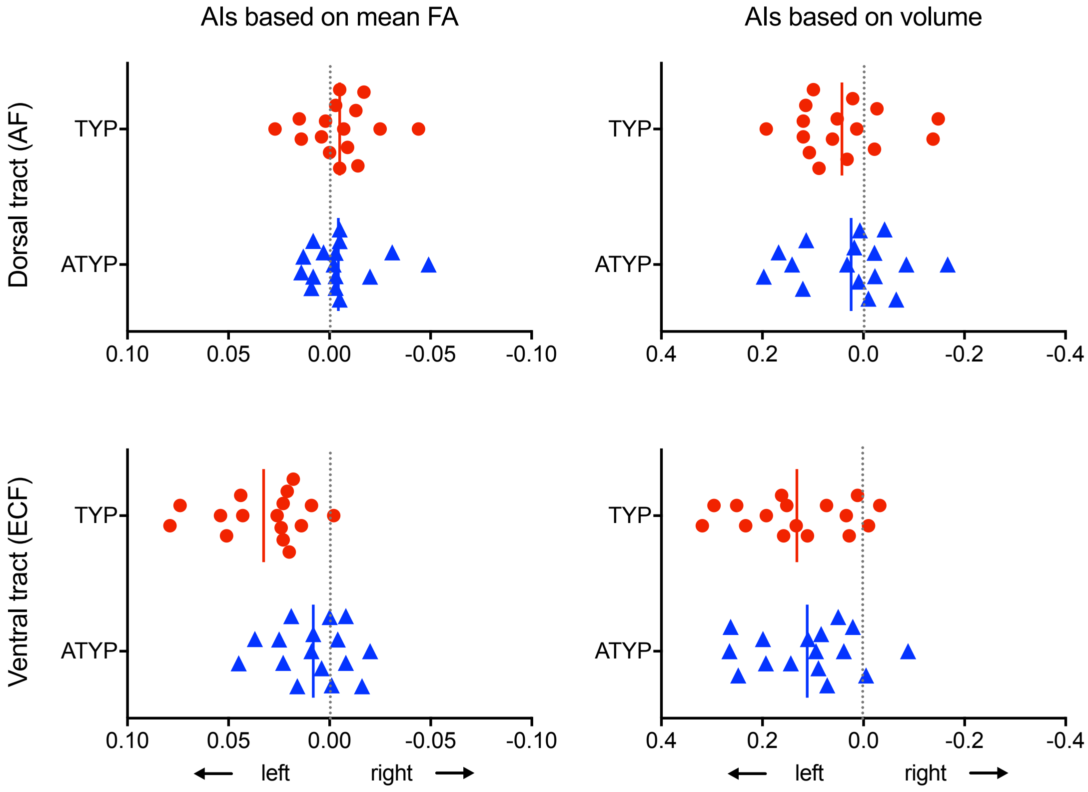


Figure 6.3. *Asymmetry indices (AI) for dorsal and ventral language pathways. Individual data are plotted for participants with typical (TYP, red circles) and atypical (ATYP, blue triangles) functional language lateralization. The upper row shows LIs for the dorsal white matter tract (arcuate fasciculus, AF) and the bottom row for the ventral one (extreme capsule fasciculus, ECF) based on mean FA (left) and volume measures (right). The mean of each group is marked with a line. Positive LIs indicate leftward and negative values rightward asymmetry.*

I ran a mixed ANOVA to test whether AIs based on mean FA values for the AF and ECF differed between the two groups. There was a statistically significant interaction between group and white matter pathway on AI ($F(1,30) = 9.40$, $p = .005$, $\eta_p^2 = .24$). Follow-up analysis showed that the two groups differed significantly in AIs for the

ECF ($F(1,30) = 11.2$, $p = .002$, $\eta_p^2 = .27$), but not AF ($p = .924$) indicating that the ECF had a stronger leftward asymmetry in typically lateralized compared to atypically lateralized participants. In addition, there was a simple main effect of tract demonstrating that in both groups AI values for the ECF were significantly higher relative to those for the AF (TYP: ($F(1,15) = 32.9$, $p < .0005$, $\eta_p^2 = .69$; ATYP: $F(1,15) = 32.9$, $p < .0005$, $\eta_p^2 = .69$). One-sample t-tests confirmed that only AI values based on mean FA from the ECF in the typical group were significantly different from zero ($t(15) = 5.71$, $p < .0005$, $d = 2.95$).

As illustrated in *Figure 6.3*, mean AIs based on the volume of the AF ($M \pm SD$: TYP -0.043 ± 0.092, ATY 0.024 ± 0.099) as well as ECF ($M \pm SD$: TYP 0.13 ± 0.11, ATY -0.11 ± 0.10) were slightly higher in typical relative to atypical participants. However, mixed ANOVA analysis revealed no significant interaction ($p = .959$) or main effect of group ($p = .431$) on AIs. The main effect of tract reached statistical significance tract ($F(1,30) = 11.6$, $p = .002$, $\eta_p^2 = .28$) indicating that ECF was more strongly left lateralized compared to AF across typical and atypical participants. This was consistent with the results from one-sample t-tests, which indicated the AI values based on ECF, but not AF volume, were significantly different from zero for both participants with typical and atypical language lateralization (TYP: $t(15) = 4.85$, $p < .0005$, $d = 2.50$; ATYP: $t(15) = 4.38$, $p = .001$, $d = 2.26$).

6.3.4 Relationship between indices of functional lateralization and structural asymmetry

Spearman's rho was calculated to assess the relationship between functional lateralization and structural asymmetry of the dorsal and ventral language pathways. For the AF, there was a significant positive relationship between AIs based on volume and LI_{FMRI} associated with PPT ($r_S(32) = .38$, $p = .032$) and AN ($r_S(32) = .39$, $p =$

.026); i.e. an increased leftward asymmetry of the dorsal language pathway was related to increased left-lateralization of functional activity during both language paradigms. There were no significant correlations between $\mathrm{LI}_{\mathrm{FTCD}}$ or $\mathrm{LI}_{\mathrm{VHF}}$ and AIs based on mean FA or volume for the AF.

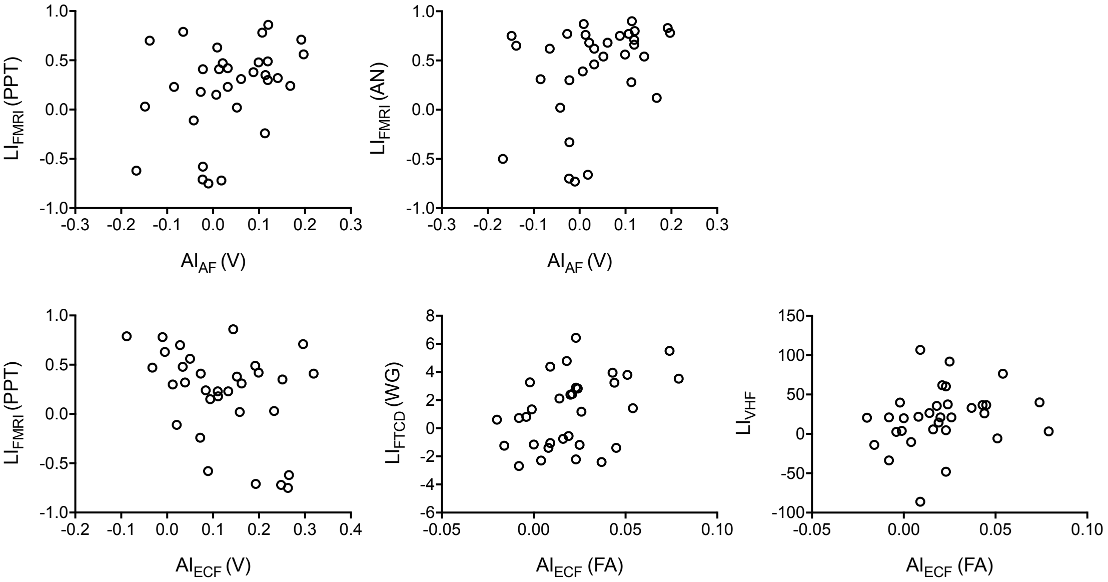


Figure 6.4*. Relationship between functional lateralization and structural asymmetry of white matter pathways. Scatterplots display asymmetry indices (AI) based on dorsal (AF, top) and ventral (ECF, bottom) language tracts on the x-axis and lateralization indices (LI) obtained by FMRI, FTCD, or VHF task on the y-axis. A positive AI/LI indicates left and negative one right asymmetry/lateralization.*

For the ECF, AIs based on mean FA correlated significantly with $\mathrm{LI}_{\mathrm{FTCD}}$ ($r_S(32) = .37$, $p = .036$) and $\mathrm{LI}_{\mathrm{VHF}}$ ($r_S(32) = .36$, $p = .044$). Both coefficients revealed a moderate positive relationship suggesting that higher LI values were associated with a stronger left-hemisphere bias of the ECF (*Figure 6.4*). In addition, AIs based on the volume of the ECF were negatively correlated with $\mathrm{LI}_{\mathrm{FMRI}}$ during PPT ($r_S(32) = -.36$, $p = .041$) indicating that increased left-lateralized activation was accompanied by reduced asymmetry of the ventral language pathway. There were no significant correlations between ECF asymmetry based on mean FA or volume and $\mathrm{LI}_{\mathrm{FMRI}}$ for WG or AN. Correlations were primarily used for exploratory data analysis, however, it should be noted that none of these function-structure relationships remained significant after correcting for multiple comparisons ($p_{\mathrm{corr}} < .005$).

6.3.5 Correlation of tract measures with neuropsychological data

Spearman's correlations were computed to explore the relationships between tract measures (mean FA and total volume) of the CC or AIs of the dorsal/ventral white matter language pathways and performance during neuropsychological assessment. The latter included standardized test of verbal (VIQ) and non-verbal (PIQ) intelligence, as assessed by the WASI, as well as measures of sight-word reading (TOWRE-sw), phonemic decoding (TOWRE-pd), receptive vocabulary (BPVS-II), and handedness (EHI, QHP, PEG). There were no significant correlations between total tract volume/mean FA obtained from the CC or AF asymmetry based on these measures and any behavioural test score.

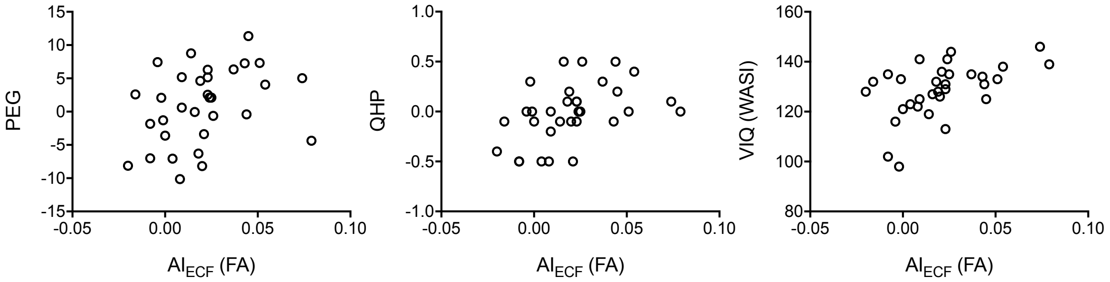


Figure 6.5. *Associations between language-related tracts and performance during neuropsychological assessment. Scatterplots display tract measures including fractional anisotropy (FA), volume in mm^3 (V), and asymmetry indices (AI) based on dorsal (AF, top two rows) and ventral (ECF, bottom two rows) pathways on the x-axis and behavioural measures on the y-axis. Positive AIs indicate leftward and negative rightward asymmetry. PEG - Peg-moving (relative hand skill quotient based on reaction times with positive values indicating right-handedness); QHP - Quantification of Hand Preference (hand preference bias based on the performance on a reaching task with positive values indicating right-handedness); VIQ - Verbal Intelligence Quotient (standard scores for verbal subtest of the WASI).*

For the ventral language tract, AIs calculated from mean FA values correlated positively with VIQ ($r_S(32) = 53$, $p = .002$) suggesting that participants with increased left-hemisphere asymmetry of the ECF scored higher on test of verbal intelligence (*Figure 6.5*). In addition, analysis revealed a significant association between handedness, as assessed by QHP ($r_S(32) = .52$, $p = .002$) and PEG ($r_S(32) = .38$, $p = .034$) and ECF asymmetry based on mean FA. The positive correlation coefficients indicated that more strongly right-handed participants showed an increased leftward asymmetry of the ventral language path (*Figure 6.5)*. While the relationship between ECF asymmetry and scores of VIQ or QHP remained significant after correcting for the number of correlations ($p_{corr} < .008$), the association between AIs and PEG did not.

6.4 Discussion

In this study, I used diffusion MRI in combination with different measures of functional lateralization including FTCD, FMRI, and VHF to assess the structure-function relationship of white matter pathways associated with language processing. Specifically, I examined differences in white matter integrity (FA), volume, and asymmetry of the dorsal (AF) and ventral (ECF) language tracts as well as inter-hemispheric connections (CC) between healthy participants with typical and atypical language lateralization. While whole-brain analysis of white matter diffusion properties revealed no differences in FA, MD, L1, or RD between the two groups, leftward asymmetry (based on mean FA) of the ventral, but not dorsal language tract, was significantly reduced in atypical compared to typical participants. I also demonstrated significant associations between structural asymmetries of white matter pathways and measures of functional lateralization. For the dorsal tract, participants with an increased leftward asymmetry based on AF volume, showed more strongly left-lateralized activation during PPT and AN in FMRI. The opposite trend was observed for the ventral tract: participants with an increased rightward asymmetry based on ECF volume were more strongly left lateralized during PPT in FMRI. Indices of asymmetry based on mean FA of the ECF, however, were positively associated with measures of language lateralization obtained by FTCD and VHF.

Considering the sample size of this study these exploratory analyses should be treated as trends; importantly, reported findings require replication, as they were not significant once corrected for the number of correlations explored. In addition, asymmetry of the ventral language pathway based on mean FA correlated significantly with behaviour indicating that participants with greater leftward ECF asymmetry were more strongly right-handed, and scored higher on standardized tests of verbal IQ.

6.4.1 Diffusion properties of cerebral white matter in typically and atypically lateralized participants

One could think of various reasons why this study did not yield any differences between participants with typical and atypical language lateralization in diffusion properties (FA, MD, L1, RD) derived from the white matter of the whole brain. With the aim of optimizing voxel-wise analysis for diffusion MRI data sets, TBSS tries to overcome smoothing and misalignment issues in DTI-based group comparisons (Smith et al., 2006). Although TBSS is a very popular approach for performing voxel-wise DTI analysis, as for all methods, there are some limitations that should be taken into account. For instance, only the closest maximal values of the investigated diffusion property are projected onto the skeleton and thus evaluated; TBSS therefore builds upon an inherent assumption that pathology/variability will mainly affect local maxima, which is not necessarily true (Van Hecke et al., 2015). More importantly, by reducing the image to a skeleton, which comprises a relatively small percentage of the total diffusion data, a lot of potentially valuable information is being ignored in this analysis. TBSS might have been not sensitive enough to detect subtle, yet significant, group differences in white matter diffusion properties - especially when comparing neurotypical adults. In addition, the TFCE correction for multiple comparisons compensates for false positives, but not false negatives; with a sample size of 16 in two group, this study would most likely only be sensitive to effect sizes that were large - obviously increasing the sample size would offer greater sensitivity. Recruiting 16 adults with atypical language lateralization, however, is not a trivial undertaking as only 4-7.5% of neurotypical right-handers and 15-27% of neurotypical left-handers show right or weak functional lateralization for language (Knecht et al., 2000a; Pujol et al., 1999).

In this study, I used FTCD to determine functional language lateralization in a large number of adults. Although it has been shown that FTCD is a suitable and very robust tool for the quantitative measurement of language lateralization (e.g. Knecht, 1998b), LI classification (left, right, bilateral) based on this technique was not always concordant with other measures of language laterality including FMRI or VHF (see Chapter 5). The question therefore unfolds - which measure should be used for grouping participants as typically or atypically lateralized? Until further validation of either method we cannot be sure which assessment - if any - is more accurate (see Chapter 7 for detailed discussion).

6.4.2 Asymmetry of dorsal and ventral language pathways in typical and atypical language lateralization

One hypothesis to explain the ontogenesis of hemispheric specialization for language suggests that structural differences between left and right hemispheres underlie functional lateralization. Despite advances in non-invasive neuroimaging techniques and extensive research, the search for a direct and unequivocal structure-function relationship is enduring. Early brain imaging studies have focussed on cortical asymmetries, in particular of the upper surface of the temporal lobe adjacent to the Sylvian fissure, the planum temporale (PT), as a potential marker for language lateralization. Although leftward asymmetries with respect to size, length and cytoarchitecture of the PT have been demonstrated (e.g. Galaburda, Sanides, & Geschwind, 1978; Geschwind & Levitsky, 1968), the extent of PT asymmetry did not correlate with lateralization of language function as assessed by the Wada procedure (Dorsaint-Pierre et al., 2006). A significant structure-function association, however, has been reported for the volume, number of streamlines, and mean FA of the AF suggesting that asymmetries of perisylvian white matter may be better anatomical substrates for language laterality (Powell et al., 2006; Vassal et al., 2016; Vernooij et al., 2007). My findings provide supporting evidence for such a direct relationship between functional lateralization as assessed by FMRI and asymmetry of the dorsal language tract: LIs based on fronto-temporal activation during word generation or auditory naming correlated positively with indices of asymmetry based on AF volume. It is important to note, that this association did not remain statistically significant after correcting for multiple comparisons and should therefore be interpreted with caution; especially when taking into account that my sample did not reveal a clear leftward asymmetry of the dorsal language tract in the first place. Across participants the volume of the left AF was numerically larger than that of the right AF, and statistical analysis indicated that the AF asymmetry was approaching, but didn't reach statistical significance ($p = .059$). Research has shown that shape and size of white matter tracts within the single hemisphere can vary considerably between participants (Bürgel, Schormann, Schleicher, & Zilles, 1999). Since half of my participants were selected for their atypical language lateralization, inter-subject variability may be further increased in this study. It is therefore reasonable to assume that the lack of significant hemispheric differences in AF volume might be due to insufficient statistical power.

For the ventral language pathway, I demonstrated a significant left-lateralized pattern of connectivity for both ECF volume and FA. Strikingly, asymmetry of the ECF based on mean FA was observed in typical but not atypical participants suggesting that hemispheric differences in the white matter integrity of the ventral language pathway may provide an anatomical substrate for language lateralization in healthy adults. While differences in the position or size of language-related white matter connections could conceivably be explained by gross anatomical variability in brain size or shape, differences in tract asymmetry based on mean FA may represent more complex white matter variations in axonal diameter, myelination, or fibre coherence that could be related to genetic inheritance, experience, or the development of new skills.

Overall, these findings are in good agreement with previous studies that have not only demonstrated a leftward asymmetry of the ventral language pathway (Parker et al., 2005), but also a correlation between measures of ECF asymmetry and functional language lateralization (Powell et al., 2006). For example, Powell and colleagues (2006) combined functional and diffusion MRI to study the relationship between activation in frontal and temporal language cortex and the white matter connecting theses regions. They found a significant correlation between the asymmetry of mean FA of the identified white matter pathways and lateralization of activation in frontal and temporal lobes, but not between tract volumes and functional activation (Powell et al., 2006). In this study, ECF asymmetry based on FA also correlated with the degree of language lateralization, as assessed by FTCD and VHF task indicating a positive relationship between structure and function. All the reported structure-function relationships, however, should be treated with caution and require replication, since no association survived correction for multiple comparisons.

6.4.3 Relationship between white matter asymmetries and behaviour

This study is the first to examine the behavioural relevance of dorsal and ventral language pathways by measuring language abilities and white matter asymmetries based on volume and mean FA in individual participants with typical and atypical language lateralization. Although the two groups did not differ in their performance on any standardized test of cognitive ability or linguistic skill, asymmetry of the ventral (but not dorsal) language tract based on mean FA correlated positively with verbal intelligence and measures of handedness. This finding is in line with previous studies that found significant associations between microstructural properties of white matter underlying the left temporo-parietal language cortex and reading abilities in children and adults (Deutsch et al., 2005; Klingberg et al., 2000). Post-mortem dissection case studies (Gluhbegovic & Williams, 1980) and diffusion MRI investigations (Makris et al., 1997, 2005) have confirmed that this area comprises sagittally oriented fibres in the ECF and AF that project from occipital, inferior parietal, and temporal cortices to inferior frontal cortex. Variability in the white mater integrity of these connections could therefore influence communication between anterior and posterior language areas resulting in inter-individual differences in language abilities more generally. In fact, the ventral language pathway has been recently implicated in verbal working memory functions (Cabeza & Nyberg, 2000; Dronkers et al., 2004). Because of the correlational nature of my analyses, however, it is not possible to determine whether variations in behaviour are caused by FA differences in the ventral language paths or vice versa. Longitudinal studies that combine diffusion MRI with standardized test of language are necessary to address this question more directly. Yeatman et al. (2012), for instance, followed a cohort of children aged 7 to 12 years longitudinally for 3 years to disambiguate the relationship between white-matter maturation and reading acquisition. They found that the pattern white matter development differed significantly among children in the left AF and left inferior longitudinal fasciculus: children with good reading skills initially had low FA that increased over the 3-year period, while poor readers had higher initial FA the decreased over time (Yeatman, Dougherty, Ben-Shachar, et al., 2012). Whether such developmental trajectories can be extended to other aspects of language remains to be elucidated.

Contrary to previous findings, I did not find any significant correlations between asymmetry indices of the dorsal language pathway and behaviour. Although most studies demonstrated such a relationship in neurotypical participants (Catani et al., 2007; Catherine Lebel & Beaulieu, 2009; Yeatman et al., 2011), the reports about the direction of this association are inconsistent. For example, Catani and colleagues (2007) found a negative correlation between AF asymmetry and verbal recall indicating that individuals with more symmetric patterns of dorsal white matter connections are better at learning word using semantic association. Lebel and Beaulieu (2009) on the other hand demonstrated a positive correlation between AF asymmetry and phonological skills measured by the NEPSY or vocabulary measured by the Peabody Picture Test in children aged 5 to 13 years. Yet another study revealed an association between verbal fluency scores (letter fluency) and axial diffusivity, but not FA, of the left AF (Phillips et al., 2011). Discrepancies between studies may result from the different strategies used for post-imaging fibre tracking. Specifically, the current study used a multiple ROI approach to reconstruct the classical arching pathway of the AF, which has been described as the long direct segment (Catani et al., 2005) or temporal component of the superior longitudinal fasciculus (SLF, Wakana et al., 2004). Other subcomponents of the left SLF - as part of the dorsal language tract -

have been shown to differ according to their end points in frontal (Broca's area vs. BA 6), parietal (supramarginal vs. angular areas), and middle or superior temporal cortex (Makris et al., 2005). Differences in tracking algorithms (deterministic vs. probabilistic) as well as the use of ROIs and their placement my thus account for differences in associations between AF asymmetry and behaviour reported in diffusion MRI studies. Further research is needed to assess the precise role of the AF with respect to language and whether or not diffusion properties of axon bundles that project dorsally to and from cortical language regions are sensitive biomarkers for language proficiency.

6.4.4 Limitations and future directions

In spite of advanced imaging analysis methods, some limitations that are relevant to the current research should be noted. First, the ROIs that I used to track white matter pathways were defined anatomically and not functionally. This may be problematic, because the exact location, shape and size of cortical language areas is likely to vary not only among individuals, but also between the left and right hemisphere. Other studies have therefore used FMRI-derived seed and target regions, which conceivably take inter-subject variability into account. Powell et al. (2006), for example, used tractography to reconstruct white matter connections of cortical regions activated by expressive and receptive language tasks and found that indices of functional lateralization correlated significantly with indices of asymmetry of the identified tracts. However, the ROI approached used in this study restricted analyses to white matter areas, and was thus not affected by cortical asymmetries or differences in brain function; on the contrary, it allowed me to use identical targets in all participants - typical and atypical ones.

Further, the precise cellular and histological basis for inter-subject variability in anisotropy is unknown. In fact, several microstructural characteristics could affect measures of FA including the coherence or thickness of axons, the amount of myelin, or structural disruptions of white matter tracts. Nonetheless, the significant correlation between FA asymmetry of the ECF and behaviour suggests that diffusion MRI can be used to provide complementary information about white matter contributions to cognition. While clearly more research in larger samples is needed, my findings support the idea that leftward asymmetry of ventral language tract might be one of the factors underlying both functional language lateralization and behaviour. Recent research has suggested that other tracts such as the uncinate fasciculus contribute to the white matter language circuitry (Dick et al., 2013; Friederici, 2009). It is possible that behaviour assessed in this study may also correlate with diffusion properties and/or asymmetry of other white matter pathways that were not included in this study.

As noted in my previous chapter, most participants of this sample scored above the normal range on standardized test of intelligence and/or language. The homogeneity within this data might have obscured associations between properties of white matter pathways and behaviour. It would be interesting - if not necessary - to examine the structure-function relationship and its behavioural relevance in a cohort that encompasses a greater range of language abilities. Extending this line of research to larger samples of healthy participants with typical and atypical language lateralization as well as individuals with (developmental) language impairment would enable us to investigate associations between functional lateralization and structural asymmetry more systematically.

Lastly, a functional interpretation of the asymmetry of language-related white matter pathways should be treated with some caution, as fronto-temporal connections may not be exclusively involved in language processing. The AF, for instance, may play a role in acoustic processing and encoding of speech sounds, which could be functionally lateralized to the left hemisphere, irrespective of the side of language lateralization (Penhune et al., 1996; Zatorre & Belin, 2001; Zatorre et al., 2002). Thus, leftward asymmetries of dorsal and ventral language tracts could be driven by their involvement in other tasks in addition to their role in language processing.

6.5 Conclusion

In summary, I have combined diffusion MRI with functional measures of language lateralization to assess the pattern of language-related white matter pathways in healthy participants with typical and atypical language laterality. I have demonstrated an asymmetry with stronger white matter connections between inferior frontal and superior temporal areas via the ECF in the left hemisphere of participants with typical language lateralization. This asymmetry was not only absent in atypically lateralized participants, but also correlated positively with right-handedness and increased scores of verbal IQ. The pattern of white matter asymmetry revealed in this study - especially with respect to ventral language tract - provides new insights into neuroanatomical markers of (atypical) language lateralization in otherwise healthy participants.

7

General discussion

Language and the ability to learn language is a trait unique to humans. In most neurotypical adults, language is lateralized to the left cerebral hemisphere, with a higher percentage of right-handed individuals displaying left-hemisphere specialization compared with left-handed ones (Knecht et al., 2000b; Pujol et al., 1999; Rasmussen & Milner, 1977). Both functional and structural cerebral asymmetries related to language processing have been discovered (see Toga & Thompson, 2003 for review). In addition, some studies have linked the direction and/or degree of hemispheric specialization to language abilities (e.g. Mellet et al., 2014; Powell, Kemp, & García-Finaña, 2012; van Ettinger-Veenstra et al., 2010). Developmental language disorders, for instance, have been associated with atypical (non-left) asymmetries in language-related brain structures and functions. One such disorder is specific language impairment (SLI), which selectively affects the domain of language processing (Bishop, 1997). Some neuroimaging studies suggest that individuals with SLI are more likely to exhibit reduced or reversed structural and functional asymmetries in posterior temporal and inferior frontal language regions (e.g. Gauger, Lombardino, & Leonard, 1997; Jernigan et al., 1991; Leonard et al., 2002). In contrast, in the general population, most individuals with atypical cerebral lateralization have typical cognitive development. With such paradoxical findings, we need further research to consolidate the evidence and guide how best to conceptualize and reliably measure language-related cerebral asymmetries.

In this thesis, I investigated the neural underpinning of language processing and its representation in the two hemispheres, combining the methods of DTI, FMRI and FTCD. My aim was to examine how asymmetries in brain structure and function relate to language abilities, both in typically developing individuals and in those with language impairment.

7.1 Summary of results and contributions

In my first study I assessed the neural correlates of SLI in the white matter underlying the cortical language network. I compared diffusion tensor imaging (DTI) data obtained from families with at least one language-impaired child versus control families. I demonstrated that language-impaired children (but not adults) have poor white matter integrity, as indicated by reduced fractional anisotropy (FA), in the corpus callosum and white matter areas corresponding to the dorsal and ventral language tracts. Since the corpus callosum is the major neural pathway linking homologous brain regions, the decrease in callosal FA is likely to reflect reduced inter-hemispheric connectivity in language-impaired children. It is conceivable that abnormalities in the white matter of the corpus callosum may relate to the altered functional lateralization observed in SLI (e.g. Chiron et al., 1999; de Guibert et al., 2011; Ors et al., 2005).

I investigated these abnormalities further in my second study, which looked at functional lateralization associated with auditory processing in SLI. Using FMRI, the same children and parents who took part in my first study were scanned while listening to pure tone patterns that differed in the temporal and functional domain. I found that children with SLI showed reduced responses to auditory stimulation relative to typically developing peers and unaffected siblings. My data, however, did not reveal the expected pattern of left-hemisphere specialization for increased temporal processing and right-hemisphere specialization for increased spectral processing - neither in families with a history of SLI nor in control families. Because I failed to replicate the predicted pattern of cerebral lateralization for temporal versus spectral processing in typically developing children and adults, it is not clear whether the non-lateralized pattern seen in language-impaired individuals is caused by a deficit in the group or by an issue with my experimental task.

While several neuroimaging studies have provided evidence of altered functional processing with reduced left-hemisphere lateralization in SLI (e.g. Badcock et al., 2012; de Guibert et al., 2011; Ors et al., 2005), the fact that different techniques and tasks were used in rather small samples calls into question the findings' robustness. More research is needed to clarify not only the relation between cortical regions involved in language processing and the white matter fibre bundles that connect them, but also whether the degree and/or direction of language-related asymmetries is behaviourally relevant. Hence, my following studies delved into the assessment of typical and atypical language lateralization in larger groups of neurotypical adults.

Using FTCD, my third study examined the influence of language production versus semantic matching on the degree of lateralization in a large number of healthy participants. First, I demonstrated that FTCD could be used to reliably assess functional lateralization across the different subcomponents of language. The strength of language lateralization, however, varied between tasks, indicating that changes in cerebral blood flow velocities were more strongly left lateralized during language than semantic matching. Given that previous studies have found no effect of task difficulty on language lateralization (Badcock, Nye & Bishop, 2012), my findings provide new insights into the sensitivity of FTCD for evaluating changes in lateralization based on different language subdomains.

With my final two studies, I aimed to elucidate the causes of lateralization of cortical and subcortical language networks and the effect of lateralization on language abilities. In study four, I was particularly interested in the following questions: Do typical and atypical participants differ in FMRI activation patterns associated with different language tasks? Can we determine cerebral lateralization concordantly using different laterality assessments, including FTCD, FMRI and VHF? Are language abilities related to the direction or degree of functional language lateralization? To address these questions, I compared different measures of language laterality obtained in a well-matched sample of typically (left) and atypically (right or bilateral) lateralized participants, as previously assessed by FTCD.

Group analyses of my FMRI data showed that participants with typical and atypical language lateralization differed significantly in their activation patterns: while the typical group robustly activated a left-lateralized language network, the atypical group showed a more bilateral pattern of activation. The degree of language laterality, however, was not associated with behavioural measures of non-verbal/verbal intelligence, reading skills, or receptive vocabulary. I demonstrated that typical participants showed varying degrees of leftward lateralization for language but were still categorized as left-lateralized on FMRI and VHF. In contrast, atypical participants showed considerable variability in functional activity across both hemispheres; further, atypical individuals classified as atypical using FTCD, were most likely to be classified as left-lateralised on FMRI and behavioural measures. Given that the accuracy of FTCD measurements was high in this sample, and that my previous study confirmed high test-retest reliability for the FTCD paradigm used, I propose that the change in category of participants with atypical language lateralization may reflect instability in laterality for such individuals. Functional lateralization for language may therefore be not a highly stable characteristic of such individuals, but could vary depending on task or other factors.

In my last study, I combined the above measures of language lateralization with diffusion MRI to directly examine the relationship between asymmetries in brain structure and function. My analyses revealed a significant leftward asymmetry of white matter fibre bundles connecting superior temporal with inferior frontal language areas via the extreme capsule fasciculus, which has been proposed to anchor the ventral language pathway. I demonstrated that this asymmetry was not only absent in atypically lateralized participants, but also correlated positively with right-handedness and increased scores of verbal IQ. My findings provided new evidence for the functional relevance of the ventral language pathway and suggest that the extreme capsule fasciculus asymmetry could be promising marker for language lateralization in neurotypical adults.

Taken together, it is clear that language laterality is a complex construct, and thus the assessment of structural and functional brain asymmetries and their synthesis provides an immense challenge - even at times when neuroimaging methods have made great progress. However, the approach to combine different methodologies, especially functional and diffusion MRI, in typically developing individuals and those with language impairment, has offered a glimpse of new insights into the enigma of language lateralization.

7.2 How to best measures language laterality?

The results described in Chapter 5 and Chapter 6 point out an important question of this thesis: What is the best method for measuring language laterality? In my last two studies, participants were classified as typical or atypical using FTCD in combination with a word generation paradigm. FTCD has not only been validated in several independent studies (e.g. Deppe et al., 2000; Knake et al., 2003; Knecht et al., 1998b; Rihs et al., 1999), but it is also an easily applied and relatively inexpensive method to examine language laterality. These characteristics make FTCD an ideal instrument for screening a large number of people for atypical patterns of functional language lateralization. Classification based on FTCD, however, was not consistent with other measures of functional lateralization including FMRI and VHF (see Chapter 5) highlighting a major issue with respect to this categorical analysis: Which LI measure should be used for identifying and grouping participants as typically or atypically lateralized? This question ties in with a long-standing controversy in the field of laterality research. While language representation is commonly divided into distinct categories (i.e. left, right, bilateral) in clinical and surgical practice, many neuroimaging studies have demonstrated a continuum of lateralization ranging from complete left-hemisphere language through various degrees of bilaterality to complete right-hemisphere language. For example, Springer and colleagues (1999) used FMRI to assess functional lateralization associated with a semantic language task in a group of 100 neurotypical right-handers. As expected, the majority of healthy participants showed left-lateralized activation (94%). However, a continuous range of LI values was observed with nearly all subjects showing some degree of right hemisphere activation (Springer et al., 1999). A similar continuous distribution of LIs was found in both neurotypical participants and epilepsy patients by several other studies using FMRI or FTCD (e.g. Binder et al., 1996; Deppe et al., 2000; Knecht, Dräger, et al., 2000; Spreer et al., 2002). Although brain imaging research has consistently found suprathreshold activity in the right-hemisphere homologues of Broca’s and Wernicke’ area, patterns of activation are still classified as left-, weak-, or right-lateralized to better match clinical assessments and findings. From the medical point of view, a clear decision is required as to whether a surgical procedure may interfere with post-operative language function. Yet, by adapting the categorical approach in research studies, we implicitly assume that activity in the 'non-dominant' hemisphere is not critical for language processing. Much of the variability in the frequency of atypical language lateralization may thus be explained by differences in the applied categorization criteria - both within and across methods for laterality assessment (Kurthen et al., 1994; Risse, Gates, & Fangman, 1997). If language lateralization is truly a continuous variable, any attempt to categorize LI data will be arbitrary and will inevitably result in loss of information and neglect of within-group variation (Cohen, 1983; Naggara et al., 2011). Hence, moving away from categorical analyses to investigating group level trends and relationships to behaviour might be a more informative and robust approach to examine functional lateralization. To circumvent the issue of categorization, one possibility would be to enter LI values as a correlate in the TBSS analysis, for example, to test whether there are any white matter regions that correlated with functional language laterality.

7.3 Final conclusions and future studies

In this thesis, I approached the much debated question as to whether language laterality is related to language abilities by combining the methods of functional and diffusion MRI as well as FTCD.

In the first half of my thesis, I assessed language-related asymmetries in brain structure and function in families with at least one language-impaired child and control families. While there were no significant differences in the white matter microstructure of adults with SLI compared with adult controls, children with SLI compared with typically developing peers showed reduced white matter integrity in all parts of the corpus callosum and in white matter areas corresponding to the dorsal and ventral language tracts. Because the corpus callosum is the major fibre bundle that connects the left and right hemispheres, the abnormal microstructure of the callosal tract would affect inter-hemispheric communication in children with SLI. These microstructural abnormalities could, in turn, underpin atypical lateralization of language structure and function associated with language impairment. This hypothesis was followed up using functional MRI in Chapter 3.

Using functional MRI, laterality assessment of auditory cortex activation in the same sample did not reveal any differences in the strength or direction of functional lateralization in children with SLI, compared with their unaffected siblings and children from control families. It is important to note, however, that none of the groups examined (including those of typically developing children and adult controls) showed the expected pattern of hemispheric specialization seen previously for the same task. It is not possible to conclude, therefore, that the non-lateralized activation seen in individuals with SLI was abnormal. Since functional activation patterns vary greatly among individuals, reliance on group maps alone can mislead (Heun et al., 2000; Miller et al., 2002). Most FMRI studies underestimate or even ignore the effect of functional variability due to factors other than anatomical differences, such as differences in cognitive strategies and/or attention. With respect to laterality studies, subject-dependent factors can have direct consequences on the extent to which a particular function is localized in one or the other hemisphere (Grafton, Woods, & Tyszka, 1994; Kirchhoff and Buckner, 2006). Future FMRI studies should assess and quantify inter-individual variability in order to improve our understanding of group activation patterns and their consistency within and across neurotypical subjects;

which in turn will help to interpret deviations from the normal pattern of functional lateralization documented in language-impaired populations.

The second half of my thesis focused on the assessment of language laterality in neurotypical adults. First, I showed that FTCD is a reliable tool to assess functional lateralization of different language tasks including word generation and semantic matching. Both paradigms revealed a significant left hemisphere bias but the word generation task was significantly more left lateralized than the semantic matching one based on the number of individuals categorized as left lateralized as well as the strength of left lateralization. I concluded, therefore, that expressive tasks are more strongly lateralized than receptive ones.

After screening 215 participants with FTCD, I then obtained imaging data and behavioural measures of language laterality and language abilities in 16 participants with typical (left) and atypical (non-left) language lateralization. I demonstrated that the two groups differed significantly in terms of lateralization assessed by functional and diffusion MRI, but not in terms of their performance on standardized tests of language. Specifically, atypical participants showed lower left and greater right hemisphere activation compared with the typical ones, and lacked the leftward asymmetry of the ventral language tract seen in the typical group. I also demonstrated that typical participants were consistently categorized as left lateralized using different functional laterality assessments, whereas the atypical participants had less concordance for categorically defined laterality. Given that most individuals, who showed weak lateralization during FTCD, revealed left lateralized activation in FMRI, I concluded that the discordance among various laterality assessments in the atypical group was predominantly driven by bilateral individuals. Furthermore, I suggest that the change in category of participants with atypical language lateralization reflects instability in language lateralization for such individuals. This remains to be tested by reproducibility assessments in individuals who are atypically lateralized; previous work, including my own, has revealed high repeatability of laterality assessments for all measures used here but this work has been dominated by assessments made in left-lateralized participants.

The MRI studies presented in my thesis included sample sizes that while reasonable for imaging studies (e.g. N=16) had the statistical power to detect only large effects (see the result section of corresponding chapters for post-hoc power analyses). As noted in my preface, I inherited the data used in my first two studies. Hence, I could not increase the sample sizes for the analyses described in Chapter 2 and Chapter 3. Following the evaluation of language lateralization in 215 neurotypical adults using FTCD, I identified 20 individuals with atypical language lateralization. This number reflects the scarcity of such individuals. Sixteen of these people were available to be scanned thus my sample size was limited to this number and could not be increased. Clearly, to evaluate the reproducibility of the laterality assessment in this group (see above) and thus determine the extent to which discordance reflects true change in functional lateralization, more research in larger samples is needed that include repeated measures within individual subjects.

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