LIBRARY
Te Tumu Herenga
THE UNIVERSITY OF AUCKLAND

RESEARCHSPACE@AUCKLAND

http://researchspace.auckland.ac.nz

ResearchSpace@Auckland

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.

Note : Masters Theses

The digital copy of a masters thesis is as submitted for examination and contains no corrections. The print copy, usually available in the University Library, may contain corrections made by hand, which have been requested by the supervisor.

Structural connectivity in the asymmetric brain: genetic and nongenetic influences

Isabelle Silvia Häberling

A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy,

The University of Auckland, 2012

Abstract

By combining fMRI and DTI, this thesis conducted three experiments exploring the relationship between functional hemispheric specialization and structural connectivity within and between the hemispheres.

In Experiment 1, the hemispheric dominance pattern for language and spatial processing was related to the efficacy of callosal connectivity. Individuals with a right-sided language network or crowding of functions to one hemisphere showed high anisotropic diffusion through the corpus callosum, suggesting that unusual hemispheric dominance is associated with enhanced interhemispheric connectivity.

Experiment 2 assessed the hypothesis of whether hemispheric language dominance might be achieved through callosal pruning by assessing structural-functional covariations in 35 monozygotic twin pairs. On the basis of genetic models of handedness and language dominance, twin pairs were classified according to their likelihood of carrying the right-shift (RS) allele, which is thought to introduce a bias towards right-handedness and left-cerebral language dominance. Twin pairs with a high probability of carrying the putative RS+ allele showed a connectivity pattern characterized by a genetically controlled, low anisotropic diffusion over the whole corpus callosum. In contrast, the high connectivity pattern exhibited by twin pairs more likely to lack the RS+ allele was under significantly less genetic influence.

In Experiment 3, the arcuate fasciculus was reconstructed in the same set of monozygotic twin pairs in order to assess whether asymmetry in the intrahemispheric language pathway corresponds to the functional laterality indices for language derived from fMRI. Results revealed a close relationship between functional and structural asymmetries with the more left-cerebrally dominant twin also showing a more leftward asymmetry of the arcuate fasciculus than his or her less left-cerebrally dominant co-twin. Because monozygotic twin pairs share the same genotype, the results indicate a strong nongenetic component in arcuate fasciculus asymmetry.

Taken together, my results suggest that the asymmetric distribution of functional networks might rely on dense intrahemispheric pathways in the dominant hemisphere, allowing efficient information transfer. Interhemispheric connectivity, on the other hand, might play a key role in the development of hemispheric specialization, possibly through a genetically controlled process of axonal pruning.

To my Father, Thomas

Acknowledgments

First and foremost I would like to thank my supervisor Professor Michael Corballis for all the support, guidance and advice which I have received from him over the past 4 years. He gave me all the encouragement I've needed and always kept his good humor even in the most difficult of situations.

Many thanks also to Dr Gjurgjica Badzakova-Trajkov for all the advice she's given me, the many hours spent together working on the project, and not least for becoming such a good friend.

I would also like to give a special thanks to Stefan Weck for his continuous support, for venturing with me into a new country, and for believing in me. Thanks also to my mother Do and my sister Simone, who despite living far away have been very supportive through the whole process. I would also like to thank my late father Thomas, who'd been so enthusiastic about this project, and to whom I dedicate this work.

And finally, thanks very much to all the participants, who took part in the studies and made this thesis possible. I would also like to thank the University of Auckland and the Marsden Fund of the Royal Society of New Zealand for their financial support.

List of Publications

Parts of this thesis are based on the following publications:

Haberling, I.S., Badzakova-Trajkov, G. & Corballis, M.C. (2013). Asymmetries of the arcuate fasciculus in monozygotic twins: Genetic and nongenetic influences. *PloS one, 8(1),* e52315.

Haberling, I.S., Badzakova-Trajkov, G., & Corballis, M.C. (2012). The corpus callosum in monozygotic twins concordant and discordant for handedness and language dominance. *Journal of Cognitive Neuroscience*, Advanced online publication.

Corballis, M.C., Badzakova-Trajkov, G., & **Haberling, I.S.** (2012). Right hand, left brain: genetic and evolutionary bases of cerebral asymmetries for language and manual action. *Wiley Interdisciplinary Reviews: Cognitive Sciences, 3(1),* 1-17.

Badzakova-Trajkov, G**., Haberling, I.S.**, & Corballis, M.C. (2011). Magical ideation, creativity, handedness, and cerebral asymmetries: A combined behavioural and fMRI study. *Neuropsychologia, 49(10),* 2896-2903.

Haberling, I.S., Badzkova-Trajkov, G., & Corballis, M.C. (2011). Callosal tracts and patterns of hemispheric dominance: a combined fMRI and DTI study. *NeuroImage, 54(2),* 779-786.

Iwabuchi, S.J**., Haberling, I.S**., Badzakova-Trajkov, G., Patston, L.L.M., Waldie, K.E., Tippett, L.J., Corballis, M.C., & Kirk, I.J. (2011). Regional differences in cerebral asymmetries of human cortical white matter. *Neuropsychologia, 49(13),* 3599-3604.

Badzakova-Trajkov, G**., Haberling, I.S**., Roberts, R.P., & Corballis, M.C. (2010). Cerebral asymmetries: complementary and independent processes. *PloS one, 5(3),* e986.

Badzakova-Trajkov, G., **Haberling, I.S**., & Corballis, M.C. (2010). Cerebral asymmetries in monozygotic twins: an fMRI study. *Neuropsychologia, 48(10),* 3086-3093.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AC-PC line	Plane defined by Anterior Commissure – to – Posterior Commissure
AI	Asymmetry Index
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BA	Brodmann Area
BOLD	Blood Oxygenation Level Dependent
C	Chance allele
CUD	Crossed-Uncrossed Difference
D	Dextral allele
DNA	Deoxiribonucleid Acid
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EPI	Echo Planar Imaging
ERP	Event Related Potentials
FA	Fractional Anisotropy
FDT	FMRIB’s Diffusion Toolbox
fMRI	functional Magnetic Resonance Imaging
FMRIB	Centre for Functional Magnetic Resonance Imaging of the Brain
FOV	Field Of View
FS	Familial Sinistrality
FSL	FMRIB’s Software Library
fTCD	functional Transcranial Doppler Sonography
FWE	Family-Wise Error
FWHM	Full Width at Half Maximum
GLM	General Linear Model
IHTT	Interhemispheric Transfer Time
LI	Laterality Index
LSD	Least Significant Difference
M1	Primary Motor Area

MD	Mean Diffusivity
MNI	Montreal Neurological Institute
MZ	Monozygotic
PET	Positron Emission Tomography
ROI	Region of Interest
RS	Right Shift gene
SD	Standard Deviation
SIENAX	Analysis of Structural Brain MRI data
SMA	Supplementary Motor Area
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
TE	Echo Time
TR	Time to Repetition
VBM	Voxel-Based Morphometry
WFU	Wake Forrest University

Chapter 1:
General introduction

"The brain's complexity arises from its connectivity"

(Paul et al., 2007, p. 287)

The human brain consists of around 20 billion neocortical neurons, which are connected through over 0.14 quadrillion synapses (Drachman, 2005). The information processing capability of the brain depends largely on short and long distance fibres maintaining and connecting intertwined functional networks. This thesis assesses structural connectivity in relation to one of the key concepts in the organization of the human brain: hemispheric specialization. By combining two imaging techniques, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), I aim to address the question of whether variability in the inter- and intrahemispheric connectivity corresponds to individual functional lateralization patterns. Furthermore, the inclusion of monozygotic twin pairs allows inferences to be drawn about possible genetic sources of interindividual variability in structural connectivity.

The first section provides an overview over the asymmetric distribution of cognitive functions, which is followed by a section on current theories of the origin of functional lateralization. The last section of the general introduction discusses in detail the anatomy and function of two main white matter tracts involved in hemispheric specialization, namely the corpus callosum and the arcuate fasciculus.

Hemispheric specialization

In 1861, Paul Broca, a French surgeon, investigated the brain of a diseased patient who had lost his ability to articulate language after a stroke. He found damage in the third frontal convolution of the left hemisphere, which let him to conclude that language is localised in the left hemisphere (as cited in Berker, Berker, & Smith, 1986). A few years later, in a post-mortem study, Wernicke (Wernicke, 1874, 1977) reported a lesion in the left posterior superior temporal cortex which had caused impaired speech comprehension in the patient. Because language was considered the most distinctive faculty of humankind, the left hemisphere was subsequently regarded as the dominant one. Language, however, is not the only lateralized function of the brain. Handedness is also an expression of hemispheric specialization, given that proficiency differences between the hands originate from the brain and not from anatomical dissimilarities of the hands themselves (Corballis, 2003). Furthermore, other cognitive functions, such as spatial processing and face processing, are also distributed asymmetrically in the brain, although probably to a lesser degree. Not all individuals, though, show the same direction and degree of hemispheric specialization. For example, some individuals develop aphasia after right-hemisphere lesions, and these are more likely to be left-handers, suggesting a common basis of language lateralization and handedness (McManus & Bryden, 1992). The following sections provide an overview of the most prominent functional hemispheric asymmetries and their relationships to one another.

Handedness

Humans show a remarkable preference for one hand over the other when performing simple everyday activities. Although the majority of individuals prefer to use the right hand, some are left-handed, and others do not show any partiality to either hand. Handedness can be defined as a matter of preference, in which case a questionnaire is administered, or of performance, in which case the proficiency to perform a simple task with each hand is measured. The two measurements are highly but not perfectly correlated and it is not yet clear whether preference arises from skill differences or vice versa (McManus & Bryden, 1992). Both approaches require the definition of a cut-off point in order to classify individuals into handedness groups. Some researchers differentiate between right- and left-handers based on writing hand, while others make a distinction between consistent and non-consistent right-handers based on preference scores for several different tasks. Annett (2004), for example, has proposed an elaborate scheme to classify subjects into six different handedness categories.

The incidence of left-handedness is somewhat dependent on the definition of the handedness categories and the population on which it is studied. In an American survey of over one million participants, the incidence of non-consistent right-handers as defined by the hand used for writing and for throwing was 11.1% (Gilbert & Wysocki, 1992), whereas in a slightly younger cohort of undergraduate students the incidence of left-handedness based on writing hand was estimated at 13.8% (Spiegler & Yeni-Komshian, 1983). The prevalence of left-handedness declines in older age cohorts (Porac, 1981), which cannot be attributed entirely to forced right-handedness (Ellis, Ellis, Marshall, Windridge, & Jones, 1998; Gilbert & Wysocki, 1992). Males are about 20-25% more likely to be left-handed than females (Papadatou-Pastou, Martin, Munafo, & Jones, 2008; Sommer, Aleman, Somers, Boks, & Kahn, 2008). Furthermore, cultural differences have been observed which can be explained, at least partly, by the cultural acceptance of left-handedness (Corballis, Badzakova-Trajkov, & Haberling, 2012), although differences in gene frequencies might also play a role (McManus, 1999), as discussed in a later section.

Despite a large number of investigations, controversy about the origin of handedness differences remains. It has been suggested that left-handedness is a deviation from the usual pattern that arises from complications in pregnancy and birth (Bakan, 1971; Coren, 1995) or following early brain injury (Silva & Satz, 1979). These theories are based on observations of higher incidence of left-handedness in schizophrenic patients (Dragovic & Hammond, 2005), in individuals with intellectual disabilities (Grouios, Sakadami, Poderi, & Alevriadou, 1999), and after childhood meningitis (Ramadhani et al., 2006). Furthermore, the higher incidence of left-handedness in twins found in some (Carter-Saltzman, Scarr-Salapatek, Barker, & Katz, 1976; Sicotte, Woods, & Mazziotta, 1999; Vuoksimaa, Koskenvuo, Rose, & Kaprio, 2009) but not all studies (Medland et al., 2009; Medland et al., 2003) has been attributed by some authors to the higher probability of birth stress and low birth weight in twins compared to singletons (Sicotte et al., 1999). However, a recent large-scale study did not find any association between birth stress and left-handedness (Bailey & McKeever, 2004), with only advanced maternal age having a weak but significant association. Although in some cases left-handedness might be related to some pre- or postnatal trauma, most left-handers do not show any neurological abnormalities, suggesting that left-handedness is not of pathological origin in the majority of individuals (Beaton, 2003).

Left-handedness tends to run in families and therefore a genetic component has been assumed. For example, only 9% of the children of two right-handed parents are left-handed compared to 19% of the children with one left-handed parent and 26% of children with two left-handed parents (McManus & Bryden, 1992). Although those numbers suggest a genetic component, handedness does not breed true in a Mendelian sense, as reflected in the occurrence of discordant handedness in around 10-25% of monozygotic twin pairs (Reiss, Tymnik, Kogler, Kogler, & Reiss, 1999; Ross, Jaffe, Collins, Page, & Robinette, 1999; Sicotte et al., 1999). Nevertheless, concordance measures for handedness tend to be higher in monozygotic than dizygotic twin pairs (Sicotte et al., 1999), at least if handedness is measured according to the hand used for throwing and not for writing (Medland et al., 2003). In a meta-analysis of 35 twin studies one quarter of the variance in handedness was attributed to genetic factors (Medland, Duffy, Wright, Geffen, & Martin, 2006). The remaining variance was controlled almost entirely by unique environmental effects, while shared environment had only a negligible influence. Similar results were obtained in a new data set of 20,000 twin pairs by the same group (Medland et al., 2009) and in a similar study of over 30,000 subjects by a different group (Vuoksimaa et al., 2009). Because genetic models of handedness assume a common basis with language dominance, these will be discussed in detail in the section on the origins of hemispheric specialisation.

Language lateralization and its relation to handedness

The language network is distributed asymmetrically in the brain favouring the left hemisphere in most individuals. Lateralization is defined as one hemisphere being more efficient or more involved than the other in performing a certain cognitive function without excluding the possibility that the non-dominant hemisphere might also contribute to at least some aspects of information processing. Although over 90% of all individuals exhibit left-cerebral dominance for language, a minority of individuals reverse or even lack this asymmetry with handedness being a weak but nevertheless important predictor for atypical language dominance.

The first reports of the relationship between language dominance and handedness were based on data from aphasic patients. The incidence of crossed aphasia, that is aphasia in a right-handed subject with a right-hemispheric lesion, was estimated at around 1% (Gloning et al., 1969, as cited in Alexander, Fischette, & Fischer, 1989). Inactivating one hemisphere with the intracarotid sodium amobarbital injection in epileptic patients revealed that 96% of right-handers and 70% of left-handers are left-cerebrally dominant for language (Rasmussen & Milner, 1977). Due to the inherent risks of chemically suppressing one hemisphere, this procedure is not suitable for application to healthy individuals, but is restricted to clinical settings, such as preoperative evaluation of patients with epilepsy. The variability in the healthy population might deviate from the one found in pathological states where reorganization processes are likely to have occurred. Indeed, epilepsy patients show more variability in language dominance patterns (Springer et al., 1999).

With the development of functional magnetic resonance imaging (fMRI) and functional transcranial Doppler sonography (fTCD) the investigation of language dominance in big cohorts of healthy subjects became feasible. In right-handers, the incidence of left-hemispheric language dominance is estimated between 92.5% with fTCD (Knecht, Deppe, et al., 2000) to 94–96% with fMRI (Badzakova-Trajkov, Haberling, Roberts, & Corballis, 2010; Springer et al., 1999). In contrast, only around 76-78% of left-handers show left-hemispheric dominance while the remaining subjects show either a right-sided or a bilateral language distribution (Pujol, Deus, Losilla, & Capdevila, 1999; Szaflarski et al., 2002). When individuals are classified into five different handedness groups according to direction and degree of hand preference, the number of individuals with right-sided language networks is lowest in the strong right-handed and highest in the strong left-handed group. For example, in 193 epilepsy patients undergoing the intracarotid sodium amobarbital procedure, the incidence of atypical language dominance increased monotonically from 9% in strong right-handers and 46% in ambidextrous individuals to 69% in strong left-handers (Isaacs, Barr, Nelson, & Devinsky, 2006). These numbers are substantially higher than those found in the healthy population where atypical language dominance increased from 4% in strong right-handers to 27% in strong left-handers (Knecht, Drager, et al., 2000). Data such as these support the idea that strength of hand preference and degree of functional language asymmetry are related. A recent neuroimaging study found that functional laterality indices, based on the differences between the activity in left and right frontal lobe during a word generation task, were indeed positively correlated with an asymmetry index derived from handedness inventory scores (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). The correlation coefficient was only 0.357, though, indicating a weak relationship, which might have been additionally influenced by the over-representation of left-handers included in the study. That is, despite the weak association between handedness and language dominance, the majority of all individuals, right-handers as well as left-handers, are left-hemispheric dominant for language.

Other cerebral asymmetries and the role of the right hemisphere

Certain cognitive functions, such as the processing of spatial information, faces and emotional stimuli, are performed more efficiently by the right hemisphere, although those asymmetries tend to be somewhat less apparent than the left-cerebral dominance for language. For example, spatial attention is predominantly processed in the right hemisphere, although the values of the functional laterality indices tend to be lower, indicating more bilateral processing, than those observed in the language network (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). While abundant research on the predominance of one hemisphere over the other has been conducted, relatively few studies have assessed the relationship between functional asymmetries themselves. Rather, it was assumed that right-hemispheric dominant processes are a secondary consequence of the left-cerebral dominance for language (Corballis, 1993; Karnath, Ferber, & Himmelbach, 2001). In early evolution, cognitive functions might have been distributed evenly between the hemispheres. With the emergence of language, the processing centres in the left might have become increasingly occupied with functions related to speech, which led to a displacement of other functions to the right (Corballis, 1997).

A causal relationship between right- and left-hemispheric processes has not been fully supported by empirical studies, though, which in contrast suggest some independence between cerebral asymmetries (Bryden, Hecaen, & DeAgostini, 1983; Whitehouse & Bishop, 2009). Bryden et al. (1983) investigated the incidence of aphasic and visuospatial deficits in 270 patients with unilateral brain damage. Although around 73% of men and 55% of women showed complementary specialization, the others had spatial and language functions localized in a single hemisphere, which led the authors to conclude that complementary organization is statistical rather than causal in nature. A similar conclusion was drawn by Whitehouse and Bishop (2009) based on the observation that almost a quarter of their 75 participants had language and spatial functions localized in the same hemisphere as established with fTCD. In a recent fMRI study of over 200 participants, the degree of lateralization for language and visuospatial processing was weakly and negatively correlated ($r = -0.176$), despite the fact that in some individuals the functions were localized in the same hemisphere (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). Handedness, though, was only correlated with asymmetry for speech but not with visuospatial processing, suggesting that at least two different and independent lateralising influences exist in the brain. Indeed, even more than two independent networks might be distributed asymmetrically between the hemispheres. A factor analysis of asymmetries of intrinsic activity, as revealed by fMRI, resulted in four independent factors, corresponding to networks involved in vision, the default network, attention, and language (Liu, Stufflebeam, Sepulcre, Hedden, & Buckner, 2009).

The above evidence suggests that crowding of functions to one hemisphere is a normal although rather rare occurrence in healthy humans. In a traditional view though, the hemispheres have limited processing resources so that crowding of functions may cause performance deficits. This view is supported by the observation that patients with early left-hemispheric lesions and subsequent shift of language functions to the right are impaired in visuospatial functions (Lidzba, Staudt, Wilke, & Krageloh-Mann, 2006). However, the shift of one function to the non-dominant hemisphere following brain injury might result in consequences other than the ones observed in healthy individuals with crowding of functions to the same hemisphere. Powell, Kemp and Garcia-Finana (2012) assessed cerebral asymmetry for language and visuospatial processing with fMRI and related the degree and pattern of asymmetry to the performance in different subscales of the Wechsler Adult Intelligence Scale (WAIS-III). Dissociation of functions was associated with better performance in verbal comprehension and perceptual organization. The groups, though, showed substantial overlap in their intelligence scores, suggesting that detrimental effects of crowding might be subtle and only detectable in specialized tests. This view is further supported by the fact that healthy individuals with unusual asymmetry patterns often completed tertiary education and their scores in standard psychological tests were found to be in within the normal range (Floel et al., 2001; Knecht et al., 2001).

Origins of hemispheric specialization

Advantages of an asymmetric brain: an evolutionary perspective

Asymmetric distribution of cognitive functions is a key concept in the organization of the human brain and diverges from the otherwise symmetric layout of the body (Corballis, 2012). Cerebral and behavioural asymmetries are not uniquely human given that a variety of other species also exhibit lateralized functions, and the asymmetries observed in modern humans have, most likely, precursors in evolution (Corballis, 2009).

One theory proposes that asymmetric processing is closely linked to increases in brain size, and to the amount and speed of interhemispheric information transfer meditated through the corpus callosum (Aboitiz, Lopez, & Montiel, 2003; Ringo, Doty, Demeter, & Simard, 1994). With increasing brain size, callosal axons had to surmount greater distances, which in turn increased the time needed for the transmission of information from one hemisphere to the other. Synaptic transmission can be accelerated through an increase in axon diameter and myelination. The thickness of fibres in species with larger brains can however not fully compensate for the longer distances (Olivares, Montiel, & Aboitiz, 2001). Rather, the ratio between callosal axons and total cortical cells tends to diminish in large brained species (Olivares, Michalland, & Aboitiz, 2000; Olivares et al., 2001). The resulting conduction delay in interhemispheric communication might have caused an increasing decoupling of the hemispheres. Furthermore, the callosal transmission delay may impede efficient information processing between the hemispheres to such an extent that cooperation between the hemispheres was no longer viable. Thus, the hemispheres became increasingly isolated and consequently, strong intrahemispheric circuits developed that formed the basis for the establishment of brain lateralization (Nowicka & Tacikowski, 2011).

In fact, hemispheric specialization might have proven to be beneficial given that it enhances the neural capacity for information processing. That is, while a specific neural network in one hemisphere processes a specific task, the processing centres in the other hemispheres are free to perform different or complementary processes (Corballis, 2009). The restriction of functional neural units to a confined intrahemispheric area might also enhance processing speed, and only the end product of the neural activity needs to be shared between the hemispheres, further decreasing the need for interhemispheric communication (Gazzaniga, 2000). Lateralization also limits the amount of redundant processing that is performed and prevents interhemispheric conflict (Corballis, 1993), which could arise through duplication of information in the two hemispheres (Hirnstein, Hausmann, & Gunturkun, 2008; Hugdahl, 2000).

Although those theories might explain the advantages of having certain functions lateralized, they cannot explain why most but not all individuals show biases in the same directions. It is possible that at least some of the asymmetries are influenced by social pressure. With regards to handedness, for example, most tools are constructed to be used with the right hand, but might be quite uncomfortable to use with the left (Corballis, 2009).

Furthermore, belonging to the majority of the group showing an asymmetric behaviour in the same direction might be beneficial, for example it might be vital to be one of many when attacked by a predator (Vallortigara, 2006). However, the benefit gained by belonging to the majority of the group contrasts with the cost for displaying a behaviour expected by the predator. Thus, a minority of prey might trade off the advantage of being part of a large group with the benefit that arises from behaving in an unexpected fashion in the eye of an attack. Thus, on the population level, an optimum equilibrium between a majority exhibiting a bias to the same side and a minority with no bias or a bias to the opposite side might be reached. In case of handedness, for example, deviations from the usual right-handedness might hold some merit in sports such as fencing or tennis, due to the surprise aspect of the behavioural response.

A completely different theory was developed by Previc (1991), who related handedness to the asymmetric position of the foetus in the third trimester of pregnancy. Most foetuses are oriented with the right ear facing outwards, which causes a greater stimulation of the left vestibular system. Infants are therefore born with a bias to use the left side for balance, which frees the right hand for explorational movements.

Genetic theories of handedness and cerebral asymmetry

Genetic models of handedness and cerebral asymmetries, such as those developed independently by Annett (1991, 1998, 2002) and McManus (1999, 2002), are based on the assumption of one lateralizing gene which codes for left-hemispheric dominance for language and right-handedness, whereas in the absence of this influence these asymmetries are established at random.

In Annett’s (1998, 2002) version, handedness is defined as a continuous normally distributed variable of skill differences between the two hands. The lateralizing gene is termed the right-shift (RS) gene, with one allele, RS+, causing the handedness distribution to be shifted to the right, while the other, RS-, cancels this shift. Based on the assumption that the two alleles combine additively, the right shift is calculated at two standard deviations for RS+/+ homozygotes and one standard deviation for RS+/- heterozygotes, while for RS-/- homozygotes the distribution is centred on zero (Figure 1). Given that the RS+ allele does not code for right-handedness per se but rather introduces a directional bias, all genotypes can express either right- or left-handedness but with substantial differences in their frequency.

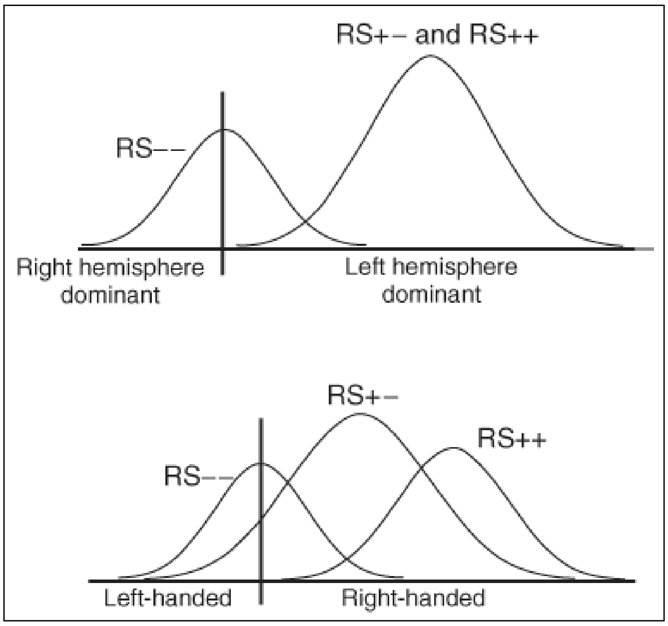

Figure 1: *Hypothesized distribution of hemispheric asymmetry for language (top panel) and handedness (bottom panel) as a function of genotype (after Annett, 2002; adapted from Corballis et al., 2012).*

McManus (1999) also postulates a lateralizing gene, again with two alleles, a dextral allele (D) coding for right-handedness and a chance (C) allele coding for random allocation of left- and right-handedness. In contrast to Annett, McManus defines handedness as a discrete variable, which categorises individuals in right- or left-handers according to preference. The frequency of right-handedness in the three genotypes is postulated to be 100% for DD homozygotes, 75% for CD heterozygotes and 50% for CC homozygotes. The two models therefore differ in their definition of handedness, and while the right-shift theory suggests that some individuals will still be left-handed even when having two copies of the lateralizing allele, this is contested by McManus. Both theories provide reasonable fit to data on the inheritance of handedness from family studies, and perhaps unsurprisingly each claims to be superior to the other (Annett, 1996; McManus, 1985a, 1985b).

Both theories assume that the same gene is also linked to the development of cerebral dominance for language. According to McManus and Bryden’s (1992) model, which assumes that the alleles also operate in an additive mode on cerebral asymmetries, all DD individuals will be right-handed and left-cerebrally dominant for speech. In the heterozygote genotype (DC) 25% will be left-handed and 25% will show right-cerebral language dominance, whereas all four combinations of handedness and speech lateralization will be equally often observed in the CC homozygotes. The model, however, cannot explain why more individuals are left-handed than right-cerebrally dominant for language (Badzakova-Trajkov, Haberling, Roberts, et al., 2010), although it might hold true under the assumption that handedness is subjected to stronger environmental pressure, resulting in a larger random component (Corballis et al., 2012).

Annett (2002) in contrast assumes that the gene acts in a dominant-recessive fashion on cerebral dominance for language so that all gene carriers and 50% of the RS-/- homozygotes will exhibit left-cerebrally dominant language networks (Figure 1). The gene might in fact be more related to cerebral asymmetries than handedness (Annett, 2009) by effectively impairing the growth of the right hemisphere and displacing language functions to the left side (Annett, 1998). It has been shown in fact that various genes are expressed differentially between the left and right perisylvian region in the human foetus, such as the transcription factor Lim Domain Only 4 (LMO4) (Sun et al., 2005), which indeed might selectively influence the growth of one hemisphere and not the other. Annett (2009) calculates the frequency of the RS-/- genotype to be 18.53%, based on the incidence of crossed aphasia estimated at 9.27%. The square root then gives the frequency of the RS- allele (0.43), and thus the frequency of the RS+ allele (0.57) can be inferred.

The occurrence of discordant handedness and language dominance in monozygotic twin pairs are explained by genetic theories with the chance component in absence of the lateralizing influence. That is, these twins are likely to lack at least one copy of the RS+ allele, so that the development of their hemispheric asymmetries is based on random fluctuations. Annett (2003) applied her model specifically to twins, by assuming a reduction of the shift in twins due to specific twinning effects, which could explain the higher incidence of left-handedness in twins reported in some studies (Carter-Saltzman et al., 1976; Sicotte et al., 1999; Vuoksimaa et al., 2009). She then predicted that 71% of twin pairs with discordant handedness and 91.2% of right-handed twin pairs should be left-cerebrally dominant for language. These values are very close to the ones found in an empirical study where 76.2% of monozygotic twin pairs discordant and 89.5% of twin pairs concordant for handedness were concordant for left-cerebral dominance for language (Badzakova-Trajkov, Haberling, & Corballis, 2010).

To account for sex differences in handedness, Annett (2009) assumed a stronger expression of the gene in females than in males. In contrast, McManus and Bryden (1992) postulated a second modifier gene on the X chromosome, which acts by turning off normally active genes. As men have only one copy of X, they are more likely to express the suppressor gene and therefore more likely to be left-handed.

According to a model developed by Crow (2010) the right-shift factor, inherent to all humans, originates from the interaction of two proteins, whose genes are located on the X and Y chromosome. Variations in handedness and cerebral dominance do not result from differences in individual genotypes. Rather, they result from epigenetic factors that influence gene expression. These factors might be passed on from one generation to the next, which explains the weak familial inheritance of at least handedness.

Although each theory can explain the higher incidence of left-handedness in males, recent meta-analyses indicate that the degree of functional language dominance is similar between the two sexes (Sommer et al., 2008; Wallentin, 2009), which poses a challenge to models assuming a common origin of handedness and language dominance (McManus, 2010).

Naturally, all genetic models must remain rather tentative until the discovery of the gene and various attempts have been made to do this. Francks et al. (2002) identified the 2p12-q11 locus on chromosome 2, which showed a strong association with relative hand skill in 191 pairs of siblings. The same locus was not obtained in a second independent sample, but was replicated in a third independent sample (Francks et al., 2003). In a further study, the locus was narrowed to the LRRTM1 (Leucine-rich repeat transmembrane neuronal 1) gene, which is downregulated on the maternally inherited chromosome but is paternally associated with handedness and susceptibility to schizophrenia (Francks et al., 2007). Using similar methods, another study found a linkage to the 10q26 locus, but the association was so weak that the authors concluded that handedness is a complex trait coded for by various genes (Van Agtmael, Forrest, Del-Favero, Van Broeckhoven, & Williamson, 2003). A similar conclusion was in fact also drawn by Francks et al. (2003), who pointed out the likelihood of many genetic and environmental factors affecting handedness and brain asymmetries. Indeed, a two gene model might explain the variations in cerebral asymmetries without having to assume that the two alleles combine differently in case of handedness and language dominance (Corballis et al., 2012). On this view, one gene would dictate cerebral asymmetry and handedness while the other would influence handedness alone (Figure 2).

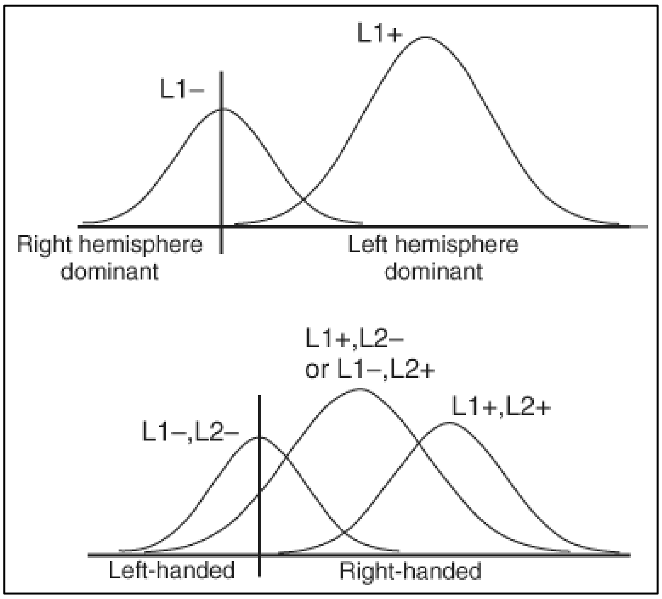

Figure 2: *Hypothetical distribution of hemispheric asymmetry for language (top panel) and handedness (bottom panel) according to a two-gene theory in which one gene, L1, influences hemispheric asymmetry and handedness, and a second gene, L2, combines additively with L1 to influence both hemispheric asymmetry and handedness (Corballis et al., 2012).*

Related to this, it might also be possible that the expression of handedness is largely dependent on the phenotypic handedness of the parents, as argued by Laland, Kumm, Van Horn and Feldman (1995). Parents might influence their children’s handedness by favouring one hand in most interactions, and thus being an implicit role model on which hand to use when performing a certain task. This model could explain the weak familial association observed in handedness variations but has some difficulties in explaining the occurrence of monozygotic twin pairs with opposite handedness. Twin studies indicate that handedness is more strongly influenced by environmental factors unique to one individual than by those shared by both twin members (Medland et al., 2009; Medland et al., 2006; Vuoksimaa et al., 2009), which is counter to the idea of a strong parental influence. It could be argued though, that twins might implicitly mirror each other when performing certain tasks, in fact substituting the parental influence with reciprocal influences on each other, and thus reinforcing the development of opposite hand preferences.

The Geschwind-Galaburda model of hemispheric specialization

In 1968, Geschwind and Levitsky found the planum temporale, an association area involved in receptive language processing, to be leftward asymmetric in 65 of 100 postmortem brains. This anatomical asymmetry was thought to be a reflection of the functional left-cerebral dominance for language, and given its prenatal development (Chi, Dooling, & Gilles, 1977; Wada, Clarke, & Hamm, 1975), to form the basis for the development of functional hemispheric specialization (Geschwind & Galaburda, 1985a). According to this theory, hemispheric specialization develops in utero through the influence of hormones, namely testosterone, on brain maturation. Excessive levels or increased sensitivity to testosterone interrupt the normal growth pattern of the left hemisphere, so that the usual anatomical asymmetries do not develop. The impact of high testosterone exposure on hemispheric specialization depends on the exact time point in the development when it occurs, affecting language dominance, handedness or both. Male and female foetuses are subjected to testosterone, but males are likely to be exposed to higher concentrations of testosterone, which in turn explains the observed sex differences in handedness. Furthermore, men are more likely to develop disorders such as autism, dyslexia and stuttering (Afifi, 2007; Liederman, Kantrowitz, & Flannery, 2005), which might be related to unusual anatomical asymmetries. The model allows for genetic effects on hemispheric asymmetries by assuming genetic control over testosterone levels and sensitivity. In addition, testosterone also affects the maturation of the thymus gland, which explains the increased risk of immune disorders in left-handers found in some (Bryden, Bruyn, & Fletcher, 2005) but not all studies (Cornish, 1996).

The Geschwind-Galaburda model (1985a, 1985b, 1985c) suggests that high testosterone concentrations are associated with left-handedness and atypical language dominance. Given the theoretical assumption that not only high levels but also increased sensitivity to testosterone might influence the growth patterns of the hemispheres, empirical evidence is difficult to obtain. One approach is to measure testosterone levels in the second trimester of pregnancies in which amniocentesis, a prenatal procedure for the diagnosis of chromosomal abnormalities and infections, is performed. The hormonal concentrations are then correlated with handedness measures when the child reaches an age where handedness and cerebral asymmetries have been established. Using such an approach, Lust et al. (2010) found that high testosterone levels in pregnancy predicted stronger left-cerebral language dominance when the children reached the age of 6 years. However, a subsequent study which included more participants revealed a linear decrease of right-handedness associated with high prenatal testosterone exposure (Lust et al., 2011). Another study, using the same methods, found that higher testosterone levels in utero were subsequently associated with stronger right-handedness in girls, but no relationship in boys was observed (Grimshaw, Bryden, & Finegan, 1995). This result is in agreement with the lower prevalence of left-handers found in female twins of opposite sex pairs, which are supposedly exposed to higher testosterone concentrations in utero than female twins of same sex pairs (Vuoksimaa, Eriksson, Pulkkinen, Rose, & Kaprio, 2010).

Although these studies did reveal an influence of testosterone on cerebral asymmetry, they found an inverse relationship to the one suggested by the Geschwind-Galaburda hypothesis. Indeed, another model developed by Witelson and Nowakowski (1991) proposed that increased testosterone levels led to right-handedness and left-cerebral language dominance. According to this view, testosterone stimulates the pruning of the corpus callosum, resulting in reduced interhemispheric connectivity and thus stronger lateralization of functions. A recent meta-analysis, though, did not find any evidence for an influence of testosterone on cerebral asymmetries in humans although hormonal effects on lateralization were observed in non-human mammals and birds (Pfannkuche, Bouma, & Groothuis, 2009). Animal studies of the effect of hormones on lateralization are easier to conduct given that the prenatal hormone concentrations can be manipulated artificially. Thus, some of the inconsistencies obtained in studies on humans might be related to the fact that reliable measurements for testosterone concentrations and sensitivity in the critical developmental stages are difficult to obtain.

Grey matter asymmetries: a structural basis for language dominance?

Geschwind and Galaburda’s (1985a) hypothesis of an anatomical substrate for language dominance has raised great interest and the overall leftward asymmetry of the planum temporale has been replicated using a multitude of methodological approaches (Barrick et al., 2005; Foundas, Leonard, & Hanna-Pladdy, 2002; Gootjes et al., 2006; Steinmetz et al., 1989; Wada et al., 1975; Watkins et al., 2001; Witelson & Pallie, 1973). In a meta-analysis of 22 studies, the surface area of the planum temporale was larger in the left than in the right hemisphere in around 78% of the subjects (Shapleske, Rossell, Woodruff, &

David, 1999), suggesting an overall population bias but also substantial interindividual variability. Neuroimaging studies indicated a reduced planum temporale asymmetry in left- compared to right-handers (Foundas et al., 2002; Habib, Robichon, Levrier, Khalil, & Salamon, 1995; Herve, Crivello, Perchey, Mazoyer, & Tzourio-Mazoyer, 2006; Steinmetz, 1996; Steinmetz, Volkmann, Jancke, & Freund, 1991), and even in the left- and right-handed monozygotic members of one pair of twins (Steinmetz, Herzog, Schlaug, Huang, & Jancke, 1995). Together with the diminished functional language lateralization found in left-handers, these results are in concordance with the Geschwind-Galaburda hypothesis.

Reports of reversed planum temporale asymmetry in subjects with a right-sided language network further supported the idea of an anatomical substrate for language dominance. For example, in one study, all subjects with leftward language dominance, as established with the Wada Test, showed leftward asymmetry while the one person with right-cerebral dominance showed rightward asymmetry of the planum temporale (Foundas, Leonard, Gilmore, Fennell, & Heilman, 1994). Similarly, a case study of one monozygotic twin pair discordant for language dominance revealed that the two twins showed reversed planum temporale asymmetry consistent with their individual language dominance pattern (Lux et al., 2008). The small numbers in those two studies, however, pose difficulties for a generalization of the results, and studies including more subjects have cast some doubt on a perfect relationship between planum temporale asymmetry and language dominance. Moffat, Hampson and Lee (1998) measured language lateralization with the dichotic listening task in 16 left-handers. Although all 9 participants with right-ear advantage, indicating left-cerebral dominance, showed the expected leftward asymmetry of the planum temporale, the 7 left-handers with left-ear advantage showed no consistent planum temporale asymmetry. That is, 3 showed leftward and 4 rightward asymmetry, indicating that individuals with a right-sided language network do not necessarily show a mirror-reversed anatomical asymmetry pattern.

Even more complex interactions were observed in a dichotic-listening study in right- and left-handed males and females by Dos Santos Sequeira et al. (2006). In the left-cerebral language dominance group, right-handed males showed a more leftward asymmetry than left-handed males, contrary to females, who showed the opposite pattern. Furthermore, an effect of speech lateralization was only found in right-handed males, so that left-cerebrally dominant men showed enhanced asymmetry compared to right-cerebrally dominant ones. This relationship did not hold true for left-handers or females. The authors further observed that the enhanced structural asymmetry in the right-handed males with left-cerebral speech lateralization originated from an enlargement of the left rather than a reduction of the right planum temporale.

The idea that the absolute size of the left rather than an asymmetry index could be related to the asymmetric distribution of the language network received further support by a Positron Emission Tomography (PET) study conducted by Josse, Mazoyer, Crivello and Tzourio-Mayozer (2003). In that study, the surface of the left planum temporale, but not an anatomical asymmetry index, predicted stronger leftward asymmetric activation during story listening. Other studies however have failed to find a relationship between measurements of planum asymmetry and cerebral language dominance, assessed with different methodologies such as dichotic listening (Jancke & Steinmetz, 1993), the intracarotid sodium amobarbital procedure (Dorsaint-Pierre et al., 2006), and fMRI (Eckert, Leonard, Possing, & Binder, 2006).

One reason for the diversity of the results might be the absence of exact anatomical boundaries which separate the planum temporale from adjacent regions such as the planum parietale (Beaton, 1997). Furthermore, individual hemispheres vary considerably in their gyral and sulcal patterns. For example, some exhibit a second transversal gyrus, usually in the right hemisphere, so that its inclusion might introduce a systematic bias into the asymmetry measurements (Dos Santos Sequeira et al., 2006).

A different approach, voxel-based morphometry (VBM), does not require a priori definitions of regions. Rather, grey matter density maps of the left and right hemisphere are subtracted for each subject, and statistical tests are applied on the resulting asymmetry maps. Such an approach was taken by Josse, Kherif, Flandin, Seghier and Price (2009), who found that the degree to which language activation was lateralized during an fMRI sequence could be predicted from asymmetry maps of the grey matter density in the pars opercularis, the posterior superior temporal region and the ventral occipito-temporal region, even though 12 of the 86 participants showed right-cerebral language lateralization.

Despite a similar approach, these results were not replicated in another VBM study by Jansen et al. (2010). Comparisons of grey matter density maps between 10 left-cerebral and 10 right-cerebral dominant individuals determined by the activity in Broca’s area during fMRI revealed no group differences in language related areas, and both groups exhibited a leftward asymmetry of the planum temporale.

Although asymmetries of the frontal language areas, namely the pars triangularis and pars opercularis, have been reported in some studies (Foundas, Eure, Luevano, & Weinberger, 1998), others have either found the leftward asymmetry to be restricted to one structure (Dorsaint-Pierre et al., 2006; Keller et al., 2007; Knaus, Corey, Bollich, Lemen, & Foundas, 2007) or have failed to replicate these asymmetries at all (Tomaiuolo et al., 1999; Watkins et al., 2001). The assessment of asymmetries in the anterior speech regions is subjected to similar problems as those described in relation to planum temporale asymmetry, and results have been even more divergent. Thus, on the basis of the current research, an association between anatomical asymmetry in these regions and functional language specialization cannot be reliably inferred (Keller, Crow, Foundas, Amunts, & Roberts, 2009).

In summary, despite the leftward population bias of the planum temporale, its predictive power for functional hemispheric specialization remains limited. It seems reasonable to assume that anatomical asymmetries are related to cerebral language dominance to a certain extent, but they are not imperative for the maintenance of an asymmetrically distributed language network.

Structural connectivity in the asymmetric brain

Cytoarchitectonic studies of the planum temporale have yielded surprising results as to the microstructural basis of the macroanatomical asymmetry. That is, in the planum temporale, the neural columns which form a functional processing unit are more widely spaced in the left, which results, despite longer dendrites, in a decreased number of interconnected columns compared to the right (Hutsler & Galuske, 2003). This connectivity pattern might reflect a less redundant and more specific processing system. On the other hand, some of the additional space between the neural columns is thought to be filled with short and long range connections given that glial cell numbers were found to be similar on the left and right side. The resulting enhanced structural connectivity to wider regions might allow for more efficient information processing on the left side. Concurrently, the axons in the left planum are more heavily myelinated than those in the right (Anderson, Southern, & Powers, 1999) and the left primary auditory cortex contains more white matter than the right (Penhune, Zatorre, MacDonald, & Evans, 1996). These results suggest that it might not be only the actual number of neurons but also the amount of connectivity between them that underlies the superior information processing capability of one hemisphere over the other. Related to this, structural connectivity between core processing areas within a hemisphere might play a crucial role in the formation of asymmetric networks. Densely interconnected networks within a hemisphere might in turn rely less on input of contralateral regions, so that interhemispheric connectivity might be reduced (Nowicka & Tacikowski, 2011). That is, intra- and interhemispheric connectivity might be important for the maintenance of functional lateralized networks.

Although the importance of fibre tracts in transferring information had already been acknowledged by Wernicke in 1874, recent developments in brain imaging techniques, namely the invention of diffusion tensor imaging (DTI), created new opportunities for the investigation of white matter pathways given that DTI is performed in vivo. Prior to DTI, the white matter architecture of the human brain was assessed in post-mortem studies, but these methods are limited, and relationships to functional hemispheric specialization were difficult to obtain.

DTI is based on the estimation of the amount of diffusion of water molecules within the brain tissue. Structures such as axonal membranes and myelin sheath provide an obstacle for the passage of water molecules. Therefore, the perfusion of the water molecules is restricted and tends to occur along one particular axis, i.e. is anisotropic. DTI tractography uses the directional information of the diffusion process to reconstruct the anatomical course of a fibre tract. Different algorithms have been developed, which can be broadly classified in two categories. Deterministic methods determine the principle fibre orientation within a voxel and then generate a single pathway by linking the directional information between adjacent voxels. Given that only one fibre orientation within a voxel is taken into account, this method cannot resolve instances where fibres cross. Probabilistic methods on the other hand estimate the probability of a certain connectivity pattern by randomly drawing a large number of possible pathways. The resulting connectivity maps allow assigning a confidence level to the estimated trajectory of a tract.

In addition, the amount of anisotropic diffusion, often expressed as fractional anisotropy (FA), allows inferences about the organization and integrity of the underlying white matter tract. Fractional anisotropy (FA) is a scalar value between 0 and 1, with a value of 0 indicating equal diffusion in all directions, and a value of 1 indicating that the diffusion process occurs entirely along one axis. High FA values are found in white matter with tightly packed axons, thick myelin sheath and few obliquely oriented fibres (Chepuri et al., 2002). Other factors such as the existence of crossing fibres and structures other than myelinated axons also influence the amount of anisotropic diffusion.

DTI has provided new insights into the organization of white matter tracts in the human brain, not at least because it allows the study of interindividual variability of structural connectivity and its relation to functional cerebral asymmetries (Doron & Gazzaniga, 2008). In the next two sections, two white matter tracts thought to be closely linked to functional cerebral dominance are discussed, namely the corpus callosum and the arcuate fasciculus, representative of inter- and intrahemispheric circuits, respectively.

Interhemispheric connectivity: the corpus callosum

Anatomy

The corpus callosum connects the two hemispheres and with over 200 million fibres forms the largest white matter tract in the human brain (Aboitiz, Scheibel, Fisher, & Zaidel, 1992b; Aboitiz, Scheibel, & Zaidel, 1992). Callosal fibres follow a rough topographic organization so that different callosal subregions are part of specific functional networks. Although most callosal fibres connect homologous cortical areas in the two hemispheres, others are directed to heterotopic sites in the opposite hemisphere (Di Virgilio & Clarke, 1997) and to subcortical structures (Jarbo, Verstynen, & Schneider, 2012). Given that no macroscopic visible anatomical landmarks delimit distinct callosal areas, geometric principles have been applied to subdivide the corpus callosum into segments according to its maximum anterior-posterior extent. Witelson’s (1989) scheme subdivides the corpus callosum in five parts (genu, anterior midbody, posterior midbody, isthmus, splenium), which roughly connect five functionally segregated regions (prefrontal, motor, somotosensory, temporoparietal, occipital). Yet, reconstructing the connectivity pattern of callosal axons with DTI tractography has shown that the geometrically devised partitioning schemes do not accurately reflect the underlying anatomy. For example, tracts connecting frontal regions extend more posteriorly than implied by the Witelson’s classification scheme (Hofer & Frahm, 2006; Hofer, Merboldt, Tammer, & Frahm, 2008; Huang et al., 2005). Furthermore, a priori defined partitioning schemes cannot capture interindividual variability in the exact location of fibre tracts (Westerhausen, Gruner, Specht, & Hugdahl, 2009). A reconstruction of callosal fibres with DTI tractography is shown in Figure 3.

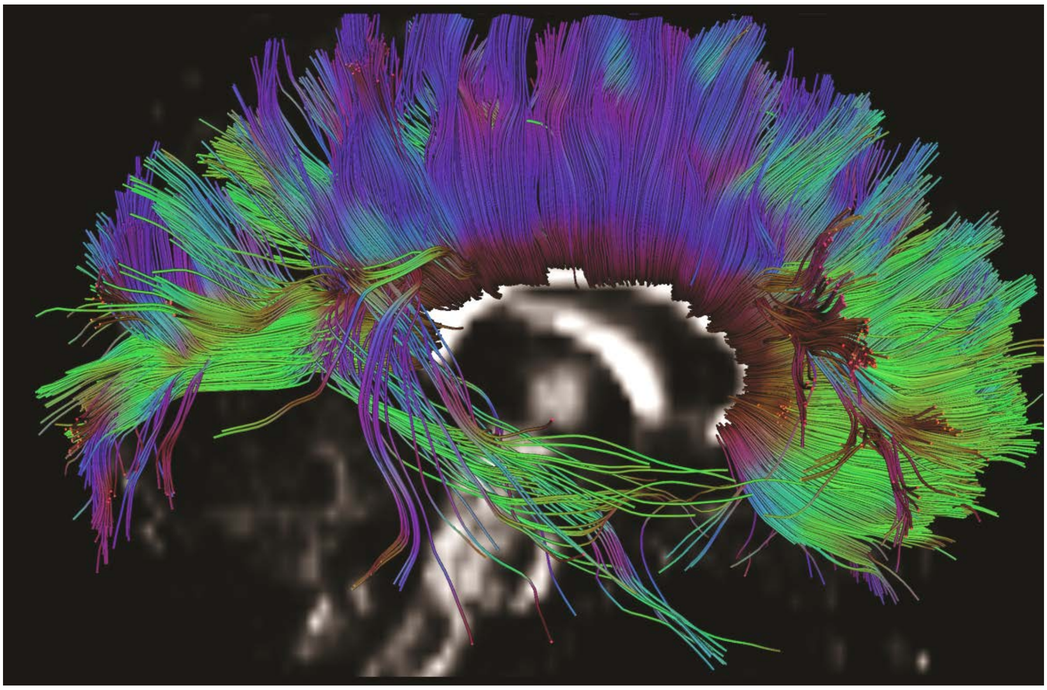

Figure 3: *Reconstruction of callosal tracts with deterministic tractography (MedINRIA v. 1.9; http://www-sop.inria.fr/asclepios/software/MedINRIA).*

Fibre size and composition vary according to the regions they connect (Aboitiz, Scheibel, Fisher, & Zaidel, 1992a). Somatosensory, auditory and visual areas are connected through highly myelinated fibres with large diameters and fast conduction velocities, whereas association areas are connected by low myelinated slow-conducting fibres with small diameters. Therefore, FA values, indicating the coherence of the underlying fibre tracts, tend to be higher in anterior and posterior region than in the body of the corpus callosum (Chepuri et al., 2002; Hofer & Frahm, 2006).

The development of the corpus callosum is characterized by an initial overproduction of axons, which are later eliminated through the process of axonal pruning (LaMantia & Rakic, 1990a). Although no additional callosal fibres are produced postnatally, the size of the corpus callosum increases from childhood into adulthood due to fibre myelination and increases in axon diameter. Full maturation of the corpus callosum is not reached until early adulthood (Giorgio et al., 2008; Keshavan et al., 2002; Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010), and in older age a loss of myelinated fibres is observed, indicated by a decrease in the white matter integrity (Lebel et al., 2010; Ota et al., 2006). Different subregions of the corpus callosum mature at different times in development, which might be associated with the acquisition of new skills (Thompson et al., 2000). For example, a growth spurt of the callosal isthmus is observed between 6 and 13 years of age commensurate with the acquisition of more sophisticated language abilities. Furthermore, periods of growth alternate with periods of shrinkage, so that some callosal subdivisions are thinner at the age of 17-18 years than at the age of 5-6 years (Luders, Thompson, & Toga, 2010). These regressive processes might reflect axonal redirection and pruning.

Interhemispheric connectivity in relation to hemispheric asymmetries

Callosal pruning has been seen as a central mechanism in the establishment of functional and anatomical asymmetries (Witelson & Nowakowski, 1991). In this theory, diminished axon loss in the corpus callosum leads to enhanced interhemispheric connectivity and thus to more symmetrically organized brains. Such a relationship was found in studies relating callosal area to anatomical asymmetries, such as the size of the perisylvian regions (Aboitiz, Scheibel, & Zaidel, 1992) or an asymmetry index derived from the differences between left and right lobar areas (Dorion et al., 2000), at least in men.

Witelson and Nowakowski (1991) based their theory largely on the finding that the callosal isthmus is larger in left-handers and ambidextrous individuals than in consistent right-handers, which is thought to reflect the more symmetrical language distribution commonly observed in left-handers (Witelson, 1985). Several subsequent investigations have revealed larger callosal areas or subsegments in left-handers (Habib et al., 1991; Witelson, 1989; Witelson & Goldsmith, 1991), but these findings have been contested by others who did not observe any handedness effects on callosal morphology (Clarke & Zaidel, 1994; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Preuss et al., 2002; Steinmetz et al., 1992).

Using DTI to additionally assess microstructrual properties of the underlying fibre tracts, Westerhausen et al. (2004) observed that the size of all callosal subregions with exception of the splenium were larger in right-handers, but anisotropic diffusion over the whole corpus callosum was higher in left-handers. The functional significance of callosal size and anisotropic diffusion remains somewhat controversial. It has been commonly assumed that a larger callosal area indicates a greater number of callosal axons and hence an enhanced connectivity between the hemispheres (Witelson, 1985). However, increased callosal size might also result from increased fibre diameters or greater interfibre distances. Aboitiz et al. (1992a, 1992b) used light microscopy to estimate the number of callosal fibres in post-mortem brains and found that the total number of thin but not of thick fibres increased when the area of the corpus callosum increased. Nevertheless, in the rhesus monkey, callosal area and fibre density were negatively correlated, so that an increase in callosal area did not result in a greater number of fibres (LaMantia & Rakic, 1990b).

Although FA values do not measure the number of fibres directly, they are thought to reflect axonal density and the degree of myelination of the fibre tracts, and these values correspond well with estimations of the interhemispheric transfer time, measured with electroencephalography (EEG). In that approach, unilateral stimuli are presented in one visual half-field, while event related potentials (ERPs) are measured over the visual cortex in both hemispheres. The latency of ERPs elicited in the cerebral hemisphere contralateral to the stimulus is then subtracted from the latency of the ERPs elicited in the ipsilateral hemisphere, and this subtraction score reflects interhemispheric transfer time (IHTT). FA values in the callosal fibres connecting primary and secondary visual areas correlated with IHTT, so that callosal tracts with the lowest FA values showed the longest delay in information transfer (Whitford et al., 2011). Similar results were also obtained when measuring interhemispheric transfer time by comparing reaction times to visual input contra- or ipsilateral to the response hand (Schulte, Sullivan, Muller-Oehring, Adalsteinsson, & Pfefferbaum, 2005). Those studies indicate that FA values indeed reveal the microstructural properties of the underlying white matter tract, and are related to the speed and efficacy of information transfer.

Westerhausen’s (2004) result of larger callosal subregions but reduced FA values in right- compared to left-handers could be construed as lower axon density or reduced proportions of myelin in the callosal tracts of right-handers. In the posterior subregion, where no handedness differences on size were detected, increased FA values might indicate enhanced structural connectivity in left-handers, consistent with Witelson’s findings.

Luders, Cherbuin, et al. (2010) investigated the effect of strength of hand preference on callosal thickness by comparing moderate left-handers to strong, moderate, or weak right-handers based on their scores on the Edinburgh Handedness Inventory. Callosal thickness in all segments, with the exception of the splenium, was negatively correlated with strength of hand preference, regardless of direction, so that individuals with the strongest hand preference exhibited the thinnest corpora callosa. Another interesting result of this study came from separate comparisons between different handedness groups. That is, when the left-handed group was compared to the strong right-handed group, larger callosal thickness was found in left-handers, concordant with Witelson's results. However, when they compared the left-handed group to the less lateralized right-handed group, then callosal thickness was larger in right-handers. Thus, the definition and classification of individuals into handedness groups might explain some of the inconsistent findings reported in previous studies.

The fact that a lack of hand preference is associated with enhanced interhemispheric connectivity might be attributed to an enhanced information transfer in more symmetrically organized brains. Studies using the dichotic listening task to assess strength of left-cerebral language dominance tended to confirm the idea of a correspondence between strong lateralization and low connectivity (Gootjes et al., 2006; Hines, Chiu, McAdams, Bentler, & Lipcamon, 1992; Yazgan, Wexler, Kinsbourne, Peterson, & Leckman, 1995). Connectivity however might also be influenced by the particular combination of different functional asymmetries in the brain. In one study, left-handers with a right-ear advantage, indicating left-cerebral language dominance, showed larger callosal areas than left-handers with right-cerebral language dominance or right-handers (Moffat et al., 1998). In the former individuals, the neural systems for speech and manual actions are localized in opposite hemispheres. Given the tight coupling of these two cognitive functions in several skills such as writing, the need for information transfer might be enhanced, resulting in stronger interhemispheric connectivity.

In contrast, recent studies using fMRI to determine language dominance suggested an inverse relationship, so that a high degree of functional lateralization was associated with higher degree of interhemispheric connectivity. Josse, Seghier, Kherif and Price (2008) predicted the degree of left-cerebral activation elicited by a picture naming and semantic decision task from the size of the corpus callosum. The amount of leftward activity in two regions, one localized in the middle temporal region and one in the posterior part of the inferior frontal gyrus, correlated positively with the size of the corpus callosum, so that individuals with the largest callosal areas also showed the highest degree of lateralized activations in those areas. In the temporal region, larger callosal areas were also associated with decreased activation on the right side. Although the two identified areas were in the vicinity of the core language areas, they did not include Broca's and Wernicke's area proper and they were relatively small compared to the extent of language activation seen over the whole brain. The relationship between interhemispheric connectivity and language lateralization was therefore confined to a relatively small part of the language network. Nonetheless, the positive relationship between lateralized activation and connectivity found in these areas suggests an inhibitory role of the corpus callosum, particularly in the temporal region.

A similar pattern between strength of left-cerebral language dominance and interhemispheric connectivity was observed in a DTI study conducted by Westerhausen et al. (2006). Individuals were classified into four groups based on the functional asymmetry indices derived from the activity elicited by a verb generation task during fMRI. The strong left-lateralized group showed lower mean diffusivity in the anterior and posterior third of the corpus callosum than the moderate left, bilateral, or moderate right-lateralized groups. An inverse effect was obtained for relative anisotropy which tended to be highest in the posterior third of the strong left-lateralized group, although the effect did not quite reach significance. Nevertheless, the data imply an enhanced interhemispheric connectivity in strongly left-lateralized individuals compared to weakly lateralized or right-lateralized ones.

The pattern observed in these two studies support a primary inhibitory role of the corpus callosum in interhemispheric communication (Cook, 1984a, 1984b). Although physiologically the corpus callosum consists of excitatory glutamatergic projections neurons (Fame, MacDonald, & Macklis, 2011), inhibitory influences might be produced by postcallosal inhibitory interneurons, which in turn reduce the overall activity in surrounding areas.

An inhibitory effect of callosal transfer has been shown in one study using PET to directly measure metabolic changes in callosal fibres (Karbe, Herholz, Halber, & Heiss, 1998). An increase of cortical activity in the left inferior frontal and the right superior temporal region was associated with a decrease in callosal activity during a word repetition task. Given that an excitatory model would predict a positive correlation, the results indicate that inhibitory information is transferred through the corpus callosum. The corpus callosum might have suppressed the activity to such an extent that it was less active compared to the resting state. The authors also observed though that 4 of the 10 participants showed the reversed pattern. In these individuals, callosal activity increased during the word repetition task, which could indicate that in those subjects the language network is organized more bilaterally, and the two hemispheres cooperated in order to resolve the task. In this study, though, neither size nor connectivity of the corpus callosum was measured. The researchers however developed a schematic model of callosal information transfer, which indicates that excitatory callosal transfer is dependent on a larger number of callosal fibres than the exchange of inhibitory information given the primary excitatory nature of callosal axons. Theoretically, only a few callosal fibres are needed to activate strategically placed interneurons, which in turn would be able to inhibit large proportions of the contralateral region. Thus, the relationship between excitatory or inhibitory influences and callosal connectivity might not be linear.

Interhemispheric interactions

The classification of callosal communication as excitatory or inhibitory forms a useful theoretical framework in which to assess the effect of interhemispheric connectivity on functional lateralization (Bloom & Hynd, 2005; Van der Knaap & van der Ham, 2011). The resulting dichotomy however might be too simplistic to fully capture the nature of interhemispheric communication. Instead, interhemispheric communication might consist of a complex interaction between the hemispheres, where the amount of inhibitory and excitatory influences depends on task difficulty and the cognitive strategies applied to resolve a certain task. That is, difficult tasks might require the collaboration of the hemispheres to enhance the capacity for information processing, whereas less demanding tasks might be processed more efficiently by one hemisphere without interference from the other (Banich, 1995).

Even so, the corpus callosum is crucial in the distribution of processing resources between the hemispheres, and one study suggested that, depending on the callosal white matter architecture, interhemispheric interactions might have differential behavioural consequences (Putnam, Wig, Grafton, Kelley, & Gazzaniga, 2008). Using fMRI, the activity in left and right prefrontal cortex during a verbal encoding task was assessed and related to the amount of anisotropic diffusion in the anterior corpus callosum. All subjects showed greater activity in the left prefrontal cortex, but only individuals with low FA in the anterior corpus callosum also activated homologous regions in the right hemisphere. Although the two groups showed similar overall accuracy in the recognition of the previously learned words, in the high FA group, right-hemispheric activation during encoding was negatively correlated with subsequent recognition, suggesting a detrimental effect of the right-hemispheric activation on performance. In contrast, individuals with low white matter integrity in the corpus callosum showed more right-hemispheric contributions during encoding, which had no negative consequences on recognition.

Aging can also serve as a model with which to explore the consequences of different interhemispheric interactions on performance and its relation to structural connectivity. Compared to younger adults, older adults tend to activate more bilateral relative to unilateral networks when performing semantic memory tasks, maybe as a compensatory strategy for cognitive decline. Such an effect has been shown by Persson et al. (2006), who compared two groups of older adults who had shown either stable or a relative decline in episodic memory performance over the last decade. As expected, the group with impaired memory functions showed more activity in the right prefrontal cortex during a word encoding task than the group where no cognitive decline was evident. The superior memory functions in the stable group were associated with higher white matter integrity in the anterior corpus callosum, which in turn correlated negatively with the activity in the right prefrontal cortex.

A similar approach was adopted by Davis, Kragel, Madden and Cabeza (2012). A group of young and old adults had to match two stimuli projected either to the same visual field (unilateral condition) or to opposite visual fields (bilateral condition). Older adults outperformed the younger ones in the bilateral condition, which was related to increased activation in the left and right prefrontal cortices. Furthermore, older adults showed increased functional connectivity between left and right prefrontal cortices, which was significantly correlated with FA values in the anterior corpus callosum. A behavioural index indicating bilateral processing advantage was derived from the difference between the accuracy in the bilateral compared to the unilateral condition. This index was positively correlated with the white matter integrity of the corpus callosum in older adults.

Intrahemispheric connectivity: the arcuate fasciculus

Anatomy

Core processing areas within a hemisphere are connected through a dense network of fibre tracts which allow them to exchange information. One of the main tracts involved in language processing is the arcuate fasciculus, which connects the anterior and posterior speech regions, classically known as Broca’s and Wernicke’s area, respectively (Friederici, 2009), as depicted graphically in Figure 4. Through the widespread use of DTI studies new insights on the anatomy and function of the arcuate fasciculus have been gained, while simultaneously introducing considerable controversy about the exact anatomical course and the cortical terminations of this fibre tract (Martino et al., 2012). The pars opercularis has been identified as the anterior endpoint of the arcuate fasciculus in some studies (Barrick, Lawes, Mackay, & Clark, 2007; Glasser & Rilling, 2008; Kaplan et al., 2010), with no or only a few fibres extending as far as the pars triangularis (Kaplan et al., 2010). Other studies though did not reveal any connections to the pars opercularis, observing instead that most arcuate fibres terminate in the precentral gyrus (Barrick et al., 2007; Bernal & Altman, 2010).

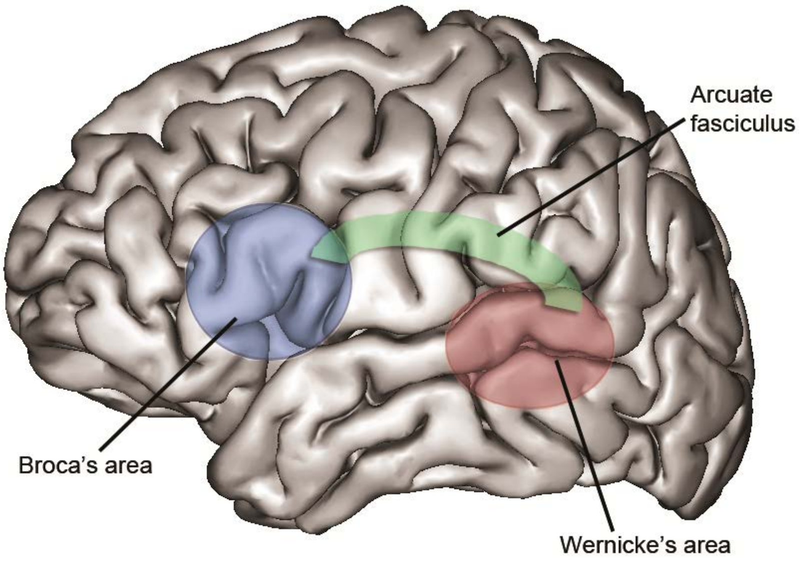

Figure 4: *A diagram showing Broca's and Wernicke's area connected via the arcuate fasciculus.*

Additionally, Glasser and Rilling (2008) identified two distinct arcuate fasciculus pathways, one which connects the posterior superior temporal gyrus to the pars opercularis and the precentral gyrus and a second one which connects the middle and inferior temporal gyri to the pars opercularis and other frontal areas. While connections to the middle and inferior temporal gyri have also been identified in other studies, they did not distinguish between these two separate pathways (Barrick et al., 2007; Catani & Thiebaut de Schotten, 2008). Rather, a second indirect route has been postulated, which connects the anterior and posterior speech regions via a relay station in the inferior parietal lobe (Catani, Jones, & Ffytche, 2005). The existence of an arcuate fasciculus tract in the right hemisphere has been challenged by studies which identified such fibres in less than half of their subjects (Catani et al., 2007), whereas others have found that the arcuate fasciculus was organized similarly in the right and left hemisphere (Gharabaghi et al., 2009).

One possible reason for the diversity of the results is the DTI methodology itself. The ability to reconstruct the anatomical course of the arcuate fasciculus depends on which tractography algorithm is applied. In one study for example, the right arcuate fasciculus could not be established in around 40% of the subjects using deterministic methods, whereas probabilistic tractography obtained a result in each individual case (Yeatman et al., 2011). Deterministic methods have tended to fail in cases of low mean FA values over the whole tract, suggesting that the inability to tract the right arcuate fasciculus might originate in the directional uncertainty introduced in locations with high numbers of intercrossing fibres.

Furthermore, determining final cortical locations with DTI methods is not optimal because single terminal branches cannot be tracked and final cortical locations have to be inferred from average tract end points (Martino et al., 2011). Ideally, results from DTI studies should be corroborated with other methodologies, such as fibre tracing and dissection studies and cortical mapping. In non-human primates, elaborate tracing methods allow detailed reconstruction of fibre tracts, but those techniques are too invasive to use in humans and inferences about the anatomy of the human arcuate fasciculus remain tentative, given the putative role of the arcuate fasciculus in language processing and the absence of comparable language skills in primates. In fact, non-human primates show an absent or diminished arcuate fasciculus (De Schotten, Dell'Acqua, Valabregue, & Catani, 2012; Rilling et al., 2008).

In humans, white matter pathways can be uncovered with fibre dissection methods in post-mortem investigations. Freezing the brain destroys grey matter areas but leaves fibre tracts intact. The surrounding brain tissue is then carefully removed to expose the white matter architecture. With such an approach, the classical arcuate fasciculus tract was found to extend from the inferior and middle temporal gyri to the posterior part of the inferior frontal gyrus in both hemispheres (Martino et al., 2011), although some inter-individual variability in the cortical terminations exists (Martino et al., 2012).

Functional connectivity between two regions can be assessed by measuring the spread of artificial currents applied directly onto the cortex in patients undergoing brain surgery. This approach illustrated that the pars opercularis and pars triangularis are indeed functionally related to sites in the posterior superior and middle temporal gyri (Conner et al., 2011), although bidirectional information flow between Broca's and Wernicke's area has been observed, which is in contrast to the traditional view (Matsumoto et al., 2004). Although the distribution of artificial currents cannot determine whether two regions are connected directly or through a third relay station, amplitude and latency of the evoked potentials were correlated with DTI parameters of the reconstructed pathways connecting the two sites (Conner et al., 2011).

Function

In the classical view, the arcuate fasciculus links speech comprehension to speech production, so that an interruption of this pathway causes conduction aphasia, a condition characterised by inability to repeat back heard words and sentences (Wernicke, 1874, 1977) . Recent reports however have shown that arcuate lesions do sometimes (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008) but not always result in conduction aphasia (Bernal & Ardila, 2009, Rauschecker et al., 2009), so that the primary role of the arcuate fasciculus might not lie exclusively in carrying signals important for the repetition of previously heard words.

Newer models of language processing suggest that the arcuate fasciculus is primarily associated with phonological processing, whereas a second pathway through the internal capsule is involved in semantic aspects of linguistic processing (Hickok & Poeppel, 2004, 2007). Both pathways have recently been reconstructed using DTI tractography methods (Barrick et al., 2007; Parker et al., 2005). According to the dual stream model, the arcuate fasciculus maps incoming phonological information to articulatory motor representations. Indeed, direct cortical stimulation of arcuate fasciculus fibres results in phonetic but not semantic paraphasias (Maldonado, Moritz-Gasser, & Duffau, 2011). Dysfunctions in aphasic patients have illustrated though that the arcuate fasciculus might also play a part in other aspects of linguistic processing. For example, patients with primary progressive aphasia (PPA) showed reduced white matter coherence in the arcuate fasciculus, which was associated with deficits in syntactic comprehension and production (Wilson et al., 2011), and similar results were also found in stroke patients (Papoutsi, Stamatakis, Griffiths, Marslen-Wilson, & Tyler, 2011). Also, low FA in the left arcuate fasciculus of stroke patients was associated with deficits in language comprehension (Breier et al., 2008), suggesting that the role of the arcuate fasciculus might not be restricted solely to phonological processing.

Given the left-hemispheric specialization for language functions, various studies have addressed the question of whether the arcuate fasciculus might form an anatomical marker for the degree of functional lateralization. As discussed previously, the planum temporale shows a leftward asymmetry and related to this, one study suggested that the white matter integrity in the arcuate fasciculus correlates with thickness measurements of Broca's and Wernicke's territory (Phillips et al., 2011). There is currently little doubt that the arcuate fasciculus is asymmetric given the observed leftward bias of various DTI parameters such as volume (Parker et al., 2005; Powell et al., 2006), fibre density (Vernooij et al., 2007) and FA values (Buchel et al., 2004; Powell et al., 2006; Takao, Hayashi, & Ohtomo, 2011; Thiebaut de Schotten et al., 2011). This asymmetry has even been observed in 1- to 4-month-old infants (Dubois et al., 2009), although the tract is not fully formed at that time and keeps maturing well into adolescence (Ashtari et al., 2007; Paus et al., 1999). It has been suggested that the leftward asymmetry originates in differences in the number of fibres, the degree of myelination (Anderson et al., 1999) and other intra-axonal properties such as average axonal diameter (Upadhyay, Hallock, Ducros, Kim, & Ronen, 2008).

The above evidence suggests that the language areas in the left hemispheres might be connected through a denser and more efficient fibre network than the homologous regions in the right, but despite several investigations it is not yet clear whether this anatomical asymmetry corresponds to the functional specialization of the left hemisphere for linguistic processing. Vernooij et al. (2007) found that although 80% of the subjects exhibited leftward asymmetry in the relative fibre density of the arcuate fasciculus, only 65% of these individuals showed left lateralized cortical activation elicited by language processing, and across all subjects the two asymmetries were not related. A correlation between the activity in parieto-temporal but not in frontal language areas and arcuate fasciculus asymmetry was only found in the seven right-handed participants. Propper et al. (2010) also found the relationship between an anatomical asymmetry index derived from the volumes of the arcuate fasciculus and a functional asymmetry index representing language dominance to be restricted to the asymmetric activity in Wernicke's area but not in Broca's area, at least in consistent left-handers. The structure-function covariation was not observed in all other handedness groups. In contrast, Powell et al. (2006) observed a positive correlation between an asymmetry index derived from the FA values in the left and right arcuate fasciculus and strength of left-hemispheric activation elicited by a verb generation task and a reading comprehension task in frontal and temporal regions in right-handers.

It seems difficult to appraise the significance of these divergent results given that the relationship appears to be affected by several factors, such as handedness, the functional regions on which language dominance is defined, and the parameters used to estimate the strength of the structural connectivity.

Ellmore et al. (2010) predicted the language dominant hemisphere according to the outcome of the intracarotid amobarbital procedure in 23 epileptic patients from the side in which the arcuate fasciculus showed the highest anisotropic pathways. Four subjects, one with a right-sided and three with a left-sided language network, were misclassified. Adding handedness and laterality scores derived from functional imaging to the predictors improved the prediction considerably, detecting the dominant hemisphere in all but one case. In a further study investigating structural asymmetry in epilepsy patients, anisotropic asymmetry indices were also correlated with a laterality index derived from functional imaging, although only for patients with right but not left temporal lobe epilepsy (Rodrigo et al., 2008). This suggests that in epileptic patients, structural and functional reorganization processes might occur, so that the functional significance of the results obtained in these two studies remains tentative.

Other neuroimaging studies addressed the question of whether a leftward asymmetry of the arcuate fasciculus is in fact beneficial for language processing abilities. In adults, this hypothesis has been contested. A symmetrical pattern of the arcuate fasciculus tract was associated with better performance in learning words by semantic association as assessed by the California Verbal Learning Test (CVLT) (Catani et al., 2007). Another study showed that in girls, but not in boys, volume differences in the arcuate fasciculus were negatively correlated with phonological memory and basic reading (Yeatman et al., 2011). This finding is in contrast with other results obtained in children, where leftward asymmetry was associated with enhanced performance on language tasks. For example, in 68 children aged 5-13 years, 90% showed a leftward asymmetry of the arcuate fasciculus and these outperformed the right-lateralized ones on a phonological processing task and a test of receptive vocabulary (Lebel & Beaulieu, 2009). In childhood, a leftward asymmetry of the arcuate fasciculus might be beneficial for reading, given that early readers tend to rely more on phonological strategies to map a word to its sound than on visual-orthographic strategies which are more often applied by expert readers. That is, young Chinese children with an extreme leftward asymmetry of the arcuate fasciculus outperformed the ones with more bilateral networks in a Chinese and an English reading tasks (Qiu, Tan, Siok, Zhou, & Khong, 2011). The same effect was not observed in older children and young adults.

This thesis

As discussed above, variability in the degree of lateralized functional networks may depend at least partly on variability in the structural connectivity within and between the hemispheres. Interhemispheric interactions are largely dependent on information transfer through the corpus callosum and this system might therefore play a key role in the establishment and maintenance of functional hemispheric asymmetries (Galaburda, Rosen, & Sherman, 1990). Despite a large number of investigations, though, controversy about the relationship between callosal connectivity and strength of hemispheric asymmetries remains. In fact, earlier studies assessing hemispheric specialization based on anatomical asymmetries between the hemispheres (Aboitiz, Scheibel, & Zaidel, 1992; Dorion et al., 2000) or with the dichotic listening task (Gootjes et al., 2006; Hines et al., 1992; Yazgan et al., 1995) support the view of an association between enhanced connectivity and more bilaterally organized brains. More recent studies using fMRI to determine language dominance have challenged these findings (Josse et al., 2008; Westerhausen et al., 2006). Using DTI methods specifically, callosal white matter integrity was found to be higher in left-handers (Westerhausen et al., 2004) but also higher in strongly left lateralized individuals based on the activity derived from functional imaging. Given that language networks of left-handers tend to be distributed more bilaterally, these data remain inconclusive.

One reason for the diversity of results might lie in the fact that various lateralizing influences act on the brain (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). Crowding of functions, such as the localization of language and spatial processing in the same hemisphere, might result in adaptations of the interhemispheric connectivity, but this has been largely neglected in previous studies. The first Experiment aims to address these questions by assessing the relationship between callosal morphology and cerebral asymmetries for manual actions, speech and spatial processing.

The second and third Experiments examine the relationship between structural connectivity and language dominance in a set of monozygotic twin pairs. Despite having the same set of genes, some monozygotic twin pairs show discordant handedness and some even reverse their language dominance pattern (Badzakova-Trajkov, Haberling, & Corballis, 2010), so that the relationship between cerebral asymmetries and structural connectivity in the framework of genetic theories on hemispheric dominance can be assessed.

The development of language dominance has been associated with the mechanisms of callosal pruning, and it has been suggested that hormones influence the amount of axon loss in the corpus callosum (Witelson & Nowakowski, 1991). A recent meta-analysis though negated a hormonal effect on cerebral asymmetry (Pfannkuche et al., 2009). Based on the assumption that the establishment of handedness and language dominance is largely under genetic control, one might also hypothesize that the lateralizing gene establishes hemispheric dominance by exerting control over the process of callosal pruning. Based on the predictions of the right-shift theory (Annett, 2003), twin pairs whose handedness and language dominance have been established can be classified according to their likelihood of possessing the lateralizing allele (RS+). By comparing callosal morphology between the two putative genotypes, possible effects of the lateralizing gene on interhemispheric connectivity can be assessed.

In the third Experiment, the relationship between language dominance and arcuate fasciculus asymmetry was investigated in the same set of monozygotic twin pairs. Previous studies on arcuate fasciculus asymmetry have been equivocal, with some investigations finding structure-function covariations only in right-handers (Powell et al., 2006; Vernooij et al., 2007) or only in left-handers (Propper et al., 2010). The problem of confounding variables such as gender and age is lessened in monozygotic twin pairs given that the two members of one pair are perfectly matched in terms of gender, age and genotype. Moreover, the inclusion of monozygotic twins also allows inferences about genetic and nongenetic influences, given that all variability within pairs must originate from nongenetic sources.

This thesis therefore assesses whether hemispheric asymmetry has a structural basis which is closely tied to a substrate of white matter tracts. The aim is to uncover whether interindividual variability in the lateralization of functions is associated with distinctive characteristics of the structural connectivity within and between the hemispheres.

Chapter 2:

Experiment 1: Callosal tracts and patterns of hemispheric dominance[1]

Abstract

Left-hemispheric dominance for language and right-hemispheric dominance for spatial processing are distinctive characteristics of the human brain. However, variations of these hemispheric asymmetries have been observed, with a minority showing crowding of both functions to the same hemisphere or even a mirror reversal of the typical lateralization pattern. Here, I used diffusion tensor imaging and functional magnetic imaging to investigate the role of the corpus callosum in participants with atypical hemispheric dominance. The corpus callosum was segmented according to the projection site of the underlying fibre tracts. Analyses of the microstructure of the identified callosal segments revealed that atypical hemispheric dominance for language was associated with high anisotropic diffusion through the corpus callosum as a whole. This effect was most evident in participants with crowding of both functions to the right. The enhanced anisotropic diffusion in atypical hemispheric dominance implies that in these individuals the two hemispheres are more heavily interconnected.

Introduction

The corpus callosum is the largest fibre tract in the human brain connecting the left and right hemispheres and relaying sensory, motor, and higher cognitive information. It is commonly suggested that the corpus callosum plays an important role in the development and maintenance of functional hemispheric asymmetries. The best documented functional asymmetry is the left-hemispheric dominance for language, first described by Paul Broca in the 1860s (as cited in Berker et al., 1986). Non-verbal functions such as spatial attention,

---

[1] This Experiment is published in Haberling, I.S., Badzakova-Trajkov, G., & Corballis, M.C. (2011). Callosal tracts and patterns of hemispheric dominance: a combined fMRI and DTI study. Neuroimage, 54(2), 779-786.

face processing, mental rotation, and emotion processing are considered to be right-hemisphere dominant (Bourne, 2008; Corballis, 1997; Vogel, Bowers, & Vogel, 2003).

Handedness is positively correlated with hemispheric dominance for language production, but not with lateralization for spatial processing (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). The correlation with language dominance has led some to propose a common genetic origin. Genetic models, such as those proposed by Annett (1998, 2002) and McManus and Bryden (1992), assume a single gene with one allele predisposing to right-handedness and left-hemispheric dominance for language, and the other leaving the direction of both asymmetries to chance.

Two contrasting models have been suggested for the role of the corpus callosum in brain asymmetry. According to the excitatory model, the corpus callosum integrates information between the hemispheres (Galaburda et al., 1990; Gazzaniga, 2000), so that bilateral processing is associated with enhanced interhemispheric transfer in order to maintain both hemispheres in a functionally activated state. In contrast, the inhibitory model proposes that fibres in the corpus callosum inhibit homotopic areas, allowing for independent functioning of the hemispheres (Cook, 1984a). Thus, where the excitatory model predicts a negative correlation between degree of lateralization and callosal connectivity, the inhibitory model predicts a positive correlation.

Studies based on handedness have been equivocal, with some showing larger callosal areas in left- than in right-handers (Habib et al., 1991; Witelson, 1985, 1989; Witelson & Goldsmith, 1991), while others report no differences (Clarke & Zaidel, 1994; Jancke, Staiger, et al., 1997; Preuss et al., 2002; Steinmetz et al., 1992), or even larger callosal areas in right-handers (Westerhausen et al., 2004). Where language lateralization was measured more directly, for example with the dichotic listening task, correlations between degree of lateralization and the midsagittal area of the corpus callosum have been negative (Gootjes et al., 2006; Hines et al., 1992; Yazgan et al., 1995), favouring the excitatory model. Similarly, bilateral processing of spatial stimuli, as indicated by a smaller leftward bias in the line-bisection test, was associated with larger callosal areas (Yazgan et al., 1995).

Using fMRI during word generation to measure language lateralization and DTI to examine the microstructure of the corpus callosum, Westerhausen et al. (2006) found that mean diffusivity (MD) in the corpus callosum was lower, while fractional anisotropy (FA) tended to be higher, in strongly left-lateralized subjects than in moderately left-lateralized, bilateral, or right-lateralized subjects, but the groups did not differ with respect to the area of the corpus callosum. The authors interpreted the MD and FA results as indicating stronger and / or faster interhemispheric connections in the strongly left-lateralized individuals, which might be taken as support for the inhibitory model. Josse et al. (2008) found that increased callosal size was associated with greater left-hemisphere activity during language tasks in posterior temporal and inferior frontal regions, together with reduced right-hemisphere activity in posterior temporal regions, again supporting an inhibitory model. In this study, though, participants with right-hemispheric language dominance were excluded.

From an evolutionary perspective, Gazzaniga (2000) has proposed that callosal function was reduced in humans relative to that in primates, to allow differential specialization of the hemispheres. Nevertheless, sufficient interhemispheric connections were retained to permit computations in the two hemispheres to be integrated. On this view, one would predict reduced callosal function in people with the typical pattern of cerebral asymmetry, including left-hemisphere dominance for language and right-hemisphere dominance for spatial processing, compared to those with atypical cerebral asymmetry, especially where the same hemisphere is dominant for both language and spatial processing. Here, I aim to test this prediction using fMRI to assess lateralization for language and spatial processing, and fractional anisotropy (FA) to measure the efficacy of callosal projections. Increased FA can be found in white matter with more tightly packed axons, thicker myelin sheath, fewer obliquely oriented fibres, and different radii of individual axons (Chepuri et al., 2002). My main hypothesis is that FA should be higher in those with atypical patterns of cerebral asymmetry.

Materials and methods

Subjects

A total of 60 participants took part in the study (30 males; mean age = 20.83, SD = 4.6; 30 females; mean age = 23.23, SD = 4.55). To establish handedness, all participants filled out a handedness questionnaire (Annett, 2002), consisting of 12 different questions on hand preference (writing, throwing a ball, holding a racquet, lighting a match, cutting with scissors, threading through a needle, broom sweeping, shovelling, dealing cards, hammering, holding a toothbrush, unscrewing a lid) (Appendix A). They were asked to indicate the hand habitually used for each of those activities by giving two ticks for a preferred hand or one tick for each hand when indifferent. Preference scores were obtained from the formula $100x(\frac{R-L}{R+L})$, where R and L are the numbers of ticks allocated to the right and left hands, respectively. 35 participants with preference scores > 0 (17 male) were classified as right-handers whereas 25 (13 males) with preference scores ≤ 0 were classified as left-handers[2]. Left-handers were deliberately over-represented in the study to allow for comparisons between handedness groups and increase the chance of including individuals with atypical patterns of hemispheric dominance.

Most participants were undergraduate students at the University of Auckland and had no history of psychiatric or neurological disorders (Appendix B). They all gave written consent prior to the study and ethical approval was obtained by the Human Ethics Participants Committee at the University of Auckland.

Functional Tasks

Word Generation Task

Experiments were programmed using E-Prime software (http://www.pstnet.com/). For the Word Generation Task, participants were instructed to silently generate as many words as possible beginning with a designated letter (F, A, S, B, and M) projected in random order and centrally onto a screen (in Courier New font, size 50). Participants were advised to avoid proper names or the same words with different endings. Experimental blocks were followed by a baseline period that consisted of a small black fixation cross. Baseline and experimental blocks lasted 30 s and were repeated 5 times resulting in a scanning time of 5 min. To obtain a behavioural performance measure, each participant undertook a comparable verbal fluency test with 3 letters (P, R, and W) outside the scanner, in which they spoke the words out loud.

Landmark Task

The Landmark Task is a variant of a line-bisection task, which has been shown to engage a predominantly right-hemispheric network in parietal and occipital cortices (Fink et

---

[2] In an earlier analysis I applied a cut-off point of 40, but due to a reviewer's suggestion this was changed to a cut-off point of 0. Note that only one participant switched from left-hander to right-hander according to the new classification scheme, and the overall results were not affected.

al., 2000). It consisted of an experimental condition during which participants decided whether a horizontal line was bisected exactly in the middle, and a control condition where participants had to judge whether a line was bisected at all. The stimuli were lines of three different lengths, 5 cm, 8 cm and 10 cm, resulting in a visual angle of 11, 22 and 33°, respectively. Stimuli were presented centrally on a white screen for 1s with an inter-stimulus interval of 1s during which time participants responded to the task by pressing one of two buttons with either their left or their right hand. They pressed with the index finger for answering “yes” to either the question “Is the line bisected exactly in the middle?” or “Is there a vertical mark?”, and with the middle finger for answering “no.” The lines were correctly bisected in the middle on 50% of trials, and deviated in 25% of the trials to the left and in 25% of the trials to the right with a bias of 2, 5 or 10% of the lengths of the line. In the control condition, the line was bisected in half of the trials, while in the other half no vertical mark was presented. Each experimental and control block lasted 30 s and was followed by a baseline of 12.5 s that consisted of a black fixation cross.

An introduction screen presented for 5 s gave instructions as to which hand to use and which condition should be performed. The ensuing experimental or control block was repeated 3 times before a new instruction screen appeared. This scheme was repeated 4 times (2 conditions x 2 hands) so that all possible combinations of hand and condition were performed three times by all subjects. The order was counterbalanced. Total scanning time was 8 min 50 s. Prior to the scanning, participants were given a practice version of the task with 2 bisection and 2 control blocks in order to familiarize them with the task.

Image acquisition

All MRI scanning was performed on a 1.5-T Siemens Avanto scanner (Erlangen, Germany). A T1-image was acquired using a 3-D MP-RAGE sequence with the following parameters: TR = 11 msec; TE = 4.94 msec; flip angle: 158; FOV: 256 x 256 mm^2; up to 176 axial slices, ensuring whole brain coverage, parallel to AC–PC line; slice thickness: 1 mm; interslice gap: 0 mm resulting in 1 x 1 x 1 mm voxels. For the functional images an EPI sequence with the following parameters was used: TR = 2500 ms; TE = 50 ms; flip angle = 90; FOV = 192 x 192 mm^2; matrix size: 64 x 64; 29 slices parallel to the AC–PC line; slice thickness: 3 mm; and interslice gap: 25% = 0.8 mm. Diffusion-weighted data were acquired using a single-shot spin echo sequence (TR = 6601 ms, TE = 101 ms, in-plane resolution: 1.8 x 1.8 mm, and FOV 230 mm). 45 axial slices (thickness 3 mm) along 30 diffusion gradient directions (b = 1000 s/mm^2) as well as one image without diffusion weighting (b = 0 s/mm^2) were acquired. This sequence was repeated twice resulting in an acquisition time of approximately 7 min.

Image pre-processing and analyses

Functional data were analysed using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm). The first two scans were discarded to allow for saturation of the MRI signal. The functional scans were realigned to the first image of the session and the T1-weighted structural image was co-registered to the mean of the functional volumes. Both, structural and functional images were normalized into standardised stereotactic space (MNI, Montreal Neurological Institute) and spatially smoothed with an anisotropic Gaussian filter of 9 x 9 x 9 mm of full-width at half maximum (FWHM). For each participant a first-level analysis was performed using the general linear model (GLM) implemented in the SPM5 software. The models were set up as a box-car function with “task” vs. “control” conditions (letter vs. baseline for the Word Generation Task; bisection vs. control for the Landmark Task) and convolved with a canonical haemodynamic response function. Movement regressors were also included in the model. To see the general pattern of activation, a second-level random-effects analysis was performed by applying a one-sample t-test to the contrast images of the first-level analyses. To correct for multiple comparisons, a family-wise error (FWE) correction was applied at $p < 0.05$ with a contiguity threshold of 20 voxels.

For each participant, laterality indices were calculated using the laterality toolbox available on the SPM website (Wilke & Lidzba, 2007). Laterality was scored after the widely-used formula LI = $\left(\frac{L-R}{L+R}\right)$, where L and R represent activation in left and right hemisphere, respectively. Because laterality indices based on one single fixed statistical threshold do not yield robust or reproducible results (Jansen et al., 2006), the LI toolbox applies a bootstrap algorithm to calculate about 10,000 indices at different thresholds yielding a robust mean, and maximum and minimum LIs. Indices range from -1 for extreme right to 1 for extreme left lateralization. Regions of interest (ROI) were defined anatomically within the toolbox. In addition, the toolbox applies a weighting factor to take asymmetric mask sizes into account. For the Word Generation Task the whole frontal lobe and for the Landmark Task the whole parietal lobe were considered. The laterality indices were used to decide whether the language processing was left dominant, symmetric or right dominant (Fernandez et al., 2003). A positive index within the ROI corresponded to a left-hemispheric dominance (LI > 0.1) and a negative index to a right-hemispheric dominance (LI < -0.1). Bilateral processing was characterized by LIs ranging from -0.1 to +0.1.

Although there has been some question as to the reliability of fMRI-based laterality measures (Jansen et al., 2006), classification of language lateralization based on this task has yielded results consistent with the Wada test, which is thought to be the “gold standard” for measuring hemispheric dominance (Woermann et al., 2003; Yetkin et al., 1998), and also yield results consistent with fTCD (Jansen et al., 2004). Moreover, the test-retest reliability of lateralization has been shown to be high (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Fernandez et al., 2003).

Diffusion-weighted image analysis and tractography based segmentation

DTI was used to divide the corpus callosum based on the projection site of specific fibre tracts (Chao et al., 2009; Zarei et al., 2006). The tractography-based segmentation of the corpus callosum was carried out using the FDT toolbox implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/). Based on the probability that a voxel in a seed mask connects to a predefined target mask, the anatomical connectivity pattern of a brain region can be determined (Behrens et al., 2003). This method was applied to the callosal fibre tracts as follows.

For each participant, the corpus callosum was manually outlined on the midsagittal slice of the individual T1 images by applying the following steps. First, the structural T1-weighted images were registered to an optimized individual target brain in the Talairach coordinate system (Kochunov et al., 2002) available at the BrainMap website (http://brainmap.org/ale/index.html). A rigid body transformation with 6 degrees of freedom (3 translations, 3 rotations) was applied without scaling the brain in order to maintain individual brain sizes. Second, the images were segmented into grey and white matter using the automated segmentation tool implemented in FSL (Zhang, Brady, & Smith, 2001). Third, the white matter segmentation image was overlaid over the structural image to facilitate the manual outlining of the corpus callosum. To assess reliability, a second independent measurement of the callosal area for 10 randomly chosen participants was made by a different rater, resulting in an intraclass correlation of 0.96. In addition, the white matter volume was calculated in order to be able to control callosal measurements for brain size.

To segment the corpus callosum into three distinct subdivisions, specific cortical target masks were created on the MNI template. The most anterior mask comprised the frontal lobe but spared the motor cortex. The motor cortex was derived from the Juelich histological atlas implemented in FSL and included M1 and premotor cortex. The posterior mask included the temporal, parietal and occipital lobes. To ensure a good alignment of these masks, the individual T1 images were nonlinearly registered to the MNI template and the resulting registration matrices were inversed and applied to the target masks transferring them back into each participant’s native space.

The diffusion data were corrected for eddy currents and head motion and the two acquisitions were averaged to improve signal-to-noise ratio. Diffusion tensors were fitted at each voxel and FA maps were generated. Then, the probability distribution of fibre direction at each voxel was calculated using previously described methods (Behrens et al., 2003). For each participant, probabilistic tractography was run from each voxel in the corpus callosum to each target mask by drawing 5000 random samples with a step length of 0.5 mm and a curvature threshold of 0.2. The resulting value in each callosal voxel represents the number of samples reaching the relevant target mask and therefore the probability of the connections between the two. The analysis was run separately for the right and left hemispheres. Using a similar threshold as in previous research, each output mask was thresholded at 10% of the maximum connectivity value to the relevant target mask (Zarei et al., 2006). Then, tracts going to the left and right hemisphere were compared and only overlapping areas were considered for further analyses (Westerhausen et al., 2009). The resulting masks were binarized and multiplied with the FA maps in order to extract the mean FA values of the corpus callosum.

To visualize the results, the callosal segments were registered to the MNI template by applying the nonlinear registration matrices calculated before, and then added together. This generates a population-based probability mask where the values in each voxel represent the number of participants that show a connection to the relevant target mask. A threshold was applied so that the resulting masks only contain voxels that were shared by at least 70% of the participants. This threshold was arbitrary and only used for the visualization of the resulting callosal segments. The tractography based segmentation of the corpus callosum is visualized in Figure 5.

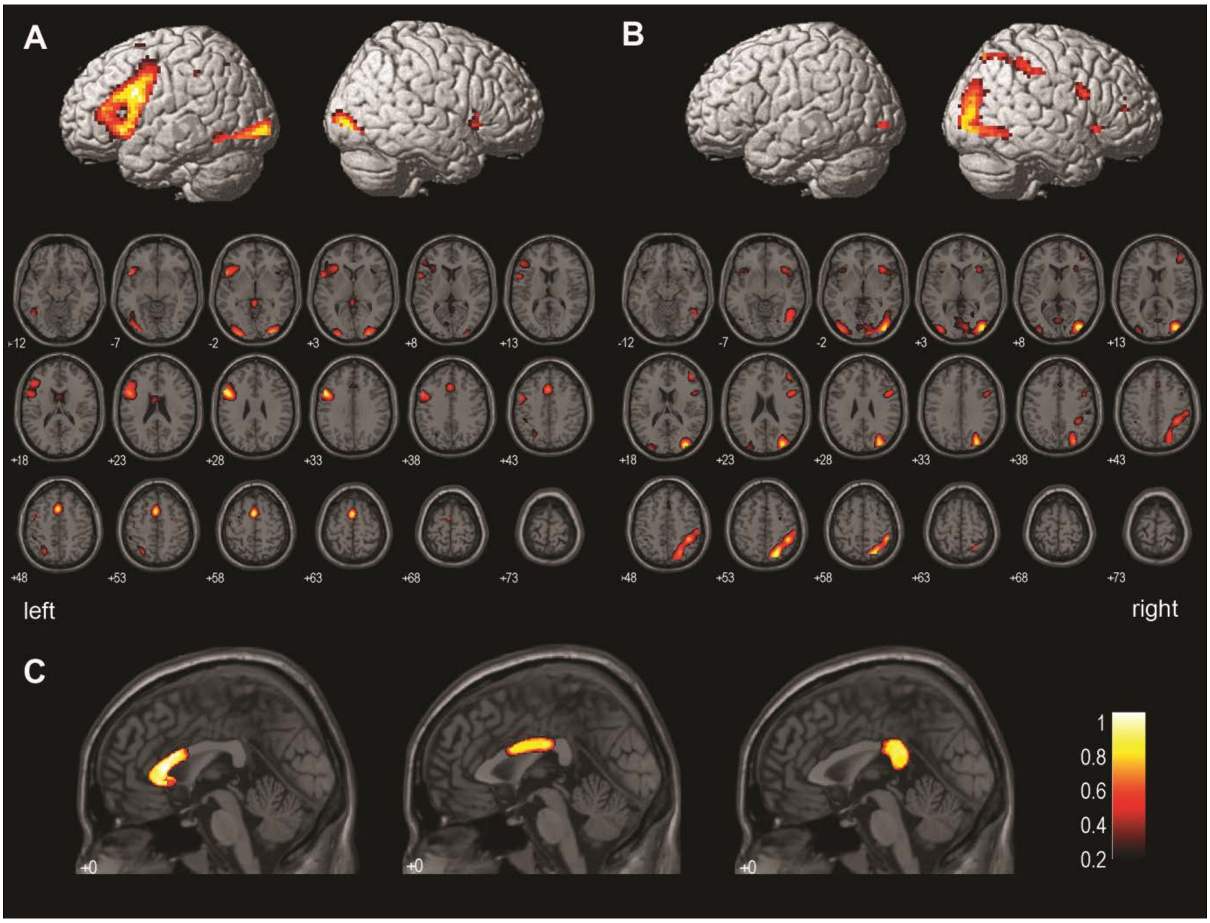

Figure 5: *fMRI activation maps for A) Word Generation Task and B) Landmark Task are displayed laterally on the cortical surface of a rendered brain. In addition, activations overlaid on slices of a single subject T1 image are shown. Displayed results are significant at* $p < 0.05$ *with family-wise error rate (FWE) correction for multiple comparisons. C) Group probability maps showing the location of the cortical connections within the corpus callosum shared by at least 70% of the participants. Areas connecting to prefrontal cortices, motor cortices, and occipital, temporal, parietal cortices are shown.*

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, v.17) software was used for all the analyses. Mean corpus callosum size was 643 mm^2 (± 88 mm^2). A factorial ANOVA with handedness and gender as between-subjects factors and white matter volume as a covariate, revealed no significant effects of either handedness or gender on the total callosal area. To test for possible effects of hemispheric dominance, separate factorial ANOVAs on the callosal segments and their corresponding FA values were performed. All analyses were controlled for age, gender, handedness, and total callosal area. To adjust for multiple comparisons, a Bonferroni correction was applied to the alpha level by dividing it by the number of applied tests (i.e. divided by three given that three callosal segments were investigated), resulting in a new alpha level of 0.017.

Table 1: *Significantly activated brain regions for the Word Generation Task and the Landmark Task. Brodmann area (BA), MNI coordinates for the peak activation voxel, and T-value are also shown.*

Anatomical location	**BA**	**MNI coordinates**			**T-value**
		x	y	z	
Word Generation					
Left hemisphere					
Precentral gyrus	6	-42	3	30	11.32
Insula	13	-33	24	3	9.79
Inferior frontal gyrus (p. orbitalis)	45	-48	18	-3	7.95
Middle occipital gyrus	18	-24	-96	0	8.83
Inferior temporal gyrus	19	-45	-57	-9	7.73
Hippocampus		-24	-36	9	6.39
Cerebellar vermis		0	-63	-12	7.06
Superior parietal lobule	7	-24	-63	48	6.47
Right hemisphere					
Hippocampus		33	-39	3	7.90
Middle occipital gyrus	18	30	-93	0	9.75
Insula	13	36	18	3	7.03
Bilateral					
Putamen		-21	3	30	7.82
Caudate nucleus		18	15	18	6.75
Thalamus		-3	-12	9	6.57
SMA	6	-3	9	54	12.64
Landmark					
Right hemisphere					
Middle occipital gyrus	19	36	-90	18	7.74
Inferior occipital gyrus	18	39	-90	-3	7.55
Inferior parietal lobule	40	39	-42	48	6.95
Superior parietal lobule	7	27	-57	54	6.87
Insula	13	36	18	-3	6.53
Inferior frontal gyrus (p. opercularis)	44	48	6	27	6.26
Left hemisphere					
Middle occipital gyrus	18	-39	-90	-3	5.67

The Anatomy toolbox was used to determine the anatomical location; Brodmann areas were derived from the Talairach demon.

Results

fMRI results

All participants completed the Word Generation Task, but one participant did not complete the Landmark Task. The results are graphically displayed in Figure 5 and the significantly activated brain areas are summarized in Table 1. For the Word Generation Task, significant activations were found in precentral gyrus, inferior frontal gyurs, insula, SMA and middle occipital gyrus predominantly in the left hemisphere. The activation maps for the Landmark Task showed significant clusters in middle and inferior occipital gyri, inferior and superior parietal lobules, and insula of the right hemisphere. For each participant, laterality indices for the Word Generation Task and for the Landmark Task were computed.

Table 2: *Number of participants showing left, bilateral or right lateralization as a function of handedness and gender.*

Task	**Hemispheric dominance**	**right-handers**		**left-handers**		**Total**
		m	*f*	*m*	*f*	
Word generation	left	17	15	11	8	51 (85%)
	bilateral	0	0	1	0	1 (1.7%)
	right	0	3	1	4	8 (13.3%)
Landmark	left	3	2	3	4	12 (20.3%)
	bilateral	2	1	0	0	3 (5.1%)
	right	12	15	9	8	44 (74.6%)

Overall, significant asymmetric activations were observed with the Word Generation Task favouring the left hemisphere ($M = 0.53$, $SE = 0.06$, $t(59) = 9.53$, $p < 0.001$) and the Landmark Task favouring the right hemisphere ($M = -0.36$, $SE = 0.06$, $p < 0.001$), $t(58) = -5.78$, $p < 0.001$). To test whether laterality indices differ between handedness groups, a factorial ANOVA with gender (male and female) and handedness (right-handers and left-handers) as between-subjects factors was performed for both tasks. For the Word Generation

Task, right-handers were significantly more lateralized (M = 0.64, SE = 0.07) than left-handers (M = 0.37, SE = 0.08) ($F_{(1,56)}$ = 6.62; p = 0.013). For the Landmark Task, left-handers (M = -0.34, SE = 0.10) were as lateralized as right-handers (M = -0.37, SE = 0.08; $F_{(1,55)}$ = 0.05, p = 0.828). No significant effect of gender was found.

Effect of language lateralization on FA values

All participants were categorized according to their laterality indices on the Word Generation Task. Eight of the 60 subjects were classified as having right-hemispheric dominance for language and 1 participant as being bilateral. The breakdown of hemisphere dominance according to handedness and gender is shown in Table 2. The participants were then grouped into those with "typical" left-hemispheric dominance for language, and those with "atypical" lateralization, which included the bilateral participant along with those with LI < -0.1. Despite the differences in the number of subjects in the two lateralization groups, both showed a similar range in the degree of laterality (typical group; range = 0.71; atypical group: range = 0.77).

Table 3: *Mean FA values and standard deviations over the whole corpus callosum and in the different callosal segments as function of atypical dominance for the Word Generation Task and the Landmark Task.*

	Word Generation Task		**Landmark Task**	
	typical	*atypical*	*typical*	*atypical*
FA				
total corpus callosum	0.55 ± 0.03	0.58 ± 0.01**	0.55 ± 0.03	0.57 ± 0.02
anterior segment	0.59 ± 0.05	0.62 ± 0.04*	0.59 ± 0.04	0.60 ± 0.05
middle segment	0.52 ± 0.04	0.53 ± 0.04	0.52 ± 0.04	0.52 ± 0.06
posterior segment	0.67 ± 0.04	0.71 ± 0.04*	0.67 ± 0.04	0.69 ± 0.05*

** significant p < 0.05

* nominal significance level p < 0.05, but not significant after Bonferroni correction

Analysis of covariance was then carried out to determine the effect of lateralization on FA values, with gender, age and handedness as covariates. The FA values in the identified segments are summarized in Table 3. A significant main effect of language lateralization on the mean FA value of the corpus callosum ($F_{(1,53)} = 6.65$, $p = 0.013$) was observed with typically left-lateralized participants showing lower mean FA values (M = 0.55, SE = 0.01) than atypically lateralized participants (M = 0.58, SE = 0.01).

With the corpus callosum considered in segments, the effects of lateralization were nominal significant for the anterior and posterior segments, but did not reach significance with Bonferroni correction for multiple comparisons, and there were no significant effects of handedness, gender, or their interactions.

The scatterplot of FA values for the corpus callosum as a whole against LI values is shown in Figure 6. Although the linear correlation was significant (r = -.287, p = 0.026), the plot is characterized by high variability in laterality indices for FA values above 0.545, with both positive and negative indices. In contrast, only participants with typical left-hemispheric dominance show FA values below 0.545. This raises the possibility that left-hemisphere dominance is achieved in part by “pruning” of callosal fibres.

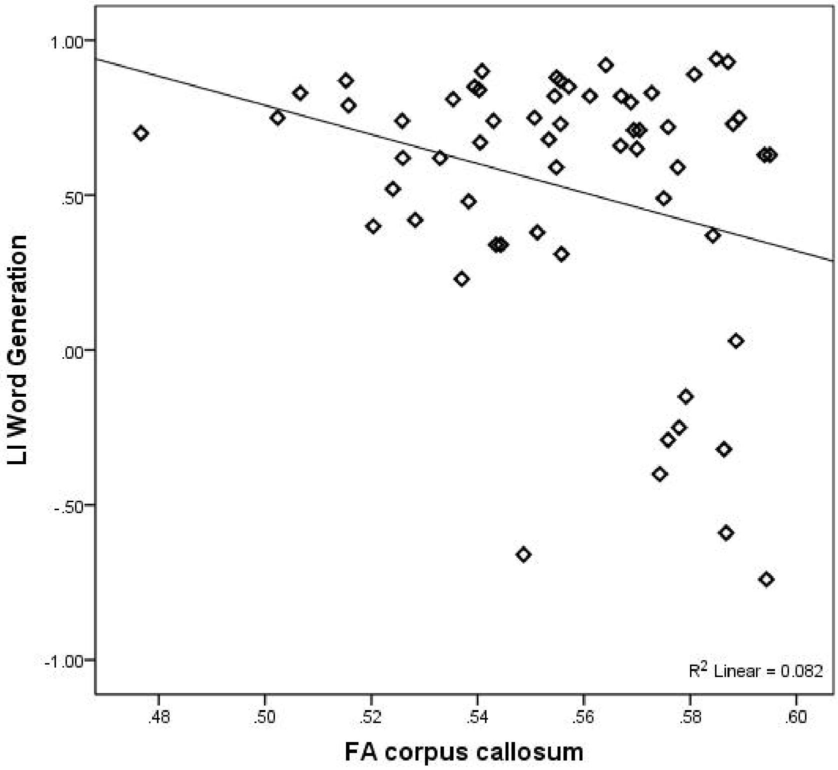

Figure 6: *Scatterplot of the mean FA values of the whole corpus callosum relative to the laterality indices for the Word Generation Task.*

Effect of spatial lateralization on FA values

12 of the 60 participants were classified as having left-hemispheric dominance for the Landmark Task and 3 participants showed a symmetrical activation pattern (Table 2). As for the Word Generation Task, one atypical lateralized group was created characterized by an LI > -0.1. No main effect of typical vs. atypical lateralization on the FA values was observed with the posterior segment failing to reach significance after Bonferroni correction. A positive correlation between mean FA values on the corpus callosum and the laterality indices failed to reach significance ($r = 0.238$, $p = 0.069$).

Combined effect of language and spatial lateralization

Depending on the lateralization pattern for both tasks, participants were reclassified as typically lateralized (Word Generation left, Landmark right), right dominant for both tasks (Word Generation right, Landmark right), left dominant for both tasks (Word Generation left, Landmark left) or mirror-reversed (Word Generation right, Landmark left) (see Table 4).

Table 4: *Number of participants and the mean and standard deviation for the laterality indices for the Word Generation Task and the Landmark Task as function of the four lateralization patterns.*

	N	**LI Word Generation** **Mean and SD**	**LI Landmark** **Mean and SD**
typical	40 (67.8%)	0.70 ± 0.03	-0.59 ± 0.04
both right	4 (6.8%)	-0.24 ± 0.09	-0.64 ± 0.09
both left	10 (16.9%)	0.60 ± 0.08	0.35 ± 0.09
mirror reversal	5 (8.5%)	-0.49 ± 0.11	0.34 ± 0.12

An analysis of covariance of FA values, with lateralization pattern as between-subject factor, and age, handedness inventory scores and gender as covariates, revealed a significant between group effect for the corpus callosum as a whole ($F_{(3,52)} = 3.28$, $p = 0.028$) and for the posterior segment ($F_{(3,52)} = 3.72$, $p = 0.017$) (see Figure 7).

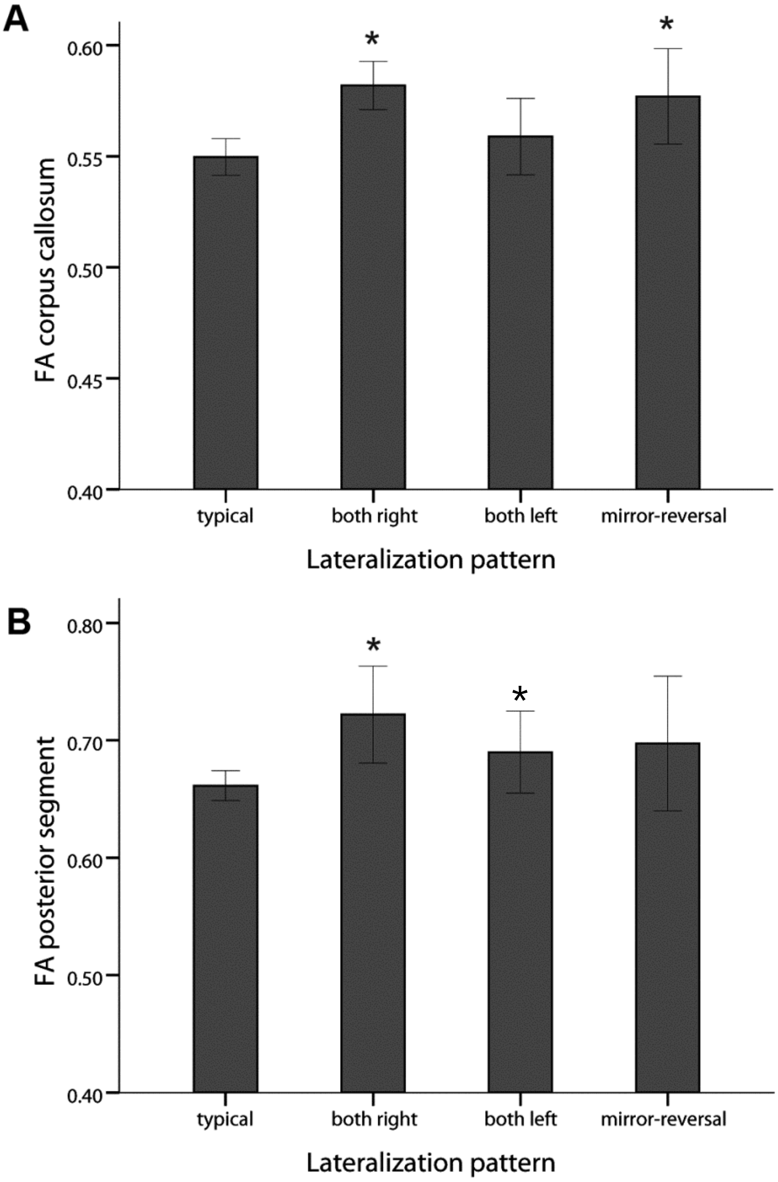

Figure 7:*Variations in the mean FA values throughout the corpus callosum and in the posterior segment according to the lateralization patterns.*

Fisher's least significant difference (LSD) post-hoc test revealed that participants who were right-hemispheric dominant for both tasks showed significantly higher mean FA values over the whole corpus callosum (p = 0.016) and in the posterior segment (p = 0.013) than participants with the typical lateralization pattern. Participants with a mirror-reversed lateralization pattern showed higher mean FA values than typical ones (p = 0.040) over the whole corpus callosum, but the effect was not significant for the posterior segment. Participants with left-hemispheric dominance for both tasks showed higher FA values in the posterior segment than participants with typical lateralization (p = 0.042). No other comparisons were significant.

An additional ANCOVA was performed on the behavioural data for the two tasks (number of words generated in the Word Generation Task; accuracy and reaction time in the Landmark Task). No significant effects were observed.

Discussion

Based on the Word Generation Task, 24% of the left-handers were considered to have atypical language lateralization, which fits well with earlier reports of between 22% (Szaflarski et al., 2002) and 24% (Pujol et al., 1999) of left-handers found to be bilateral or right-hemispheric dominant for language. The incidence of 8% of atypical lateralization for right-handers is slightly higher than the one found in older studies with the Wada test, where estimates ranged around 4% (Rasmussen & Milner, 1977). However, more recent studies with functional transcranial Doppler sonography (fTCD) and the intracarotid sodium amobarbital procedure, respectively, have reported incidences of atypical lateralization ranging from 7% (Knecht, Deppe, et al., 2000) to 9% (Isaacs et al., 2006) in right-handers. Based on the Landmark Task, 73% of the participants showed a right-hemispheric dominance for spatial processing with no evident differences in the incidence of atypical lateralization between the handedness groups.

Considering both tasks together, all possible lateralization patterns were observed, with most participants showing the typical pattern, some showing crowding of both functions to the same hemisphere, and others showing a mirror reversal of the typical lateralization pattern. Based on the observations in patients with early left-hemispheric brain lesions with normal language skills but deficits in visuospatial abilities, it has been suggested that crowding of language and spatial processing in a single hemisphere limits computational capacity in that hemisphere (Lidzba et al., 2006; Strauss, Satz, & Wada, 1990). However, research in healthy participants has revealed that the same hemisphere can be dominant for both language and spatial attention without compromising intellectual, linguistic or spatial skills (Floel et al., 2001) and this is probably due to additional recruitment of the other hemisphere (Jansen, Floel, Menke, Kanowski, & Knecht, 2005). This may explain the enhanced callosal function in those with atypical lateralization in my study, especially those in which both language and spatial functions are crowded into the right hemisphere. Although linguistic and spatial abilities were not specifically tested, the majority of the participants had completed tertiary education. That is, there was no indication of negative impacts of crowding.

Atypical language lateralization was characterized by enhanced anisotropic diffusion through the corpus callosum as a whole. Atypical spatial dominance influenced callosal morphology to a much lesser degree, resulting in only slightly enhanced FA values in the posterior segment of the corpus callosum connecting parietal, temporal and occipital regions. My results suggest that atypical representation of language, at least, is associated with enhanced interhemispheric connectivity. Also, given that highest FA values were observed when both functions were lateralized to the right, enhanced connectivity may be especially prominent if crowding occurs in the right hemisphere. Conversely, the lower FA values associated with typical cerebral asymmetry, with left-cerebral dominance for language and right-cerebral dominance for spatial processing, are consistent with Gazzaniga’s (2000) proposal that these asymmetries depend on reduced interhemispheric connectivity.

My data are somewhat in conflict with those of Westerhausen et al. (2006), who found a trend toward higher FA values for those who were strongly left-lateralized for language. However, in an earlier study they found higher FA values in left-handers than in right handers (Westerhausen et al., 2004), and another study showed greater mean callosal area in epileptic patients with right-hemispheric speech lateralization as measured by the Wada test (O'Kusky et al., 1988).

The results plotted in Figure 6 suggest a more precise demarcation at an FA value of 0.545. Those with FA scores above 0.545 show roughly equal proportions of left- and right-cerebral dominance for language, while those with FA scores below 0.545 are exclusively left-cerebral dominant for language. This suggests that cerebral dominance for language might be achieved by callosal pruning, as proposed by Annett (1991). Indeed, the putative lateralizing gene, as proposed by Annett (2002) or McManus and Bryden (1992) might act at the level of the corpus callosum, with one allele pruning callosal function to produce left-cerebral dominance for language and the other leaving callosal function intact, leaving cerebral asymmetry to chance.

Interhemispheric conduction delay has been viewed as a possible reason for the development of functional asymmetries (Aboitiz et al., 2003; Ringo et al., 1994). On this view, the efficacy of the interhemispheric communication is restricted by the conduction time of the commissural fibres so that, for larger brains, efficient interhemispheric cooperation cannot be established. As a result, short-distance asymmetric networks have evolved. According to the axon loss hypothesis, naturally occurring elimination of callosal axons during development leads to right-handedness and left-hemispheric dominance for language (LaMantia & Rakic, 1990a; Witelson & Nowakowski, 1991). Weaker axon loss during this period enhances the likelihood of left-handedness and establishes more bilateral functional networks.

The results fit well with the idea that in strongly lateralized participants interhemispheric communication is reduced given that less information has to be transferred through the corpus callosum (Gazzaniga, 2000), furthermore supporting the predictions of the excitatory model. However, it seems likely that interhemispheric communication is more complex, involving a dynamic and probably simultaneous interplay between inhibitory and excitatory influences that might vary according to the characteristics of the task at hand (Clarke & Zaidel, 1994). In complex, computational demanding tasks, a collaboration of the hemispheres might enhance the capacity for information processing, whereas less demanding tasks might be processed more efficiently by one hemisphere without inference from the other (Banich, 1995). This dynamic interplay between the hemispheres may be largely determined by hemispheric dominance patterns. In some instances, the benefit of independent processing could outweigh the potential decrease in efficiency caused by the interaction between the hemispheres. In other instances, however, this cost to benefit ratio could be reversed. Depending on the underlying hemispheric dominance patterns, different strategies might be applied to solve a behavioural task which could be reflected in variations in the integrity of the white matter in the corpus callosum (Doron & Gazzaniga, 2008).

A possible limitation of this study is that the resolution of the anatomical connections inferred from DTI remains coarse relative to that of chemical tracing techniques applied in non-human primates. At present this is largely unavoidable since chemical tracing is too invasive to use on human participants (Nowicka & Tacikowski, 2011). Further, the precise microstructural correlates of FA are not fully understood since FA values are influenced by a variety of parameters, as mentioned earlier (Chepuri et al., 2002). Even so, by combining topography results with regional microstructural differences, DTI provides a useful method to study functional-structural relationships associated with cerebral lateralization and interhemispheric integration (Doron & Gazzaniga, 2008). Moreover, a recent reaction-time study provides some confirmation that interhemispheric transfer time (IHTT) may indeed be associated with FA values. IHTT was measured using the paradigm devised by Poffenberger (1912) in which the reaction time under uncrossed conditions, where visual input and response hand are on the same side, is subtracted from that under crossed conditions, in which visual input and response hand are on the opposite sides. This crossed-uncrossed difference (CUD) is negatively correlated with callosal FA values (Schulte et al., 2005). That is, high FA values in the corpus callosum may indicate a faster interhemispheric communication that could form the basis for unusual hemispheric dominance patterns.

Chapter 3:
Experiment 2: The corpus callosum in monozygotic twins concordant and discordant for handedness and language dominance[3]

Abstract

I used diffusion tensor imaging (DTI) to assess callosal morphology in 35 pairs of monozygotic twins, of which 17 pairs were concordant for handedness and 18 pairs were discordant for handedness. Functional hemispheric language dominance was established for each twin member using fMRI, resulting in 26 twin pairs concordant and 9 twin pairs discordant for language dominance. On the basis of genetic models of handedness and language dominance, which assume one “right-shift” (RS) gene with two alleles, an RS+ allele biasing toward right-handedness and left-cerebral language dominance, and an RS- allele leaving both asymmetries to chance, all twins were classified according to their putative genotypes, and the possible effects of the gene on callosal morphology was assessed. Whereas callosal size was under a high genetic control that was independent of handedness and language dominance, twin pairs with a high probability of carrying the putative RS+ allele showed a connectivity pattern characterized by a genetically controlled, low anisotropic diffusion over the whole corpus callosum. In contrast, the high connectivity pattern exhibited by twin pairs more likely to lack the RS+ allele was under significantly less genetic influence. The data suggest that handedness and hemispheric dominance for speech production might be at least partly dependent on genetically controlled processes of axonal pruning in the corpus callosum.

---

[3] This Experiment is published in Haberling, I.S., Badzakova-Trajkov, G., & Corballis, M.C. (2012). The corpus callosum in monozygotic twins concordant and discordant for handedness and language dominance. *Journal of Cognitive Neuroscience,* Advanced online publication.

Introduction

Individual variations in brain structures result from a complex interaction between genetic factors and environmental influences. Brain volume, for example, is under substantial genetic control with heritability estimates at around 90% (Baare et al., 2001; Bartley, Jones, & Weinberger, 1997). In contrast, the overall gyral patterning of the cortex is astonishingly dissimilar in identical twins (Bartley et al., 1997), suggesting underlying environmental influences. Heritability of the cross-sectional area of the corpus callosum, the main fibre tract connecting the two cerebral hemispheres, is high, with estimates ranging between 79% and 94% in adults (Hulshoff Pol et al., 2006; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000; Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003), and remaining stable over a life time (Pfefferbaum, Sullivan, & Carmelli, 2004). Diffusion tensor imaging (DTI) of the corpus callosum has yielded a heritability estimate of fractional anisotropy (FA), which is a measure of the coherence of the white matter tracts, at around 60% (Chiang et al., 2009).

Since the corpus callosum plays the major role in interhemispheric communication, its size and morphological structure may also influence functional hemispheric asymmetries. Some studies have shown, for example, that the corpus callosum is larger in left-handers than in right-handers (Habib et al., 1991; Witelson, 1985, 1989), which may explain why left-handers are more likely to be right-hemisphere dominant for language, or to have a greater degree of right-hemispheric involvement. Other studies, though, have found no differences in callosal morphology between handedness groups (Jancke, Staiger, et al., 1997; Preuss et al., 2002). Handedness is at best an indirect measure of cerebral asymmetry for language, but even when more direct measures are used, such as fMRI or dichotic listening, the results have been conflicting, with some studies suggesting higher connectivity in more lateralized brains (Dos Santos Sequeira et al., 2006; Josse et al., 2008) and others the reverse (Gootjes et al., 2006; Hines et al., 1992; Yazgan et al., 1995).

In this chapter, I examine hemispheric asymmetry and callosal morphology in monozygotic twins. Some 20-25% of monozygotic twins are of opposite handedness (Annett, 2002; McManus, 1980) with some even showing reversed cerebral asymmetries (Badzakova-Trajkov, Haberling, & Corballis, 2010; Sommer, Ramsey, Mandl, & Kahn, 2002). Although this may seem counter to the idea that handedness is genetically inherited, genetic models can account for discordant handedness in twins by postulating a chance influence. The simplest such models propose a single gene with two alleles, one disposing to right-handedness, and the other leaving the direction of handedness to chance (Annett, 2002; McManus, 2002). There is abundant evidence that right-handedness and left-cerebral dominance for language are correlated, suggesting that the same laterality gene is involved in both (Annett, 2002; McManus, 2002). In support of these two-allele models, Geschwind, Miller, DeCarli, and Carmelli (2002) compared monozygotic and dizygotic twins, and found the genetic influence on structural asymmetries of frontal, temporal and parietal brain volumes to be much higher in right-handed twin pairs than in pairs in which at least one twin was left-handed. Nevertheless, asymmetry of the planum temporale, as a structural marker for language lateralization, has been shown to be only weakly influenced by genes in twin studies, with some evidence for a diminished asymmetry in the left-handed twin member only (Eckert et al., 2002; Steinmetz et al., 1995). However, a recent study investigating the planum temporale in 274 subjects has shown a reduced asymmetry in subjects with familial sinistrality whereas no immediate handedness effect was evident (Tzourio-Mazoyer et al., 2010).

Here, I choose Annett’s (2002) version of the genetic model to generate estimates of the incidence of the laterality allele in monozygotic twins of differing combinations of handedness and cerebral dominance, since she has applied her model specifically to twins (Annett, 2003) and it provides a reasonable fit to twin data on handedness and cerebral asymmetry (Badzakova-Trajkov, Haberling, & Corballis, 2010). In her terminology, the laterality gene is termed the “right shift” (RS) gene, with one allele (RS+) which biases toward right-handedness and left-cerebral dominance, and the other (RS-) which leaves both asymmetries to chance. This gives rise to three genotypes, labelled RS++, RS+–, and RS--. The RS+ allele operates in dominant-recessive fashion on cerebral dominance, so that RS++ and RS+– genotypes will show typical left-hemisphere dominance, while RS-- genotypes have the direction of cerebral dominance assigned at random. For handedness, though, the RS+ operates additively. In adapting the model for twins, Annett (2003) assumes a 14% incidence of left-handedness (slightly higher than in the singly born), with a shift of 1.72 standard deviations to the right in RS++ individuals and 0.73 standard deviations to the right in RS+- individuals. Although the genetic influence in RS- - individuals is assumed to be neutral, she assumes that the ratio of right-to-left-handedness in RS-- individuals is 65:35, due to environmental pressures toward right-handedness.

Table 5: *Calculation of the probability of the RS+ allele in the RS+ and the RS- group, respectively.*

***A:** Estimates of handedness combinations per 1000 pairs of twins according to Annett's Table 3 (2003).*

Genotype	Handedness combinations		
	Right-right	Right-left	Left-left
RS++	305	20	0
RS+-	369	113	8
RS--	78	84	23

***B:** Genotypic probabilities for the RS+ and the RS- group*

Group	RS++	RS+-	RS--	Total
RS+	.305	.369	.020	.694
RS-	.020	.121	.165	.306

***C:** Probability of the RS+ allele in the RS+ and the RS- group*

Phenotype	RS++	RS+-	RS--	p (RS+)
RS+ group	.439	.532	.029	.971
RS- group	.065	.395	.539	.460

Part A of Table 5 reproduces Annett's predictions of the genotypes for each handedness combination per 1000 pairs of twins. Following Annett, I assume that all RS++ and RS+– pairs, and 25% of RS-- pairs will have left-hemispheric representation of language. Thus I can compute the probabilities of the different genotypes for twin pairs that are right-handed and left-cerebrally dominant for language (RS+ group) and for twin pairs where at least one member is left-handed or right-cerebrally dominant (RS- group), as shown in part B of Table 5. From this table I can convert the percentage to the probability of the RS+ allele in the RS+ and RS- group (see part C of Table 5). The expected probability of carrying at least one copy of the RS+ allele in twins who are both right-handed and left-cerebrally dominant for language is 0.971, whereas in twins who at least one member is left-handed or right-cerebrally dominant for language it is 0.460. Comparison of these groups should therefore provide an assessment of the effects of the RS+ gene on callosal morphology.

In a further analysis I removed twin pairs with left-handers in the immediate family from the RS+ group, which should further increase the probability of carrying the RS+ allele (McManus, 1995). Although familial sinistrality has been criticised as a reliable measure in that it depends on family size and the accuracy of the handedness reports, I show it to enhance the difference in callosal morphology between the putative RS+ and RS- groups. In a recent study, FS+ subjects showed an increase in grey matter, especially in the right hemisphere, which led to an absence of hemispheric grey matter asymmetry typically found in FS- subjects (Tzourio-Mazoyer et al., 2010). This might be explained by a reduced synaptic pruning in subjects with familial left-handedness. Annett (1991) further suggested that cerebral asymmetry might arise through pruning of neurons in the corpus callosum. I therefore hypothesize that the corpus callosum might be smaller and / or the FA values lower in the group with the highest likelihood of carrying the RS+ allele.

Material and Methods

Subjects

A total of 35 monozygotic (MZ) twin pairs (14 male/male; 21 female/female; mean age = 24.7; SD = 8.8; range = 15-49 years) took part. A short zygosity questionnaire was filled out by each twin member separately, asking about their physical resemblance, the difficulty for family and friends to tell them apart, and their hair and eye colour in childhood (Christiansen et al., 2003) (Appendix C). In 7 twin pairs, where zygosity could not be established beyond doubt based on the answers and the physical appearance, additional DNA testing was carried out. DNA was extracted from mouth swab samples and the individuals were genetically typed using the multiplex PCR kit AmpFISTR Identifier (Applied Biosystems). The kit compares the STR (short tandem repeat) profiles on 15 highly polymorphic loci. Twins were considered as monozygotic when no differences in the 15 loci were detected (Yang, Tzeng, Tseng, & Huang, 2006).

Based on writing hand, 16 pairs were both right-handed (RR pairs; 7male/male; 9 female/female; mean age = 22.6, SD = 7.2), 1 pair were both left-handed (LL pair; 1 female/female; age = 21), and 18 pairs were of opposite handedness (RL pairs; 7male/male;

11 female/female; mean age = 26.8, SD = 10.0). Twin pairs with discordant handedness were deliberately over-represented in the study. Each twin also filled out a handedness inventory, in which they indicated the preferred hand in 12 activities: writing, throwing a ball, holding a racquet, lighting a match, cutting with scissors, threading a needle, sweeping with a broom (top hand), shoveling, dealing cards, hammering, holding a toothbrush, unscrewing a lid (Annett, 2002)(Appendix A). They gave two ticks for the preferred hand or one tick for each hand if there was no preference. A laterality index (LI) was then calculated from the formula $100x(\frac{R-L}{R+L})$, where R and L represent the number of ticks for the right and left hand, respectively. Although the primary criteria for handedness was the writing hand, as has been suggested by McManus (2002), all left-handed twin members had LIs < 40 and all right-handed twin members LIs > 50, resulting in a classification scheme similar to that used in previous research (e.g.,Whitehouse & Bishop, 2009). Ethic approval was obtained by the Human Ethics Participants Committee at the University of Auckland, New Zealand, and all subjects gave written consent prior to the study.

Information concerning familial left-handedness was collected by asking the participants to state the handedness of their immediate family members (Appendix B). Familial sinistrality was defined as the presence (FS+) or absence (FS-) of at least one left-hander among the parents or siblings of the subject.

Word Generation task

To assess language dominance, all participants undertook a Word Generation task adapted from the Controlled Oral Word Association test (Lezak, 1995) during fMRI. Participants were asked to silently generate as many words as possible starting with a designated letter (F, A, S, B, and M) which were randomly and centrally projected onto a screen (in Courier New black font, size 50). They were instructed not to use proper names or the same words with different endings. The letters were presented for 30 s, followed by a 30 s baseline period that consisted of a black cross, resulting in an acquisition time of 5 min. Prior to the experiment, all participants completed a comparable short version of the task, naming the words overtly, in order to obtain a behavioural performance measure.

Image acquisition and processing

MRI scanning was performed on a 1.5-T Siemens Avanto scanner (Erlangen, Germany). A T1-weighted structural image was acquired using a 3-D MP-RAGE sequence with 176 axial slices parallel to the AC-PC line, ensuring whole brain coverage. The following parameters were used: TR = 11 ms; TE = 4.94 ms; flip angle: 158; FOV: 256 x 256 mm^2. Slice thickness was 1 mm and the interslice gap 0, resulting in isotropic voxel resolution of 1 x 1 x 1 mm. For the diffusion weighted images a single-shot spin echo sequence along 30 diffusion gradient directions with a b0 of 1000 s/mm^2 was used with the following parameters: TR = 6601 ms, TE = 101 ms, FOV = 230 mm; in-plane resolution: 1.8 x 1.8 mm; slice thickness 3 mm. In addition, one image without diffusion weighting was acquired. The sequence was repeated twice resulting in an acquisition time of approximately 7 min. The EPI acquisition had the following parameters: TR = 2500 ms; TE = 50 ms; flip angle = 90; FOV =192 x 192; matrix size: 64 x 64; 29 slices parallel to AC-PC line; slice thickness: 3 mm; interslice gap: 25% = .8 mm.

Diffusion image preprocessing and analyses

The tractography-based segmentation of the corpus callosum was carried out using the FDT toolbox implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/). Based on the probability that a voxel in a seed mask connects to a predefined target mask, the anatomical connectivity pattern of a brain region can be determined (Behrens et al., 2003). This method was applied to the callosal fibre tracts as follows.

For each participant, the corpus callosum was manually outlined on the midsagittal slice of the individual T1 images by applying the following steps. First, the structural T1-weighted images were registered to an optimized individual target brain in the Talairach coordinate system (Kochunov et al., 2002) available at the BrainMap website (http://brainmap.org/ale/index.html). A rigid body transformation with 6 degrees of freedom (3 translations, 3 rotations) was applied without scaling the brain in order to maintain individual brain sizes. Second, the images were segmented into grey and white matter using the automated segmentation tool implemented in FSL (Zhang et al., 2001). Third, the corpus callosum was manually outlined on the white matter segmentation image. To assess reliability, a second independent measurement of the callosal area for 15 randomly chosen participants was made by a different rater, resulting in an intraclass correlation of 0.96. In addition, total brain volume was calculated with SIENAX, an algorithm for automated brain extraction implemented in FSL (Smith et al., 2002).

To segment the corpus callosum into four distinct subdivisions, specific cortical target masks were created on the MNI template. The most anterior mask comprised the frontal lobe but spared the motor cortex. The motor cortex was derived from the Juelich histological atlas implemented in FSL and included M1 and premotor cortex. A further mask included the temporal and parietal lobes whereas the most posterior mask comprised the occipital lobes[4]. To ensure a good alignment of these masks, the individual T1 images were nonlinearly registered to the MNI template and the resulting registration matrices were inversed and applied to the target masks, transferring them back into each participant's native space.

The diffusion data were corrected for eddy currents and head motion and the two acquisitions were averaged to improve signal-to-noise ratio. Diffusion tensors were fitted at each voxel and FA maps were generated. Then, the probability distribution of fibre direction at each voxel was calculated using previously described methods (Behrens et al., 2003). For each participant, probabilistic tractography was run from each voxel in the corpus callosum to each target mask by drawing 5000 random samples with a steplength of 0.5 mm and a curvature threshold of 0.2. The resulting value in each callosal voxel represents the number of samples reaching the relevant target mask and therefore the probability of the connections between the two. The analyses were run separately for the right and left hemisphere. Using a similar threshold as previous research, each output mask was thresholded at 10% of the maximum connectivity value to the relevant target mask (Zarei et al., 2006). Then, tracts going to the left and right hemisphere were compared and only overlapping areas were considered for further analyses (Westerhausen et al., 2009). The resulting masks were binarized and multiplied with the FA maps in order to extract the mean FA values. A distribution of the FA values in the twin pairs is depicted in Figure 8.

---

[4] In contrast to Edxperiment 1, here I segmented the corpus callosum into four parts given that a more specific hypothesis of the relationship between the language network and interhemispheric connectivity was tested.

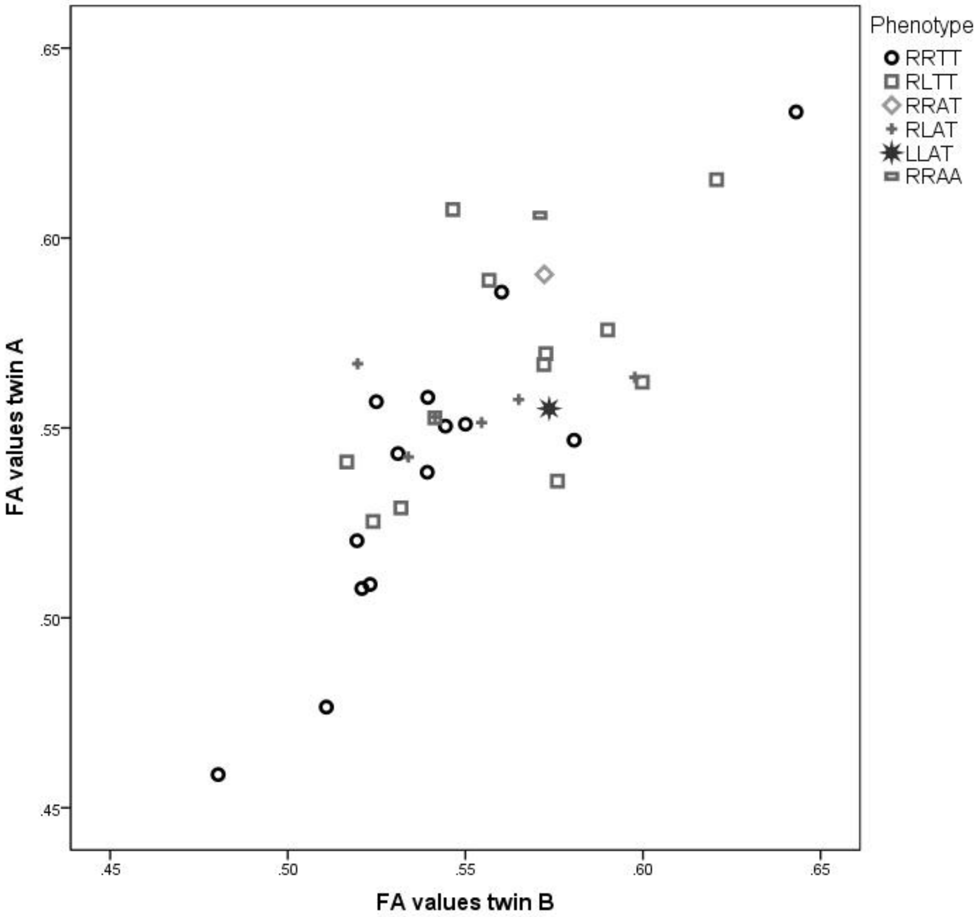

Figure 8: *Correlation of the FA values between one twin member and the other, with annotations of handedness and cerebral asymmetry. Twin members were allocated to x and y axes randomly. First two letters correspond to handedness (RR = both right-handed, RL = one twin right-handed and the other left-handed, LL = both left-handed), two last letters to language dominance (TT = both typical left-hemispheric dominant, AT = one twin left-hemispheric dominant and one twin atypical right-hemispheric dominant, AA = both twins atypical right-hemispheric dominant).*

Functional imaging processing and analyses

The functional images were analyzed using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk). First, the standard pre-processing steps (realignment, coregistration, normalization and smoothing) were applied. The functional scans were realigned to the first image of the session and the mean of the functional volumes was calculated. The T1-weighted structural image was then coregistered with the previously obtained mean of the functional volumes. Then, all images were normalized into standardized stereotactic space (MNI, Montreal Neurological Institute) and spatially smoothed with an anisotropic Gaussian filter of 9 x 9 x 9 mm of full-width at half maximum (FWHM). For each participant, the functional volumes were subjected to a fixed-effects analysis using the general linear model that was applied at each voxel across the whole brain. The model was set up as a box-car function with the two alternate conditions letter vs. baseline. The resulting function was convolved with a canonical haemodynamic response function and movement regressors were also included in the model. For the group analysis, a second-level random effects analysis was performed by applying a one sample t-test to the contrast images of the first-level analyses. A family-wise error (FWE) correction was applied at $p < 0.05$ with a contiguity threshold of 10 voxels.

To establish language dominance, laterality indices were calculated by comparing the activity between the left and right Broca's region[5] using the formula $\left(\frac{L-R}{L+R}\right)$, where L and R represent activations in the left and right hemisphere, respectively. The laterality toolbox available on the SPM website was used to calculate the laterality indices (Wilke & Lidzba, 2007). Laterality indices based on one single fixed statistical threshold do not yield robust or reproducible results (Jansen et al., 2006). Therefore, the toolbox applies a bootstrap algorithm to calculate about 10,000 indices based on the asymmetry of the voxel values at different thresholds yielding a robust mean LI ranging between -1 for extreme left to 1 for extreme right lateralization. For each participant, the weighted mean LI for Broca's area was computed. Broca's area was defined using the WFU Pick Atlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) and included Brodmann areas 44 and 45. The masks were smoothed with a 6 mm Gaussian filter to control for inter-individual variability. In addition, the toolbox integrates a mask weighting factor that represents the relation of the volumes of the masks on the left and on the right to rule out influences of different mask sizes. A positive index within the ROI corresponded to a left-hemispheric dominance ($LI > 0.1$) and a negative index to a right-hemispheric dominance ($LI < -0.1$) (Fernandez et al., 2003). Due to the small numbers in the bilateral group (LI's ranging from -0.1 to +0.1), those two subjects were assigned to the right-hemispheric group, since their hemispheric dominance pattern is also atypical in nature.

---

[5] In contrast to Experiment 1, here the ROI was restricted to Broca's area given that a more specific hypothesis of the relationship between the language network and interhemispheric connectivity was tested, and this method concords with the study done by Badzakova-Trajkov et al. (2010) on the cerebral asymmetries in monozygotic twins. Correlation between the two measurements was high: $r = 0.763$, $p < 0.001$.

The word generation paradigm induced significant leftward activations in the inferior frontal gyrus, including pars opercularis and pars triangularis, insula, precentral gyrus, SMA, and inferior temporal gyrus (see Figure 9, Table 6). Additional right-hemispheric clusters were observed in the inferior and middle occipital gyri. Overall, a one-sample t-test revealed that the laterality indices were leftward asymmetric in Broca's area (M = 0.61, SE = 0.051, t(69) = 12.1, $p < 0.001$). Classification of the twin pairs according to the laterality indices of both twin members revealed that overall, 26 pairs were concordant left-hemispheric dominant for language processing, 8 pairs (6 pairs of opposite handedness, 1 right-handed twin pair, 1 left-handed twin pair) showed opposite hemispheric dominance, and 1 right-handed twin pair was concordant for atypical language dominance. As discussed elsewhere, these results do not differ significantly from expectations derived from Annett's right-shift theory of the inheritance of handedness and cerebral asymmetry (Badzakova-Trajkov, Haberling, & Corballis, 2010).

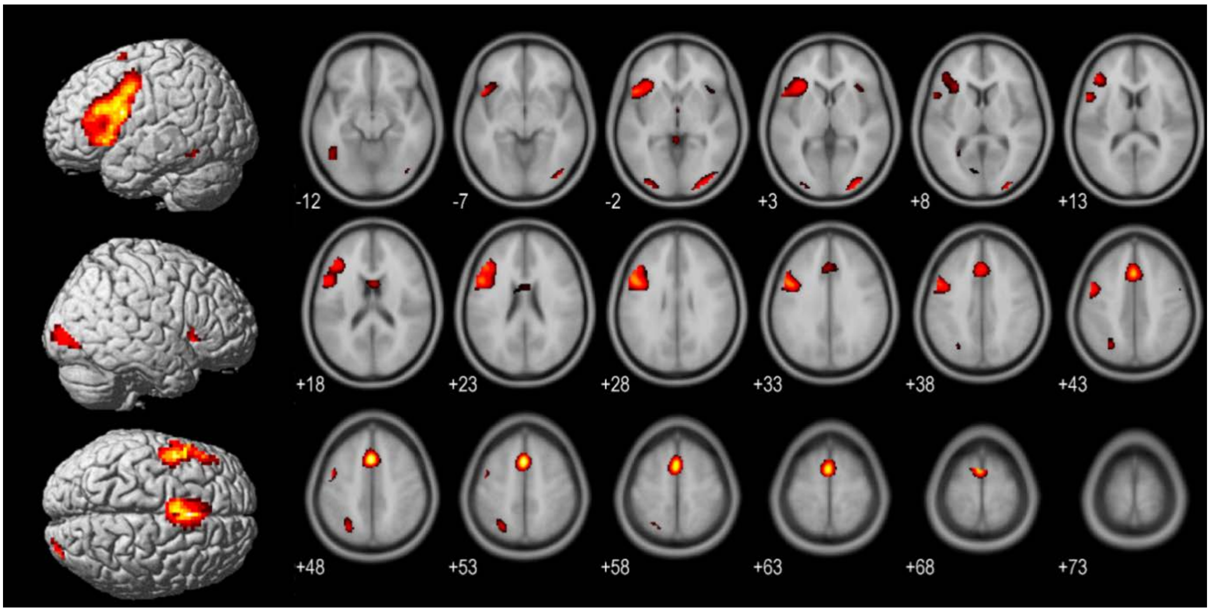

Figure 9: *Activation map for the Word Generation Task displayed laterally on the cortical surface of a rendered brain. In addition, activations overlaid on slices of a template of 152 brains are shown.*

Table 6: *Significantly activated brain regions for the Word Generation Task. Brodmann area (BA), MNI coordinates for the peak activation voxel, and T-value are also shown.*

Anatomical location	**BA**	**MNI coordinates**			**T-value**
		x	y	z	
Word Generation					
Left hemisphere					
Insula	13	-30	24	3	11.86
Inferior frontal gyrus (p. opercularis)	44	-45	9	27	11.61
Inferior frontal gyrus (p. triangularis)	45	-45	24	24	10.65
SMA	6	-3	12	51	12.84
Caudate Nucleus		-15	-6	24	8.68
Superior frontal gyrus	10	-27	60	9	6.66
Inferior temporal gyrus	37	-45	-48	-12	6.42
Putamen		-21	6	12	6.31
Right hemisphere					
Insula	13	33	24	3	8.44
Caudate nucleus		18	0	24	8.49
Middle occipital gryus	18	33	-93	3	8.23
Hippocampus		33	-42	6	7.57

The Anatomy toolbox was used to determine the anatomical location; Brodmann areas were derived from the Talairach demon.

Statistical analysis

To assess the degree to which twin members resemble each other, intraclass correlation coefficients were computed. Intraclass correlations compare the variations within a pair with the variation between pairs and allow inferences about possible genetic influences. To compare intraclass correlations between different groupings of twins, a Fisher r-to-z transformation was applied and the significance of the difference between the two correlation coefficients was assessed. In order to detect potential differences in the mean values between different groupings of twins, an ANCOVA was performed where twin pair was treated as a random factor, group as between-twin factor, and gender and age as covariates. Subjects (twins) were treated as nested within each twin pair. For the analysis of the individual segments, a Bonferroni correction for multiple comparisons was applied to the alpha level by dividing it by the number of applied tests (i.e. divided by four given that four callosal segments were investigated), resulting in a new alpha level of 0.013. Due to previous reports on gender differences in language lateralization (Shaywitz et al., 1995) and callosal morphology (Davatzikos & Resnick, 1998; Habib et al., 1991), an ANCOVA on the laterality indices with gender as between-twin factor, age as covariate and twin pair as a random factor was conducted. Lateralization in male twin pairs (M = 0.65, SE = 0.082) did not differ significantly from that in female twin pairs (M = 0.59, SE = 0.067, $F_{(1,32)} = 0.395$, $p = 0.534$). Further analyses revealed no gender differences on callosal volumes or FA values. Although a trend for larger total callosal volumes in male (M = 705 mm^3, SE = 21.8) than in female twin pairs (M = 652 mm^3, SE = 17.8, $F_{(1,32)} = 3.56$, $p = 0.068$) was observed, the effect disappeared if callosal size was taken as a proportion of the total brain volume ($F_{(1,32)} = 0.99$, $p = 0.327$). That is, the observed sex differences in callosal size might be attributed to differences in overall brain size, as has been suggested previously (Jancke, Staiger, et al., 1997).

Results

Comparing groups defined by handedness and cerebral asymmetry

As explained above, I combined handedness measures and LIs for Broca’s area to group the twin pairs according to their likelihood of carrying the RS+ allele. Of the 35 twin pairs examined, 14 were both right-handed and left-cerebrally dominant and therefore constituted the RS+ group (handedness inventory scores: M = 88.8, SD = 15.3, laterality indices language M = 0.75, SD = 0.16), while the remaining 21 included at least one left-handed or right-cerebrally dominant member and were placed in the RS- group (handedness inventory scores: M = 23.0, SD = 80.5; laterality indices language M = 0.52, SD = 0.51).

Intraclass correlations for the RS+ and the RS- group are shown in Table 7. For measures of callosal volume, they are high and reveal no differences between the two groups. For callosal FA, though, the intraclass correlations were significantly higher for the RS+ group ($r = 0.882$, $p < 0.001$) than the RS- group ($r = 0.519$, $p = 0.005$, $z = 2.12$, $p = 0.034$) over the whole corpus callosum.

The mean volumes and FAs are shown in Table 8. The RS+ and RS- groups did not differ significantly in volumes, but the FA values were significantly lower for the corpus callosum as a whole for the RS+ group (M = 0.538, SE = 0.008) than for the RS- group (M = 0.563, SE = 0.007; $F_{(1,30)} = 4.77$, p = 0.037). This effect was also nominally significant for the anterior corpus callosum, but did not reach significance with Bonferroni adjustment.

The groups did not differ in the number of words generated before the scanning session ($F_{(1,33)} = 1.492$, p = 0.231).

Table 7*: Intraclass correlations for the two genetic groups (RS+/RS-) are listed. The z-transformation and associated p-values are also shown.*

	RS+ group (N=14)	**RS- group** (N=21)	**z**	**p**
Area				
total	.931, p < .001	.932, p < .001	-.02	.984
area/white matter ratio	.972, p < .001	.936, p < .001	1.1	.271
anterior	.535, p = .017	.466, p = .013	.24	.810
middle	.569, p = .011	.506, p = .007	.23	.811
parieto-temporal	.808, p < .001	.802, p < .001	.04	.968
posterior	.683, p = .002	.542, p = .004	.60	.549
FA				
total	.882, p < .001	.519, p = .006	2.12	.034**
anterior	.797, p < .001	.325, p = .067	1.97	.049*
middle	.456, p = .039	.269, p=.109	.57	.569
parieto-temporal	.760, p < .001	.503, p = .008	1.16	.246
posterior	.552, p = .014	.511, p = .007	.15	.881

** significant at p<.05.

* nominal significance level p<.05, but not significant after Bonferroni correction

Table 8*: Mean and standard deviation of the callosal area and the FA values are shown. They are listed for the total sample, separately for the RS+ and RS- group, and separately for the RS+/FS- group and the RS-/FS+ group, respectively.*

	All twins (N=35)	RS+ group (N=14)	RS- group (N=21)	RS+/FS- (N=9)	RS-/FS+ (N=26)
Area					
corpus callosum	673 ± 86.1	666 ± 80.2	678 ± 90.4	678 ± 91.5	671 ± 85.0
anterior	209 ± 48.1	200 ± 46.8	215 ± 48.6	210 ± 51.0	208 ± 47.5
middle	174 ± 44.9	159 ± 46.5	184 ± 41.4	159 ± 52.5	179 ± 41.2
parieto-temporal	198 ± 47.2	192 ± 57.5	202 ± 39.0	200 ± 65.2	197 ± 39.9
posterior	67 ± 20.9	65 ± 24.5	69 ± 18.2	69 ± 30.0	67 ± 18.2
FA					
corpus callosum	.55 ±.034	.54 ± .040	.56 ± .027**	.53 ± .035	.56 ± .031**
anterior	.59 ± .051	.58 ± .055	.6 1± .046*	.58 ± .056	.61 ± .047*
middle	.52 ± .048	.51 ± .050	.53 ± .046	.51 ± .047	.53 ± .047
parieto-temporal	.64 ± .042	.63 ± .048	.65 ± .035	.62 ± .040	.65 ± .039*
posterior	.72 ± .046	.72 ± .055	.72 ± .040	.70 ± .054	.72 ± .046

**Significant at $p < 0.05$.

* Nominal significance level $p < 0.05$, but not significant after Bonferroni correction

Comparing groups additionally defined by familial sinistrality

Familial sinistrality was added as an additional factor to enhance the homogeneity in the RS+ group. In a first step the twins were regrouped such that in the first group twin pairs who were both right-handed and left-cerebral dominant for language and who had no immediate family member that is left-handed were included (RS+/FS- group, N = 9). The second group contained the remaining twin pairs of the RS+ group but who had a history of familial sinistrality (RS+/FS+ group, N = 5). The third group (RS- group, N = 21) remained the same given that in this group a distinction between FS+ and FS- is not meaningful. A preliminary analysis run on the FA values over the whole corpus callosum revealed a significant group effect ($F_{(2,30)}$ = 3.32, p = 0.050). Post-hoc analysis with Bonferroni adjustment revealed that the RS+/FS- group showed lower FA values over the whole corpus callosum (M = 0.531, SE = 0.010) than the RS- group (M = 0.563, SE = 0.007, p = 0.015), whereas the RS+/FS+ group did not differ in the FA values compared to the RS- group (M = 0.551, SE = 0.015, p = 0.457). Therefore, in a second step the RS+/FS+ twin pairs were placed in the RS- group and compared to the RS+/FS- group, which contains the twins most likely to be homozygous for the RS+ allele, as shown in Table 8. Subsequent analysis revealed that the RS+/FS- group showed lower FA values over the whole corpus callosum (M = 0.531, SE = 0.010) than the new RS-/FS+ group (M = 0.561, SE = 0.006, $F_{(1,31)}$ = 6.15, p = 0.019). The same effect was evident in the prefrontal segment ($F_{(1,31)}$ = 4.20, p = 0.049) and the parieto-temporal segment ($F_{(1,31)}$ = 6.30, p = 0.018) but did not reach significance after Bonferroni adjustment.

Could frequency of interhemispheric transfer play a role?

The foregoing analyses offer support for the view that the RS+ gene plays a role in reducing callosal connectivity between the cerebral hemispheres. An alternative possibility, though, is that callosal connectivity is increased in those with opposite hemispheric asymmetry for hand control and language, perhaps because activities such as writing require interhemispheric transfer. The sheer frequency of interhemispheric transfer might therefore have increased connectivity. To test this possibility, all twins were reclassified into those having hand control and language localized in the same hemisphere and those having localized those two functions in opposite hemispheres. The first group consisted of 46 right-handers with left-cerebral language representation and 5 left-handers with right-cerebral language representation, while the second consisted of 4 right-handers with right-cerebral language dominance and 15 left-handers with left-cerebral language dominance. Then, all twins were reclassified into those with consistent and those with inconsistent asymmetries for hand control and language, as shown in Table 9.

If the frequency of the interhemispheric transfer increases connectivity I might expect that twin members who have the two functions localized in opposite hemispheres should exhibit higher FA values in the corpus callosum than their co-twins who support both functions unilaterally. Thus, a paired t-test on the FA values in the 15 discordant twin pairs was carried out, but no significant effect was evident (p = 0.450).

Table 9*: Number of twin pairs allocated to the different genotypes and their cerebral connectivity pattern. Allocation to the genetic groups is also shown.*

Phenotype	**Connections**			**Total**	**Allele**
	both intra	both inter	discordant		
RR/TT	14	-	-	14	RS+
RL/TT	-	-	12	12	RS-
LL/TT	-	-	-	-	
RR/TA	-	-	1	1	
RL/AT	-	2	-	2	
RL/TA	4	-	-	4	
LL/AT	-	-	1	1	
RR/AA	-	-	1	1	
RL/AA	-	-	-	-	
LL/AA	-	-	-	-	
Total	18	2	15	35	

First two letters correspond to handedness (RR = both right-handed; RL = one twin right-, the other left-handed, LL = both left-handed), last two letters to language dominance (TT = both typical left-hemispheric dominant; TA = first twin left-hemispheric dominant, second twin atypical right-hemispheric dominant, AT = first twin atypical right-hemispheric dominant, second twin left-hemispheric dominant; AA =both twins atypical right-hemispheric dominant).

Discussion

For callosal volume, the high intraclass correlations suggest a strong genetic component, regardless of handedness or cerebral dominance. This finding fits well with an earlier study reporting intraclass correlations of 0.87 for total callosal area in monozygotic twins (Scamvougeras et al., 2003). DTI allows the assessment not only of the macrostructure of callosal tracts, but also of certain characteristics of their microstructure. Fractional anisotropy (FA), for example, reflects the degree of the alignment or integrity of the underlying tissue structure. That is, high anisotropy might indicate a greater number and / or greater density of axons, and a stronger proportion of myelin material (Chepuri et al., 2002). Consequently, the intraclass correlations observed for the FA values were generally lower than those for the volumetric measurements, suggesting dynamic adaptations of the fibre tracts. For example, the FA values in the body of the corpus callosum have been shown to correlate with bimanual coordination skills (Johansen-Berg, Della-Maggiore, Behrens, Smith, & Paus, 2007), and in professional musicians the number of hours practiced on the piano in childhood correlates with FA values in the body of the corpus callosum (Bengtsson et al., 2005).

Using Annett's (2003) predictions for the probability of the RS+ allele in different phenotypes, the twins were grouped according to their likelihood of carrying the RS+ allele. While no effect on callosal volume was found, those allocated to the RS+ group showed lower FA values throughout the whole corpus callosum than those allocated to the RS- group. The relationship between callosal volume and number of fibres remains somewhat unclear given that increased callosal area might be associated with decreased fibre density. In macaques, a lack of correspondence between number of fibres and callosal areas has been reported (LaMantia & Rakic, 1990b), while in men callosal area was found to be correlated with the number of fibres with thin axons but not with large ones (Aboitiz, Scheibel, et al., 1992a). In contrast, indices of anisotropy are thought to be sensitive to the density and orientation of axons (Beaulieu, 2002). Moreover, a recent imaging study showed that the FA values in the corpus callosum are related to axonal density, intra-axonal volume fraction within the white matter and axonal diameter (Alexander et al., 2010).

The low FA values in those allocated to the RS+ group might therefore indicate diminished interhemispheric connectivity. Indeed, the lowest FA values were observed in the twin pairs of the RS+ group with no left-handedness in the immediate family. In right-handers without familial sinistrality the planum temporale asymmetry is most pronounced (Tzourio-Mazoyer et al., 2010). Concurrently, I found low connectivity in the parietotemporal segment in this group, which could indicate a reduced interhemispheric connectivity related to the enhanced planum temporale asymmetry. Differences in interhemispheric communication might influence individual cognitive processing styles. For example, FS+ individuals outperform FS- subjects in an episodic memory task where the participants are required to recall previously seen words but not in an implicit memory task where participants have to complete word fragments (Christman & Propper, 2001). The episodic memory task involves integration of processing between the hemispheres whereas the implicit memory task is supported unilaterally. That is, in individuals with familial sinistrality the interhemispheric communication might be enhanced, which is advantageous for some memory processes but not for all.

In terms of Annett's right-shift theory, the data suggest that the putative RS+ gene exerted some control over interhemispheric connectivity, and that in the absence of this control connectivity was subject to a random component. Annett (1991) suggested that left-hemispheric dominance for language arises from axonal pruning of the corpus callosum. That is, the development of the corpus callosum is initially characterised by an overproduction of neurons, axons, and synapses that are subsequently eliminated. In monkeys for example, 70% of the callosal axons are eliminated between birth and adulthood (LaMantia & Rakic, 1990a). The mechanism of selection and elimination of axons is poorly understood and seems to depend on a number of factors, such as sensory input, competition among axonal systems for chemotropic substances, hormones, and expression of molecules that identify appropriate targets (Innocenti & Price, 2005).

Leftward asymmetry for processing auditory stimuli is present from birth onwards, probably due to a stronger excitability of the left auditory areas but without discrimination between linguistic and non-linguistic stimuli (Dehaene-Lambertz, Hertz-Pannier, & Dubois, 2006). For example, in 4-month-old infants higher event-related potentials were recorded over the left than the right hemisphere for both tones and syllables (Dehaene-Lambertz, 2000). Concurrently, fMRI activation to forward and backward speech stimuli was greater in the left than the right temporal lobe in 3-months old infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). The development of language functions in childhood and early adolescence is accompanied by the thinning of cortical language areas. For example, better performance in generating words in the verbal fluency task was accompanied by the thinning of grey matter in language areas in 9- to 23-year-old children and young adults (Porter, Collins, Muetzel, Lim, & Luciana, 2011). This decrease in grey matter is accompanied by an increase in white matter. Both processes have been attributed to axonal pruning. That is, non-preferred connections are removed while those that support frequent information transfer are retained. Callosal maturation is far from completed by birth with the structure increasing in size well into adulthood, probably due to ongoing myelination and increase in axonal size (Keshavan et al., 2002). This late white matter maturation might interplay with the thinning of the cortical grey matter areas resulting in the establishment and maintenance of hemispheric dominance.

The human brain is characterized by a variety of functional hemispheric asymmetries with at least some of them evolving independently (Badzakova-Trajkov, Haberling, Roberts, et al., 2010). Different combinations of these hemispheric asymmetries seem to exert unique influences on the interhemispheric connectivity (Haberling, Badzakova-Trajkov, & Corballis, 2011). Nevertheless I found no evidence that differences in callosal connectivity could be attributed to more frequent interhemispheric coordination between language and hand motor functions, although the possibility that callosal connectivity might be influenced by different patterns of hemispheric asymmetry cannot be excluded.

My data suggest that axonal pruning in the corpus callosum might be influenced by the same genetic factors that also control handedness and cerebral dominance for language. On this view, individuals who carry the RS+ allele might exhibit enhanced axonal pruning in the corpus callosum, reducing interhemispheric connectivity and leading to right-handedness and left-hemispheric dominance for language. Individuals who lack this allele, in contrast, might be right- or left-handed but generally exhibit high connectivity patterns through the corpus callosum. It has been suggested that symmetric or bi-hemispheric functional networks rely on the exchange of information to coordinate processing (Galaburda et al., 1990; Witelson & Nowakowski, 1991) and thus, the enhanced interhemispheric connectivity found in left-handers (Westerhausen et al., 2004) and in those with atypical hemispheric dominance (Haberling et al., 2011) could reflect an adaptation to the underlying functional dominance pattern. According to this hypothesis, however, the twin member with hemispheric asymmetries localized in opposite hemispheres should exhibit high FA values whereas his or her co-twin who supports those functions unilaterally should exhibit low FA values. My data do not support this notion, given that all subjects assumed to lack the RS+ allele showed high FA values through the corpus callosum independently of their individual hemispheric dominance patterns. Thus, although the high interhemispheric connectivity found in this group might enable the enhanced information exchange that is crucial for an efficient functioning of the hemispheres in cases of atypical hemispheric dominance, it does not determine the hemispheric dominance pattern in itself. That is, the diminished axonal pruning of the corpus callosum creates the basis for a random establishment of either lateralized or bilateral networks.

In conclusion, the data reported here suggest that the genetic mechanisms involved in determining handedness and hemispheric dominance for language act on the level of the corpus callosum by exerting control over the interhemispheric connectivity, and therefore influencing the degree to which unilateral and bilateral networks are established.

Chapter 4:

Experiment 3: Asymmetries of the arcuate fasciculus in monozygotic twins: Genetic and nongenetic influences

Abstract

I assessed cerebral asymmetry for language in 35 monozygotic twin pairs. Using DTI, I reconstructed the arcuate fasciculus in each twin. Among the male twins, right-handed pairs showed greater left-sided asymmetry of connectivity in the arcuate fasciculus than did those with discordant handedness, and within the discordant group the right-handers had greater left-sided volume asymmetry of the arcuate fasciculus than did their left-handed co-twins. There were no such effects in the female twins. Cerebral asymmetry for language showed more consistent results, with the more left-cerebrally dominant twins also showing a more leftward asymmetry of high anisotropic fibres in the arcuate fasciculus, a result applying equally to female as to male twins. Reversals of arcuate fasciculus asymmetry were largely restricted to pairs discordant for language dominance, with the left-cerebrally dominant twins showing leftward and the right-cerebrally dominant twins rightward asymmetry of the white matter integrity. Because monozygotic twin pairs share the same genotype, my results indicate a strong nongenetic component in arcuate fasciculus asymmetry, particularly in those discordant for cerebral asymmetry.

Introduction

Broca’s and Wernicke’s area are dorsally connected via the arcuate fasciculus, which transfers linguistic information important for phonological and syntactic processing of words and sentences (Friederici, 2009; Hickok & Poeppel, 2007). The strength of the anatomical connections in the arcuate fasciculus might therefore play an important role in the asymmetric distribution of the language network and in the maintenance of hemispheric specialization. Imaging techniques such as diffusion tensor imaging (DTI) allow the study of white matter tracts in vivo by reconstructing their anatomical locations and quantifying the underlying white matter coherence. There is some evidence that the arcuate fasciculus might be asymmetric in showing a larger volume (Parker et al., 2005; Powell et al., 2006) or a higher fiber density (Vernooij et al., 2007) in the left hemisphere than the right. Studies investigating white matter coherence by extracting FA values, an indirect measure of myelination and / or axonal density in white matter (Beaulieu, 2002), generally show higher FA values in the left arcuate fasciculus than the right, using different methods such as whole brain voxel-based statistics (Buchel et al., 2004), or reconstruction by tractography (Powell et al., 2006).

The functional significance of this leftward asymmetry remains somewhat unknown, given that several studies correlating arcuate fasciculus asymmetry with functional language lateralization have yielded conflicting results. One study showed the asymmetry of the fibre density of the arcuate fasciculus to be correlated with functional language lateralization in right-handers in Wernicke’s area but not in Broca’s area, but there was no such correlation in left-handers (Vernooij et al., 2007). In a similar study, though, a structure-function covariation was evident only in consistent left-handers (Propper et al., 2010). Another study showed left-lateralization of the FA values to be positively correlated with left-hemispheric language dominance (Powell et al., 2006), but this study included only right-handers. In a study of epilepsy patients in which language lateralization was established using sodium amobarbital injection, considered the gold standard in determining functional language dominance, asymmetry of arcuate fasciculus fibres with high anisotropy values determined language lateralization correctly in 16 of the 19 left-cerebrally dominant and in 3 of the 4 right-cerebrally dominant patients, suggesting moderate correlation at best (Ellmore et al., 2010).

The conflicting results obtained in previous studies might be partly due to other factors such as gender and handedness influencing arcuate fasciculus asymmetry, obscuring relations to language dominance. One way to reduce the interindividual variability is to study monozygotic (MZ) twins, who share the same set of genes and are therefore perfectly matched for age, gender and genotype. Moreover, some 20-25% of monozygotic twins are of opposite handedness (Annett, 2002; McManus, 1980) and some twins also show reversed cerebral asymmetry for language (Badzakova-Trajkov, Haberling, & Corballis, 2010; Sommer, Ramsey, et al., 2002), suggesting sufficient variation to test for correlation with arcuate fasciculus asymmetry. In particular, any variation within pairs of twins would indicate a nongenetic source.

I used a verbal fluency paradigm during fMRI to measure functional language dominance in 35 monozygotic twin pairs of which 18 pairs were of discordant handedness. All twins also underwent a DTI sequence and the arcuate fasciculus in each twin was reconstructed. This enabled me to compare the arcuate fasciculus in two perfectly matched individuals but with different strength and / or direction of hemispheric language dominance. If arcuate fasciculus asymmetry is related to functional language dominance I might expect that the more left-hemispheric twin shows a more left-hemispheric asymmetric arcuate fasciculus than his or her less left-hemispheric dominant co-twin.

Material and methods

Subjects

Ethics approval was obtained by the Human Ethics Participants Committee at the University of Auckland, New Zealand, and all subjects gave written consent prior to the study. 35 pairs of monozygotic twins (14 male/male, mean age = 23.5, SD = 7.8, 21 female/female; mean age = 25.5, SD = 9.4) took part in the study. Each twin member filled out a short zygosity questionnaire consisting of questions regarding their physical resemblance, the difficulty for family and friends to tell them apart, and their hair and eye colour in childhood (Christiansen et al., 2003) (Appendix C). In 7 twin pairs, where zygosity could not be established beyond doubt based on the answers and the physical appearance, additional DNA testing was performed. DNA was extracted from mouth swab samples and the individuals were genetically typed using the multiplex PCR kit AmpFISTR Identifiler (Applied Biosystems). The kit compares the STR (short tandem repeat) profiles on 15 highly polymorphic loci. Twins were considered as monozygotic when no differences in the 15 loci were detected (Yang et al., 2006).

Based on writing hand, 16 pairs were both right-handed (RR pairs; 7 male/male; 9 female/female; mean age = 22.6, SD = 7.2), 1 pair were both left-handed (LL pair; 1 female/female; age = 21), and 18 pairs were of opposite handedness (RL pairs; 7 male/male; 11 female/female, mean age = 26.8, SD = 10.0). Twin pairs with discordant handedness were deliberately over-represented in the study. Each twin also filled out a handedness inventory, in which they indicated the preferred hand in 12 activities: writing, throwing a ball, holding a racquet, lighting a match, cutting with scissors, threading a needle, sweeping with a broom (top hand), shoveling, dealing cards, hammering, holding a toothbrush, unscrewing a lid (Annett, 2002) (Appendix A). They gave two ticks for the preferred hand or one tick for each hand if there was no preference. A laterality index (LI) was then calculated from the formula $100x\left(\frac{R-L}{R+L}\right)$, where R and L represent the number of ticks for the right and left hand, respectively. Although the primary criteria for handedness was the writing hand, as has been suggested by McManus (2002), all left-handed twin members had LIs < 40 and all right-handed twin members had LIs > 50, resulting in a classification scheme similar to that used in previous research (e.g.,Whitehouse & Bishop, 2009).

Word Generation task

To assess language dominance, all participants undertook a Word Generation task adapted from the Controlled Oral Word Association test (Lezak, 1995) during fMRI. Participants were asked to silently generate as many words as possible starting with a designated letter (F, A, S, B, and M) which were randomly and centrally projected onto a screen (in Courier New black font, size 50). They were instructed not to use proper names or the same words with different endings. The letters were presented for 30 s, followed by a 30 s baseline period that consisted of a black cross, resulting in an acquisition time of 5 min. Prior to the experiment, all participants completed a comparable short version of the task, naming the words overtly, in order to obtain a behavioural performance measure.

Image acquisition and processing

MRI scanning was performed on a 1.5-T Siemens Avanto scanner (Erlangen, Germany). A T1-weighted structural image was acquired using a 3-D MP-RAGE sequence with 176 axial slices parallel to the AC-PC line, ensuring whole brain coverage. The following parameters were used: TR = 11 ms; TE = 4.94 ms; flip angle: 158; FOV: 256 x 256 mm^2. Slice thickness was 1 mm and the interslice gap 0, resulting in isotropic voxel resolution of 1 x 1 x 1 mm. For the diffusion weighted images a single-shot spin echo sequence along 30 diffusion gradient directions with a b0 of 1000 s/mm^2 was used with the following parameters: TR = 6601 ms, TE = 101 ms, FOV = 230 mm; in-plane resolution: 1.8 x 1.8 mm; slice thickness 3 mm. In addition, one image without diffusion weighting was acquired. The sequence was repeated twice resulting in an acquisition time of approximately 7 min. The EPI acquisition had the following parameters: TR = 2500 ms; TE = 50 ms; flip angle = 90; FOV =192 x 192; matrix size: 64 x 64; 29 slices parallel to AC-PC line; slice thickness: 3 mm; interslice gap: 25% = 0.8 mm.

Functional imaging processing and analyses

The functional images were analysed using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk). First, the standard pre-processing steps (realignment, coregistration, normalization and smoothing) were applied. The functional scans were realigned to the first image of the session and the mean of the functional volumes was calculated. The T1-weighted structural image was then coregistered to the previously obtained mean of the functional volumes. Then, all images were normalized into standardized stereotactic space (MNI, Montreal Neurological Institute) and spatially smoothed with an anisotropic Gaussian filter of 9 x 9 x 9 mm of full-width at half maximum (FWHM). For each participant, the functional volumes were subjected to a fixed-effects analysis using the general linear model that was applied at each voxel across the whole brain. The model was set up as a box-car function with the two alternate conditions letter vs. baseline. The resulting function was convolved with a canonical haemodynamic response function and movement regressors were also included in the model. For the group analysis, a second-level random effects analysis was performed by applying a one sample t-test to the contrast images of the first-level analyses. A family-wise error (FWE) correction was applied at $p < 0.05$ with a contiguity threshold of 10 voxels.

To establish language dominance, laterality indices were calculated by comparing the activity between the left and right Broca's region using the formula LI = $\frac{L-R}{L+R}$, where L and R represent activations in the left and right hemisphere, respectively. The laterality toolbox available on the SPM website was used to calculate the laterality indices (Wilke & Lidzba, 2007). It applies a bootstrap algorithm to calculate about 10,000 indices at different thresholds yielding a robust mean LI ranging between -1 for extreme right to 1 for extreme left lateralization. For each participant, the weighted mean LI for Broca's area was computed. Broca's area was defined using the WFU Pick Atlas toolbox (Maldjian et al., 2003) and included Brodmann areas 44 and 45. The masks were smoothed with a 6 mm Gaussian filter to control for inter-individual variability. In addition, the toolbox integrates a mask weighting factor that represents the relation of the volumes of the masks on the left and on the right to rule out influences of different mask sizes. A positive index within the ROI corresponded to a left-hemispheric dominance (LI > 0.1) and a negative index to a right-hemispheric dominance (LI < -0.1) (Fernandez et al., 2003). Due to the small numbers in the bilateral group of 2 subjects (LI's ranging from -0.1 to +0.1), these were assigned to the right-hemispheric group since their hemispheric dominance pattern is also atypical in nature.

The word generation paradigm induced significant leftward activations in the inferior frontal gyrus, including pars opercularis and pars triangularis, insula, precentral gyrus, SMA, and inferior temporal gyrus (see Figure 10 A). Additional right-hemispheric clusters were observed in the inferior and middle occipital gyri. Overall, a one-sample t-test revealed that the laterality indices were significantly leftward asymmetric in Broca's area (M = 0.61, SE = 0.051, t(69) = 12.1, p < 0.001).

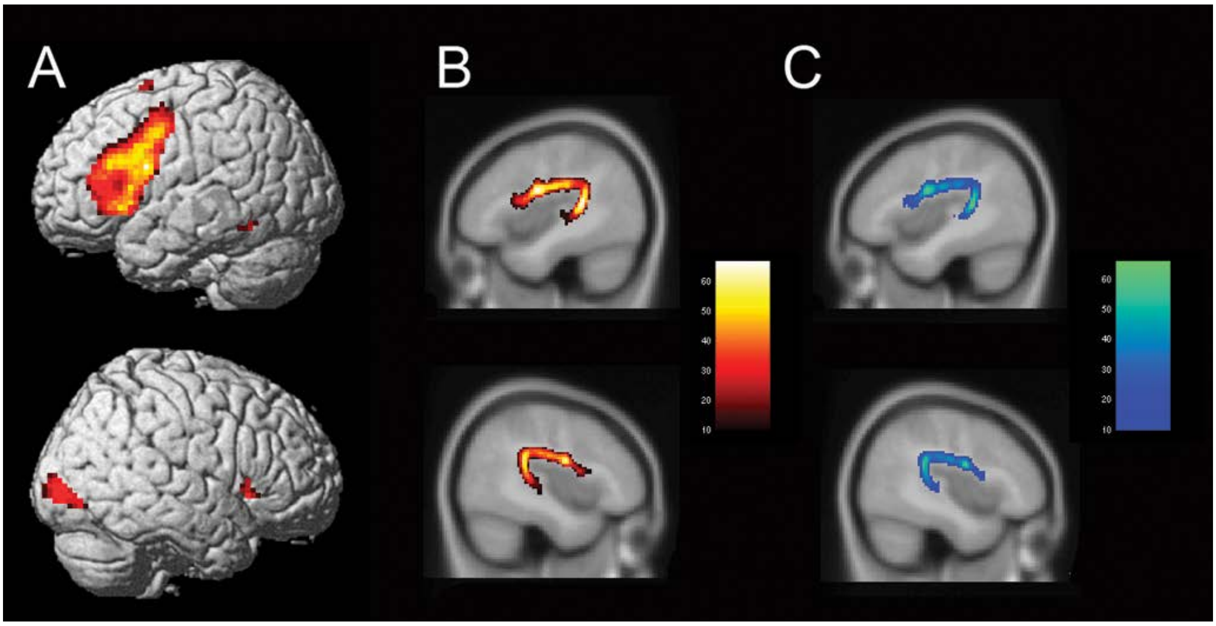

Figure 10: *A) Averaged brain activity during word generation task and reconstruction of the arcuate fasciculus on the B) 1% threshold and C) 2% threshold, respectively. Colour bars represent the number of subjects showing arcuate fasciculus fibres in that voxel.*

DTI preprocessing and analysis

The tractography of the arcuate fasciculus was carried out using the software programme FSL (http://www.fmrib.ox.ac.uk/fsl/). The diffusion data were corrected for eddy currents and head motion and the two acquisitions were averaged to improve signal-to-noise ratio. Diffusion tensors were fitted at each voxel and FA maps were generated. Then, the probability distribution of fibre direction at each voxel was calculated using previously described methods (Behrens et al., 2003). A seed mask was drawn on a coronal section at the level of the precentral sulcus by identifying voxels in which the principal diffusion direction was anterior-to-posterior (voxels colored green)(Rilling et al., 2008). For each participant, probabilistic tractography was run from this seed mask by drawing 5000 random samples with a steplength of 0.5 mm and a curvature threshold of 0.2. In order to separate arcuate fasciculus tracts from erroneous tracts, a further two ROI approach was used by defining a posterior ROI comprising fibres reaching the white matter beneath the middle and superior temporal gyrus, and an anterior ROI containing fibres in the white matter beneath the inferior frontal gyrus. Then, the arcuate fasciculus was tracked twice, once from the anterior to the posterior ROI, and once from the posterior to the anterior ROI. The resulting tracts were visually inspected for consistency with the known anatomy. Given inconsistent reports of the exact anatomical terminations of the arcuate fasciculus (Barrick et al., 2007; Bernal & Altman, 2010; Catani et al., 2005; Glasser & Rilling, 2008; Kaplan et al., 2010), fibres were only tracked between the two ROIs, and it cannot be excluded that some might have extended even further. Voxels with FA < 0.2 were considered grey matter and excluded from the analysis (Thiebaut de Schotten et al., 2011).

The two pathways were then added together and were thresholded at 1% and 2%, respectively of the total streamlines connecting the target ROIs. The results were analysed on two different thresholds given that laterality indices for FA values increase over higher thresholds (Powell et al., 2006) and to ensure that the results were not threshold dependent. To extract the FA values, the tracts were binarized and multiplied with the individual FA images to get the mean FA over the whole tract. To extract the volume of the tracts that were corrected for brain size, all images were normalized to MNI standard space and the normalized volumes were calculated (Powell et al., 2006). In 3 of 70 subjects the arcuate fasciculus was intractable in one of the hemispheres and the pairs to which they belonged were excluded from analysis. Previous studies have shown that normal variation in this structure results sometimes in intractability (Catani et al., 2007; Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Propper et al., 2010).

Statistical analyses

In order to detect potential differences in the mean values between different groupings of twins, twin pair was treated as a random factor whereas group and twin gender were entered as between-twin factors into the analysis of variance. Subjects (twins) were treated as nested within each twin pair. All post-hoc tests were performed with a Bonferroni correction for multiple comparisons.

Results

I established cerebral asymmetry for language by computing laterality indices (LI) based on activity in Broca's area, with an LI > 0.1 reflecting left-hemispheric language dominance (see Figure 10 A). A classification of the twin pairs according to handedness, language dominance and gender is shown in Table 10. Overall, 24 pairs were concordant for left-hemispheric language dominance, 7 pairs were discordant for language dominance and 1 pair was concordant for atypical language dominance. I then carried out tractography of the arcuate fasciculus in each twin (Figure 10 B) and assessed connectivity by calculating the normalized tract volumes and the mean fractional anisotropy (FA) value over the whole tract. For both measurements, I calculated asymmetry indices (AI) according to the formula $AI_{FA} = \frac{FA_L - FA_R}{FA_L + FA_R}$ and $AI_{Vol} = \frac{Vol_L - Vol_R}{Vol_L + Vol_R}$, for FA values and volumes, respectively.

Table 10: *Concordance for handedness and language dominance in male and female twin pairs. Twin pairs who were excluded from the analysis due to the intractability of the arcuate fasciculus are shown in brackets.*

	Handedness	**Language dominance**			**Total**
		both left	discordant	both atypical	
male	both right	6 (1)	-	-	7
	discordant	4	2 (1)	-	7
	both left	-	-	-	
female	both right	6 (1)	1	1	9
	discordant	8	3		11
	both left	-	1	-	1
Total		26	8	1	35

Handedness effects

I first tested the effect of handedness on FA asymmetry by assigning the pairs to two groups, one in which both were right-handed (RR group; N = 14) and one in which the pairs were of opposite handedness (RL group; N = 17). One pair was excluded because both members were left-handed. In the RL group, twins were sorted so that the first twin in each pair was the right-handed twin member. Analysis of variance showed an interaction between gender and handedness group ($F_{(1,27)} = 4.31$, $p = 0.048$), as shown in Figure 11. For males, the RR group showed a higher AI_{FA} index (mean = 0.018) than the RL group (mean = -0.004, p = 0.017), but for females there was no significant difference (means = 0.004 and 0.005, respectively, p = 0.888). Within the RL group, it was possible to compare the left-handed twins with their right-handed co-twins, with left-handers (mean = -0.004) not significantly different from right-handers (mean = 0.005, p = 0.547).

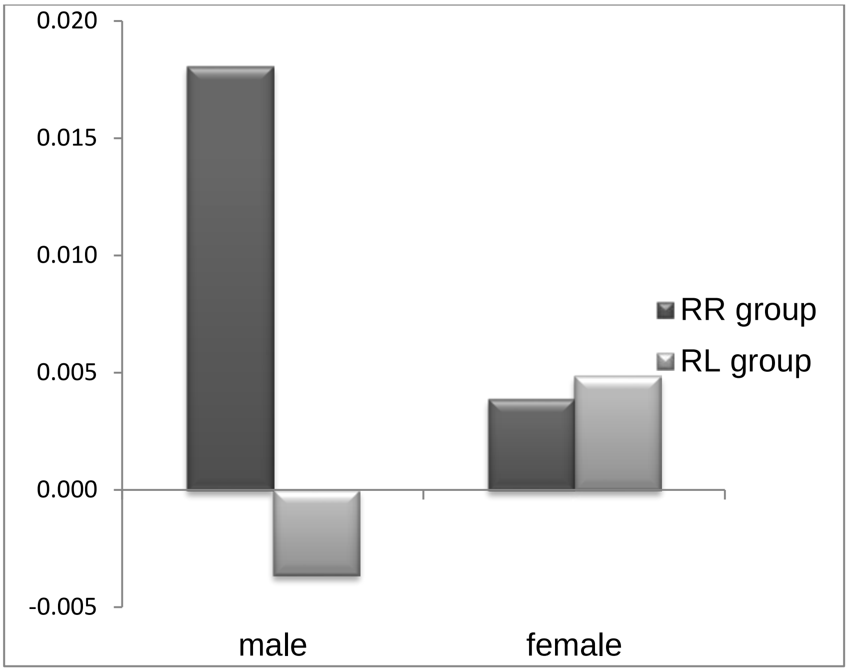

Figure 11: *Asymmetry indices (AI) for the FA values of the arcuate fasciculus according to handedness and gender are depicted. Male twin pairs with discordant handedness showed significantly lower AI_{FA} than right-handed male twin pairs whereas the same effect was not observed for the female twin pairs.*

For volume asymmetry I found an interaction between handedness and gender that was restricted to the RL group ($F_{(1,27)} = 4.92$, $p = 0.035$). In the RL group, right-handed male twins (M = 0.288, SE = 0.073) showed a higher AI_{vol} than their left-handed co-twins (M =

0.068, SE = 0.102, p = 0.043), whereas the female RL twin pairs did not significantly differ (for right-handers, M = 0.140, SE = 0.054; for left-handers, M = 0.225, SE = 0.076, p = 0.277).

Cerebral asymmetry effects

Handedness is only weakly related to cerebral asymmetry for language, so I next examined the effect of LI values on asymmetry of the arcuate fasciculus. I sorted the twins so that the first twin in each pair had the higher LI, indicating stronger left-cerebral asymmetry for language. They were then allocated to two groups, one (24 twin pairs) in which the pairs were concordant for left-cerebral asymmetry, the other (7 twin pairs) in which one showed typical left-cerebral asymmetry and the other did not (LI < 0.1). One pair was excluded because both members showed atypical language dominance. In the concordant group, LIs ranged from 0.51 to 0.96 (mean = 0.861) for twin A (the more lateralized) and from 0.14 to 0.93 (mean = 0.668) for twin B (the less lateralized). In the discordant group the ranges were 0.18 to 0.99 (mean = 0.716) for twin A and 0.09 to -0.93 (mean = -0.377) for twin B.

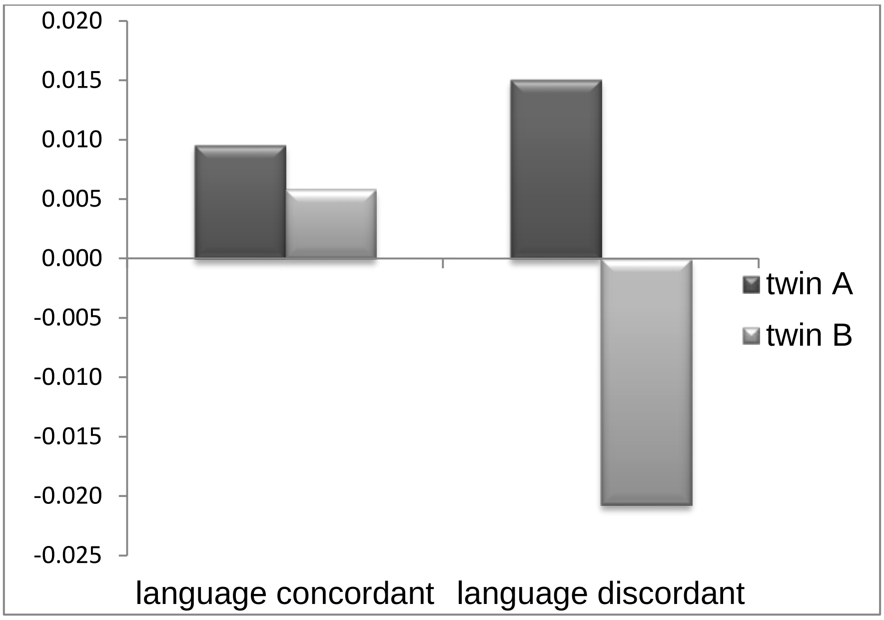

FIGURE 12: *Asymmetry indices (AI) for the FA values of the arcuate fasciculus according to cerebral language dominance are shown. Twin pairs with discordant language dominance showed reversed* AI_{FA} *asymmetry.*

Analysis of variance, with concordance and gender as between-twins factors, showed a positive AI_{FA} (mean = 0.0123) in the more left-lateralized twin and negative AI_{FA} (mean = -0.0074) in the less left-lateralized twin ($F_{1,27}$ = 8.17, p = 0.008). A significant interaction revealed reversal of AI_{FA} to be restricted to the discordant group ($F_{1,27}$ = 5.373, p = 0.028) with the left-cerebrally dominant twin showing leftward (M = 0.015, SE = 0.008) and the right-cerebrally dominant twins rightward (M = -0.021, SE = 0.010) asymmetry (see Figure 12). The relationship did not hold true in each individual case though, as depicted for the twin pairs with discordant language dominance in Figure 13.

In addition, the laterality indices for language and the asymmetry index for FA values were significantly and positively correlated on both thresholds (1% threshold: r (67) = 0.390, p < 0.001; 2% threshold: r (67) = 0.362, p = 0.003).

Gender had no significant effects. Analysis of volume asymmetry, AI_{vol}, revealed no significant effects of either language dominance or gender. In addition, no significant effect on the number of words generated in the Word Generation Task was observed.

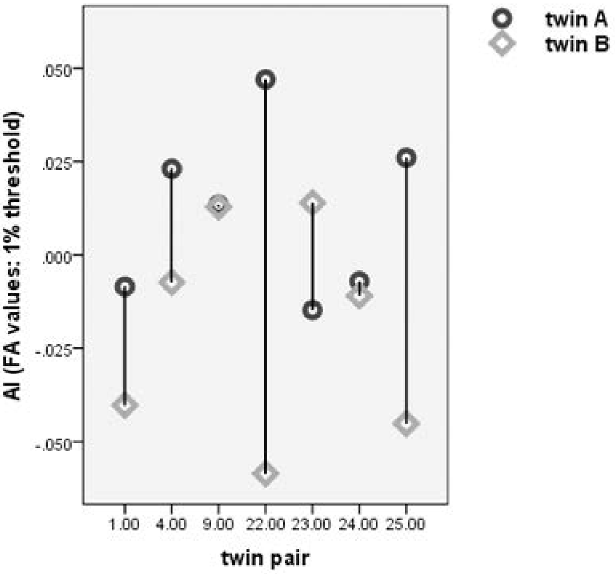

Figure 13: *Plotting of the AI_{FA} on the 1% threshold for the 7 twin pairs with discordant language dominance. Although most twin pairs showed the expected reversal of arcuate fasciculus asymmetry, one twin pair exhibited a reversed but inconsistent asymmetry pattern.*

Discussion

The effect of handedness on arcuate fasciculus asymmetry was evident only in males, but not in females, with right-handed male twin pairs showing a stronger asymmetry in the FA values than those with discordant handedness, and the left-handed males of the RL group showing a diminished volume asymmetry. This result accords with another study of male monozygotic twins, in which right-handed pairs showed asymmetries of lobar volumes while pairs discordant for handedness showed loss of asymmetry, especially in the temporal lobe (Geschwind et al., 2002). In that study, moreover, the genetic control over the lobar volumes was twice as high in the right-handed pairs as in the discordant pairs. These results fit moderately well with genetic theories of handedness and brain asymmetries, assuming a gene with two alleles, with one (RS+) introducing a bias toward right-handedness and left-cerebral dominance for language, and the other one (RS-) cancelling this shift (Annett, 2002; McManus, 2002). This lack of bias has been attributed either to an allele that does not express the bias (McManus & Bryden, 1992), or to epigenetic cancelling of the gene (Crow, 2010).

Nevertheless I found no effect of handedness in the female twins. Effects of gender on brain asymmetry have been reported before, with the majority of studies showing more pronounced anatomical asymmetries in males (Luders & Toga, 2010). For example, in a meta-analysis reduced planum temporale asymmetry in left-handers and females was reported (Shapleske et al., 1999) and white matter asymmetries in frontal and temporal regions were found to be more pronounced in males (Pujol et al., 2002). Furthermore, right-handed males exhibited a leftward connectivity of the arcuate fasciculus which was absent in left-handed males whereas women showed a bilateral distribution irrespective of handedness (Hagmann et al., 2006). The more symmetrical connectivity of the arcuate fasciculus in females has been replicated in some (Catani et al., 2007) but not all studies (Powell, Parkes, et al., 2012; Takao, Abe, et al., 2011).

Handedness is at best an indirect measure of cerebral asymmetry for language, and the effects of cerebral asymmetry for language, as derived from fMRI, showed more clear-cut results, at least with respect to fractional anisotropy of the arcuate fasciculus. Left-cerebrally dominant twin pairs showed higher FA on the left, while twin pairs with discordant language asymmetry showed reversal, with the left-cerebrally dominant twins showing leftward asymmetry of the FA and the right-cerebrally dominant co-twins showing rightward asymmetry. These effects were independent of gender. Thus asymmetry of language representation was directly mapped onto structural asymmetry of the arcuate fasciculus. This influence may be nongenetic, and due to neural potentiation resulting from activation of the language circuits.

That is, high FA values in the hemisphere dominant for language might reflect rapid transmission of linguistic information (Ellmore et al., 2010), given the involvement of the arcuate fasciculus in phonologic (Glasser & Rilling, 2008; Hickok & Poeppel, 2004; Yeatman et al., 2011) and syntactic processing (Friederici, 2009). Reduced FA values in the left arcuate fasciculus are also associated with deficits in syntactic processing in patients with primary progressive aphasia (Wilson et al., 2011) and after left-hemispheric stroke (Papoutsi et al., 2011). The reversal of FA asymmetry in those with atypical language dominance is also consistent with emerging evidence that the usual left-hemisphere structures associated with language are reversed in some individuals (Chang, Wang, Perry, Barbaro, & Berger, 2011; Duffau, Leroy, & Gatignol, 2008; Knecht et al., 2002).

Other activity may also alter connectivity; for example, musicians have larger tract volume and higher FA values in the left and right arcuate fasciculus than non-musicians (Halwani, Loui, Ruber, & Schlaug, 2011). The effects of environmentally-induced plasticity are also likely to accumulate with age, reducing heritability. In a large scale study investigating over 700 twins and their siblings, heritability of the FA values dropped from 70-80% in adolescents to only 30-40% in adults (Chiang et al., 2011), due to influences of sex, age, intellectual performance and socio-economic status.

Although my results suggest a nongenetic influence, they can also be considered consistent with the genetic model outlined above. The majority of twin pairs concordant for left-cerebral language dominance may well inherit the gene biasing cerebral asymmetry for language to the left, while discordant pairs lack this influence so that both cerebral dominance and arcuate fasciculus asymmetry are matters of chance. Of course some twins lacking the gene may also fall by chance in the concordant group, although most of the twins in that group may be assumed to inherit the lateralizing gene. Indeed, the results for cerebral asymmetry fit the genetic model better than those for handedness, supporting Annett's (2009) conjecture that the gene is primarily a cerebral asymmetry gene, with only indirect effects on handedness. Indeed, although some 22% of MZ twins are of opposite handedness (Sicotte et al., 1999), some 70% of them both show left-cerebral asymmetry for language

(Badzakova-Trajkov, Haberling, & Corballis, 2010), illustrating the relatively poor correspondence between handedness and cerebral asymmetry for language.

In summary, my results show a strong correspondence between cerebral asymmetry for language and asymmetry in connectivity within the arcuate fasciculus in monozygotic twins. They also show weaker evidence for an effect of handedness, although this was restricted to male twins. The fact that asymmetry of the arcuate fasciculus would be reversed between twins sharing the same genotype suggests a strong nongenetic influence, although the data are also consistent with a genetic model in which lack of a lateralizing allele leaves the direction of asymmetry open to chance.

Chapter 5:
General discussion

The main aim of this thesis was to investigate the relationship between functional cerebral asymmetries and structural connectivity by combining two imaging techniques, namely functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). Furthermore, through the inclusion of monozygotic twin pairs inferences about possible genetic and nongenetic sources of the observed variability could be drawn. The main aspects of the three studies are briefly summarized next.

In Experiment 1, the cerebral dominance pattern for language and spatial processing was established in each participant using fMRI (see chapter 2). In addition, DTI was performed to assess micro- and macrostructural properties of the corpus callosum. The aim of Experiment 1 was to investigate how individual variability in the cerebral dominance for language and spatial processing was related to the efficacy of interhemispheric connectivity. Results revealed that atypical hemispheric specialization, such as a right-sided or bilateral language network or crowding of spatial and language processing to the same hemisphere, was associated with high anisotropic diffusion through the corpus callosum. This suggests that individuals with unusual distributions of lateralized networks might rely on enhanced interhemispheric information transfer.

Experiment 2 tested the hypothesis that hemispheric dominance might be linked to a genetically controlled process of callosal pruning by evaluating the relationship between language dominance and interhemispheric connectivity in a group of monozygotic twin pairs (see chapter 3). On the basis of the genetic models of handedness and language dominance, the twin pairs with a high likelihood of possessing the lateralizing allele showed low anisotropic diffusion through the corpus callosum. Twin pairs more likely to lack the lateralizing allele, on the other hand, showed a high connectivity pattern. Given that a genetic contribution on callosal microstructure could only be inferred for the first group, the results suggest that the lateralizing allele might enhance the axon loss in the corpus callosum, which in turn favours the establishment of strongly lateralized networks.

In Experiment 3, the relationship between the asymmetric distribution of the functional language network and asymmetry of the arcuate fasciculus, one of the main fibre tracts involved in language functions, was investigated in the same set of monozygotic twin pairs (see chapter 4). The results revealed a close relationship between the leftward asymmetry of the functional language network and asymmetry in the white matter integrity of the arcuate fasciculus, given that the twin with a more leftward dominance for the processing of speech also showed a more leftward asymmetry of the arcuate fasciculus. Twin pairs with opposite language dominance showed reversed asymmetry in the white matter integrity of the arcuate fasciculus. Given that monozygotic twins share the same set of genes, arcuate fasciculus asymmetry might originate, at least in part, from a nongenetic source.

In this chapter, the findings from the individual experiments will be discussed together in order to evaluate: 1) how structural connectivity relates to hemispheric specialization, 2) genetic and nongenetic factors in structural connectivity, and 3) handedness and gender effects. The limitations and further implications that arise from the current work are also discussed.

The relationship between structural connectivity and hemispheric specialization

This section evaluates how structural connectivity contributes to hemispheric specialization by discussing the relationship between inter- and intrahemispheric connectivity and the functional language network, and the impact of more than one lateralized function on callosal morphology.

The role of interhemispheric connectivity in functional language dominance

In all three experiments, participants performed a Word Generation task during an fMRI scanning session while BOLD signal response was recorded. The asymmetry of the BOLD signal then provided a measure of the degree and direction of functional language dominance in each participant. This measure is known to conform to the identification of the hemisphere dominant for language determined by the intracarotid sodium amobarbital procedure in 91% to 100% of participants (Woermann et al., 2003; Yetkin et al., 1998).

In Experiment 1 and 2, the white matter integrity of the callosal tracts was assessed by calculating the amount of anisotropic diffusion in the tissue, indexed by fractional anisotropy (FA). FA is thought to reflect microstructural properties such as axonal density, axonal diameter, alignment of fibres and myelination (Beaulieu, 2009). Furthermore, FA values have been shown to correspond with interhemispheric transfer time, and may therefore indicate the efficacy of callosal communication (Schulte et al., 2005; Whitford et al., 2011).

Results in both studies revealed a similar pattern. That is, a subgroup of individuals with left-cerebral language dominance showed very low anisotropic diffusion in the corpus callosum as a whole, whereas a high connectivity pattern, indicated by high FA values, could be associated with left-cerebral or right-cerebral language dominance. Two implications can be drawn from these data. First, some individuals with left-cerebral language dominance show reduced interhemispheric connectivity, suggesting that in these individuals less information might be transferred between the hemispheres. That is, in these individuals, linguistic functions might largely rely on intrahemispheric processing circuits. Evolutionary theories suggest that asymmetric distribution of functions might have originated in a decrease of interhemispheric information transfer, which resulted from the larger interhemispheric distances to be covered with increasing brain sizes (Aboitiz et al., 2003; Ringo et al., 1994). The ensuing decoupling of the hemispheres and development of intrahemispheric networks might have in turn caused a further loss of interhemispheric connections, although a certain amount of fibres was still retained in order to share the end product of the computation between the hemispheres (Gazzaniga, 2000). Even in cases of strong hemispheric specialization both hemispheres contribute to some aspects of linguistic processing. For example, prosodic information might be predominantly processed in the right hemisphere, and the integration of prosodic and syntactic aspects of speech requires interhemispheric information transfer (Friederici, von Cramon, & Kotz, 2007).

Second, atypical language dominance was always associated with high connectivity through the corpus callosum, probably due to an enhanced cooperation of the hemispheres in information processing. These results are concordant with findings from the dichotic listening task, which showed the highest interhemispheric connectivity in individuals with a left ear advantage in the processing of speech stimuli, indicating right-cerebral dominance for language (Gootjes et al., 2006; Hines et al., 1992). Similarly, the largest callosal areas were found in patients with right-hemispheric speech representations as measured by the intracarotid amobarbital procedure (O'Kusky et al., 1988). Furthermore, a post-mortem study revealed that a reduced asymmetry in the number of minicolumns in the planum temporale, which might indicate a more symmetrically organized language network, was associated with more callosal projections in the isthmus of the corpus callosum (Chance, Casanova, Switala, & Crow, 2006). This notion is further supported by the enhanced interhemispheric connectivity in cases of crowding of functions to one hemisphere, as discussed in the next section.

Based on the assumption that bilateral networks rely more on interhemispheric information transmission than on strong intrahemispheric circuits, the relationship between high connectivity and a lack of strong left lateralization supports the excitatory model of callosal information transfer (Galaburda et al., 1990; Gazzaniga, 2000), and is further supported by the significant negative correlation between laterality indices for language and FA values found in Experiment 1. According to this model, callosal fibres share information between the hemispheres by activating contralateral regions, enabling an efficient interhemispheric cooperation. However, some individuals with left-cerebral language dominance also showed a high connectivity pattern and in Experiment 2, no differences in callosal connectivity between the two twin members of one pair but with opposite language dominance were observed. Therefore, the relationship between the degree of asymmetry for linguistic processing and the strength of callosal connectivity might not be linear, suggesting that interhemispheric connectivity might in fact be related to the development of hemispheric specialization, as further discussed in a later section on the genetic and nongenetic factors in structural connectivity.

Interhemispheric connectivity and lateralization of various functions

Although language is one of the most asymmetrically distributed functions of the brain, other cognitive processes are also lateralized to one hemisphere and the individual combinations of different lateralizing influences might affect the efficacy of interhemispheric connectivity. Thus, Experiment 1 assessed the combined effect of hemispheric dominance for language and for spatial processing on interhemispheric connectivity. The results revealed that individuals with the typical lateralization pattern, that is left-cerebral dominance for language and right-cerebral dominance for spatial processing, showed the lowest anisotropic diffusion through the corpus callosum. In contrast, individuals with both functions to the right and individuals with a mirror-reversed lateralization pattern showed significantly higher anisotropic diffusion over the whole corpus callosum. In the posterior segment of the corpus callosum, individuals with crowding of functions, irrespective of whether both functions were localized in the left or right hemisphere, showed increased anisotropic diffusion.

Crowding of functions might impact callosal connectivity in two distinct ways. One hypothesis suggests that individuals with crowding of functions might rely more on compensatory activations of the nondominant hemisphere. With increasing task difficulty additional recruitment of the nondominant hemisphere is observed (Banich, 1995), probably due to limited information processing capabilities of a single hemisphere (Lidzba et al., 2006; Powell, Kemp, et al., 2012; Strauss et al., 1990). This effect might be more pronounced when crowding of functions occurs. For example, it has been shown that the localization of language and spatial functions in the right hemisphere is associated with increased bilateral activations during the processing of spatial tasks (Jansen et al., 2005). The reliance on compensatory strategies involving the nondominant hemisphere might in turn influence the efficacy of interhemispheric information transfer.

A second hypothesis relates to the amount of cooperation which is needed in tasks involving the simultaneous interplay of various lateralized functions. For example, Moffat et al. (1998) suggested that individuals who have functional asymmetry for speech and manual actions localized in opposite hemispheres might rely more on interhemispheric information transfer in tasks such as writing, based on their finding of largest callosal areas in left-handers with left-cerebral language dominance as assessed with the dichotic listening task. This hypothesis was tested in Experiment 2, where the twins were grouped according to the ones who support functional lateralization for hand motor control and speech in opposite hemispheres and those who support them unilaterally. According to the above suggested model, twins who dissociate these two functions should show enhanced interhemispheric connectivity due to an increased need for information transfer in tasks requiring the simultaneous interplay between language and hand motor control. However, no significant differences between the two groups were observed. Nevertheless, the interaction of different lateralized functions and its influence on structural connectivity warrants further investigation.

Intrahemispheric connectivity in the language network

In contrast to the interhemispheric communication, the anisotropic diffusion in the arcuate fasciculus corresponded more linearly to the underlying distribution of the language network. That is, a structural asymmetry index derived from the FA values in the left and the right arcuate fasciculus corresponded with the degree and direction of the hemispheric lateralization for language, even in monozygotic twin pairs. The more left-cerebral dominant twin showed a more leftward asymmetric arcuate fasciculus than his or her less left-cerebral dominant co-twin and reversals of arcuate fasciculus asymmetry were largely restricted to twins with a right-sided language distribution. According to the model of Hickok and Poeppel (2007), frontal and temporal language regions are connected via two distinct pathways, a ventral stream, which is organized bilaterally and processes semantic aspects of speech signals, and a leftward asymmetric dorsal stream which maps acoustic speech signals to the articulatory networks in the frontal lobe. The arcuate fasciculus plays a key role in the dorsal route and my results suggest that the strength of structural intrahemispheric connectivity is directly related to the distribution of the functional language network, probably because in the dominant hemisphere more rapid transmission of linguistic information is required (Ellmore et al., 2010).

Genetic and nongenetic factors in structural connectivity

Genetic models of handedness and cerebral dominance, such as those developed by Annett (2002) and McManus (2002), propose a single gene with two alleles, one coding for right-handedness and left-cerebral language dominance and the other one leaving those asymmetries to chance. Both theories have been discussed in detail in the section of the General Introduction on the origins of hemispheric specialization (pages 9-13). In the following two sections, the genetic theories will be related to models proposing a tight coupling between the development of hemispheric specialization and the maturation of brain structures. More specifically, it has been proposed that hemispheric specialization might be achieved through callosal pruning (Annett, 2002; Witelson & Nowakowski, 1991) or through differential growth patterns of structures in the left and right hemisphere (Geschwind & Galaburda, 1987). Thus, the implications of my results for a genetic basis of structural connectivity and its role in the development of hemispheric specialization will be discussed next.

Callosal pruning: genetically controlled?

Experiment 1 and 2 suggest that a genetically controlled process of callosal pruning might play a role in the development of hemispheric specialization. In Experiment 1, a distinct pattern of the relationship between interhemispheric connectivity and language lateralization emerged. That is, individuals with FA scores below 0.545 were exclusively left-cerebrally dominant for language, whereas individuals with FA scores over 0.545 showed an inconsistent lateralization pattern with about half of them being left- and half right-cerebrally dominant for language (see Figure 6, p. 47). According to the genetic models of language dominance, individuals with at least one copy of the lateralizing allele develop left-cerebral language dominance whereas those lacking the allele are equally divided into left and right sided language dominance groups (Annett, 2002; McManus, 2002). If the lateralizing allele exerts influence over callosal connectivity, a similar distribution as the one found in Experiment 1 would be expected. This hypothesis was further evaluated in the second experiment, in which callosal morphology in 35 monozygotic twin pairs was assessed.

Given that attempts to identify the lateralizing gene have been equivocal (Francks et al., 2003; Francks et al., 2002; Francks et al., 2007; Van Agtmael et al., 2003), it is not yet possible to compare different genotypes on the basis of the DNA sequence. Nevertheless, based on the predictions of the right-shift theory (Annett, 2003), twin pairs can be classified according to their likelihood of possessing the lateralising allele. That is, twin pairs who are right-handed and left-cerebrally dominant for language (RS+ group) have over 90% probability of having at least one copy of the RS+ allele, whereas in twin pairs with discordant handedness or even reversed asymmetry for speech (RS- group) the probability is less than 50% (see Table 5, p.57).

Comparisons of callosal connectivity between the groups revealed that the twin pairs in the RS+ group showed lower FA values in the corpus callosum than the twin pairs in the RS- group, which was concordant with the findings of Experiment 1. To further increase the homogeneity of the RS+ group, all twins with left-handers in the immediate family were removed from the RS+ group. Previous studies indicated reduced functional language dominance (Isaacs et al., 2006; Knecht, Drager, et al., 2000) and reduced planum temporale asymmetry (Tzourio-Mazoyer et al., 2010) in individuals with a positive familial history of sinistrality. As expected, the new RS+ group showed the lowest connectivity over the whole corpus callosum, and tended to show lower white matter integrity in the prefrontal and parieto-temporal segments of the corpus callosum.

To assess the degree of resemblance between the twin members within each pair, intraclass correlations were computed. Intraclass correlations compare the variation within a pair with the variations between the pairs. A high coefficient signifies that the variation within a pair is very small in relation to the total variance in that group, and suggests a possible genetic source of the observed variability. Both groups showed high intraclass correlations for callosal areas, which concords with the high heritability estimates of around 79-94% reported in previous studies of monozygotic and dizygotic twin pairs (Hulshoff Pol et al., 2006; Pfefferbaum et al., 2000; Scamvougeras et al., 2003). Data such as these, together with the results of no differences in callosal size between twin pairs with reversed cerebral asymmetries, suggest a strong genetic component in callosal size which is unrelated to hemispheric specialization itself.

In contrast, FA values were only under high genetic control for the RS+ group, and not the RS- group. Based on the assumption that FA values reflect axonal density, callosal pruning might be at least partly under the same genetic control as handedness and language dominance. Individuals with the putative lateralising allele might show a reduction in interhemispheric communication which might favour the establishment of strong intrahemispheric left-cerebrally dominant networks for language and hand motor control. However, individuals who lack the lateralizing allele might retain more callosal connections, which might enable the establishment of more bilateral networks at least in some cases. Although the current results suggest a relationship between callosal pruning and the putative lateralizing allele, it is unlikely that it is the only gene influencing callosal morphology. Rather, a set of genes is thought to control the development of callosal projection neurons with different genes being active at different stages of the maturation process (Fame et al., 2011). Related to this, genetic control over callosal pruning might also be achieved indirectly through control over testosterone concentrations or sensitivity, which in turn might affect the amount of axon elimination in the corpus callosum, as suggested by Witelson and Nowakowski (1991). That is, hormonal and genetic models of callosal pruning might not be contradictory but might indeed complement each other (Beaton, 2003).

A key role of callosal fibres in the establishment of functional lateralization has been questioned because hemispheric specialization also develops in absence of the corpus callosum, as observed in individuals with callosal agenesis. For example, five acallosal patients, whose language dominance was established with fMRI, did not differ in their laterality pattern compared with IQ matched controls (Pelletier et al., 2011). A case study of one patient with total callosal agenesis reported the usual hemispheric dominance pattern for language and motor hand control (Jancke, Wunderlich, Schlaug, & Steinmetz, 1997). However, the structural asymmetries were unusual with both the planum temporale and the planum parietale favouring the left side. Furthermore, the left hemisphere also showed superiority for tactile object recognition, suggesting that spatial processing might also be localized in the left hemisphere. Thus, although some of the typical asymmetries were established, others deviated from the usually observed pattern.

Callosal agenesis though is a heterogeneous developmental disorder, which can be associated with a wide range of clinical symptoms. That is, some individuals show no symptoms at all whereas others exhibit severe cognitive impairments. The functional outcome of the disorder might be associated with the amount of cortical reorganization processes that occur pre- and postnatally. For example, a recent DTI study observed the existence of additional aberrant white matter tracts not seen in healthy brains (Tovar-Moll et al., 2007), and those together with other alternate pathways such as the anterior commissure might take over some of the functions usually performed by the corpus callosum (Paul et al., 2007).

The assumption that callosal morphology might at least be partially genetically controlled does not exclude the possibility that also environmental influences affect the number and the degree of myelination of callosal fibres. Indeed, several neuroimaging studies have confirmed plasticity of callosal tracts through experience and learning. For example, the anterior portion of the corpus callosum is enlarged in professional musicians who start musical training in early childhood (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). In adults, even short-term learning schemes have been shown to alter the callosal white matter integrity. For example, a two-month period of working memory training resulted in increased FA in the anterior part of the body of the corpus callosum and the intraparietal sulcus (Takeuchi et al., 2010). Experience-induced plasticity is observed through the whole life-span so that even in adults aged 65-80 years a cognitive training induced plastic changes in callosal tracts (Lovden et al., 2010). Environmental influences on fibre tracts are not only observed in laboratory settings, since everyday activities such as learning a second language or regular meditation also result in structural changes of the corpus callosum (Luders, Phillips, et al., 2012; Schlegel, Rudelson, & Tse, 2012).

Arcuate fasciculus asymmetry: nongenetically determined?

The close relationship between arcuate fasciculus asymmetry and language dominance observed in the current work suggests a dynamic interaction between the developments of the functional language network and the strength of the intrahemispheric connectivity. In Experiment 3, the more left-cerebrally dominant twin also showed more leftward asymmetric arcuate fibres than his or hers less left-cerebrally dominant co-twin, and twin pairs with opposite language dominance showed reversed asymmetry of the arcuate fasciculus. Given that monozygotic twin pairs share the same set of genes, my results indicate that arcuate fasciculus asymmetry might originate from a nongenetic source.

These findings contrast somewhat with the hypothesis that structural asymmetries might form the basis for hemispheric specialization given that they arise during the course of prenatal development (Geschwind & Galaburda, 1987). Recent neuroimaging studies of foetuses in utero detected the first structural asymmetries at around 23 week gestation when the left temporal lobe becomes larger than the right one (Kasprian et al., 2011; Rajagopalan et al., 2011). This anatomical data have been linked to differential gene expression in the left and right hemisphere, suggesting that the inherent architecture of the brain might favour the localization of language functions to the left hemisphere. Similarly, the arcuate fasciculus is already leftward asymmetric in 1-4 months old infants (Dubois et al., 2009) and in children (Eluvathingal et al., 2007; Lebel & Beaulieu, 2009).

An asymmetric distribution of arcuate fibres at such an early age suggests that there might be an intrinsic predisposition for hemispheric specialization, which seems counter to the idea of nongenetic influences shaping arcuate fasciculus asymmetry. Nevertheless, my results can still be reconciled with genetic theories given that most individuals exhibited a leftward asymmetry in the white matter integrity of the arcuate fasciculus. The twins who showed opposite arcuate fasciculus asymmetries were also discordant for language dominance. Based on the assumptions of the right-shift theory (Annett, 2002), these twins are of the RS-/- genotype, which is associated with a loss of the genetic bias of structural and functional asymmetries to either hemisphere.

In all other cases though, the functional asymmetry in language processing might be genetically controlled, and this is reflected in the structural asymmetry of the arcuate fasciculus, probably because the dominant hemisphere requires enhanced information transfer. It remains unclear however whether the structural asymmetry is driven by the functional asymmetry or vice versa. Most likely, though, the two networks reciprocally influence each other, so that an initial predominance of the left hemisphere to process linguistic stimuli might result in a strengthening of the structural connectivity in the left hemisphere, which in turn might further displace the processing of speech sounds to the core language areas on the left side.

Gender and handedness effects

Gender differences in brain functions have been linked to differences in the cognitive functioning between the sexes. Sexual dimorphism of brain structures has often been observed ranging from differences in overall brain size, grey and white matter volumes, and to specific structures, such as the corpus callosum (Luders & Toga, 2010). For example, several neuroanatomical studies have reported larger callosal areas (Beaulieu, 2009; Liu, Buckner, et al., 2009; Westerhausen et al., 2004) or enhanced white matter integrity (Takeuchi et al., 2010; Westerhausen et al., 2011; Westerhausen et al., 2004) in men compared to women. However, gender effects on callosal size depend largely on the method which is applied to correct for brain size. That is, comparisons based on the ratio between callosal size and brain size result in larger areas in females, while no significant results are observed when brain size is added as a covariate into the analysis (Chance et al., 2006; Liu, Buckner, et al., 2009). It has been suggested that smaller brains tend to have relatively larger corpora callosa than larger brains, which could explain the observed gender effects (Jancke, Staiger, et al., 1997). Concordant with previous studies (Hasan, Ewing-Cobbs, Kramer, Fletcher, & Narayana, 2008; Luders, Kurth, et al., 2012), I found no evidence for any gender effects on callosal macro- or microstructure. It is possible though, that the numbers of males and females included in my work were not sufficient to detect an effect, given that gender differences are usually relatively small compared to the whole variance in a population.

Whilst not consistent across all studies, several have indicated more pronounced functional and structural asymmetries in men compared to women, such as increased functional language dominance (McGlone, 1980), increased leftward asymmetry of the minicolumns and the grey matter density of the planum temporale (Chance et al., 2006; Good et al., 2001), and more pronounced arcuate fasciculus asymmetry (Catani et al., 2007; Hagmann et al., 2006; Thiebaut de Schotten et al., 2011). The more bilaterally distributed language network in females could explain the verbal advantage commonly attributed to them (Sommer et al., 2008). Two recent meta-analyses however failed to reveal consistent differences in functional and structural lateralization between the two sexes (Sommer, Aleman, Bouma, & Kahn, 2004; Sommer et al., 2008). In line with these findings, no gender effects on the functional cerebral asymmetries were observed in any of the three experiments in this thesis.

As discussed in the General Introduction, handedness effects on callosal morphology have widely been reported. However, it remains somewhat unknown whether handedness effects on callosal morphology are mainly due to the association between handedness and language dominance, or whether handedness has an effect on callosal morphology independent of the hemispheric specialization for language. Luders et al. (2010) found a negative correlation between strength of hand preference and callosal thickness, indicating that a lack of hand preference might be associated with enhanced interhemispheric information transfer. It is reasonable to assume that individuals with weak hand preferences might show superior performance in tasks requiring the simultaneous use of both hands. Also, individuals with superior bimanual coordination skills show higher FA in the callosal pathways connecting the SMAs of each hemisphere (Johansen-Berg et al., 2007), and patients with multiple sclerosis who show impairment in the control of bimanual finger opposition movements show significant reduction in the callosal white matter integrity (Bonzano et al., 2008). The degree of hand skill and preference might therefore directly influence interhemispheric communication.

On the other hand, individuals with less hand preference have also been shown to be more likely to have bilateral language distribution (Knecht, Drager, et al., 2000), which makes it difficult to disentangle differential effects of handedness and language dominance on interhemispheric communication. In Experiment 1, handedness inventory scores were added as a covariate, suggesting that the observed effects are due to the functional asymmetries for language and spatial processing and not asymmetry for hand motor control itself. However, the results in Experiment 2 indicate that callosal morphology might be largely influenced by a genetic predisposition for a certain hemispheric specialization. Based on the right-shift theory (Annett, 2002), which assumes a common origin of language dominance and hand preference, a distinction might not be meaningful. On the other hand, the relationship between hemispheric specialization for hand motor control and speech might also be explained by a two gene model (Corballis et al., 2012), where one gene affects language dominance and handedness and the other one handedness alone. Similarly, callosal morphology might be influenced only by the first but not the second gene, which might explain why callosal morphology is more closely related to language dominance than handedness itself.

Several neuroanatomical studies have also indicated an interaction between sex and handedness, such as enhanced rightward asymmetry of the planum parietale in right-handed males and left-handed females (Jancke, Schlaug, Huang, & Steinmetz, 1994), or a leftward asymmetry of the arcuate fasciculus, which was only evident in right-handed males but not in left-handers or females (Hagmann et al., 2006). Gender and handedness interactions might arise because they are influenced by the same factors, such as genotype and hormonal exposure. For example, Perrin et al. (2009) suggested that gender effects arise due to different maturational trajectories of white matter tracts, which originate from differential testosterone exposure. On this view, testosterone causes the axons to grow thicker, which alters the microstructural properties of the white matter tracts, also impacting the speed of information transfer. Based on the assumption that handedness and cerebral specialization are also influenced by testosterone, as suggested by Geschwind and Galaburda (1987), the structural connectivity in right- and left-handed males might be significantly different. In females, testosterone concentrations might not affect functional and structural lateralization to the same degree. This might explain why in Experiment 3, an effect of handedness on arcuate fasciculus asymmetry was only evident in males but not in females. That is, right-handed male twin pairs showed more leftward asymmetry in the FA values of the arcuate fasciculus than male twin pairs with discordant handedness, and the right-handed twin member of pairs with discordant handedness showed a more leftward asymmetric volume than his or her left-handed co-twin. In females, probably due to a lack of hormonal exposure, handedness and arcuate fasciculus asymmetry is not related. In both sexes though, the asymmetry of the white matter integrity of the arcuate fasciculus corresponded with the underlying functional language dominance patterns.

Limitations, implications and future research

In the next section, I will discuss 1) limitations that arise from the DTI methodology, 2) limitations due to the inclusion of twins, 3) implications of the laterality research, and 4) suggestions for future research.

DTI methodology

Diffusion tensor imaging has provided useful insight into the anatomy and microstructure of white matter tracts. However, the reconstruction and quantification of the white matter tracts is based on mathematical algorithms which draw inferences from the directional information provided by the random motion of water molecules. Thus, the accuracy of the DTI measurements also depends on the accuracy of the algorithms which are applied to extract the anatomical information. For example, the resolution of the DTI images is relatively coarse and does not allow visualization of single fibres. In addition, uncertainty about the exact course of fibre tracts is introduced through the existence of crossing fibres (Nowicka & Tacikowski, 2011).

Throughout this thesis, FA values were interpreted as a measure of fibre integrity and degree of connectivity between different regions. However, there is no direct relationship between the size of the FA values and any specific structural component, given that the degree of anisotropic diffusion is impacted by various factors, such as number of axons, axon density, axon size, packing and myelin thickness (Beaulieu, 2002). The efficacy of information transfer in white matter might be closely linked to the degree to which the fibres are myelinated. FA, even though it is modulated by the degree of myelination, does not correspond linearly to the amount of myelin in a certain tissue with the exact determinants being unknown (Beaulieu, 2002, 2009; Madler, Drabycz, Kolind, Whittall, & MacKay, 2008). Future studies assessing also other diffusion properties, such as mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) might provide further insight into the underlying microstructural components, given that those parameters provide additional information to the organization and myelination of the fibre tracts.

Twins

A large part of the current work is based on data from monozygotic twin pairs. However, the generalizability of findings in twins to non-twin populations might be inadequate given that twins might be subjected to unique prenatal and perinatal events. For example, more limited space and competition in utero, lower gestational age, and increased risk of birth complications are all factors which might affect brain development (Hulshoff Pol et al., 2002).

For example, twins show smaller white matter volumes compared to their siblings, whereas the grey matter volume might only be reduced in the second born twin (Hulshoff Pol et al., 2002). Most of these differences though seem to be related to the smaller intracranial volume observed in twins, so that the development of grey and white matter might still be similar in twins and singletons. A recent imaging study compared total brain volume, lobar volume and the area of the corpus callosum in a large set of twin pairs and unrelated singletons (Ordaz et al., 2010). Although there were significant differences in birth weight, gestational age, and IQ, brain structures in adult twins and non-twins did not differ, suggesting that the process of twinning itself does not affect the maturation and development of individual brain structures. Nevertheless, the possibility that twins might not be representative of the general population in all respects cannot be ruled out entirely.

The inclusion of twins allowed the possibility of drawing inferences about possible genetic and nongenetic sources for structural connectivity differences, given that all variability between twins of one pair must originate from a nongenetic source. However, by including not only monozygotic but also dizygotic twin pairs the amount of variance attributed to genetic and environmental factors could be estimated.

Implications and relevance of laterality research

The understanding of the normal variations in hemispheric specialization and its structural correlates is of considerable importance given that altered structural and functional asymmetries have been linked to various disorders such as schizophrenia (Crow, 1997), autism (Knaus et al., 2010), dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985) and developmental stuttering (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Foundas et al., 2003; Sommer, Koch, Paulus, Weiller, & Buchel, 2002). In the following section, the relevance of the understanding of hemispheric specialization and its structural correlates is illustrated using the example of schizophrenia.

According to a model proposed by Crow (1997), schizophrenia might result from a failure in the establishment of language dominance to one hemisphere. Psychotic symptoms such as the hearing of voices are explained by a failure to differentiate between internal thoughts, speech output, and speech received from others, which might originate from an incomplete lateralization of the phonological processing circuits (Crow, 2000).

Several neuroimaging studies have confirmed reduced functional language dominance and reduced planum temporale asymmetry in schizophrenics compared to controls (Artiges et al., 2000; Bleich-Cohen et al., 2012; Oertel et al., 2010; Sommer, Ramsey, Mandl, Van Oel, & Kahn, 2004) and this reduction in asymmetry measurements correlated with the severity of positive symptoms, such as auditory hallucinations (Oertel et al., 2010). In a post-mortem study, reduced neuronal density in both plana was observed (Simper et al., 2011), although the reduced lateralization and cell density have been contested by others (Shapleske, Rossell, Simmons, Davis, & Woodruff, 2001; Smiley et al., 2011).

Sommer, Ramsey, Mandl, Van Oel, and Kahn (2004) assessed functional language dominance with fMRI in a sample of monozygotic twin pairs discordant for the disease. Reduced functional lateralization was observed for the affected twin and his or her unaffected co-twin. A similar result was obtained by Oertel et al. (2010) who showed that individuals with a high genetic risk for schizophrenia show intermediary lateralization values between schizophrenics and healthy controls. The disruption of the language network might therefore constitute a genetic predisposition for the disease and thus, the same gene or epigenetic events coding for handedness and language dominance have also been implicated in schizophrenia (Annett, 1999; Crow, 2000, 2012).

Also contributing to the altered hemispheric dominance for language might be a dysfunction in the interhemispheric connectivity, as proposed by the disconnection hypothesis (Friston, 1998). For example, reduced functional connectivity between the left and right inferior frontal gyri (Bleich-Cohen et al., 2012) and lower white matter integrity in the corpora callosa of schizophrenics and individuals with high risks for schizophrenia have been reported (Henze et al., 2012; Knochel et al., 2012).

Several other neuroimaging studies, however, reported enhanced interhemispheric connectivity in schizophrenics compared to controls, at least in the callosal sections connecting the auditory regions (John, Shakeel, & Jain, 2008; Mulert et al., 2012). The discrepancy might be due to the large variety of schizophrenic symptoms. That is, a hyperconnectivity between the auditory cortices in each hemisphere might be only evident in schizophrenics who suffer from auditory hallucinations but not in schizophrenics without hallucinations or in healthy controls (Mulert et al., 2012). Altered microstructural properties of the arcuate fasciculus have also been implicated in auditory hallucinations (De Weijer et al., 2011; Hubl et al., 2004).

Taken together, even though some of the findings are heterogeneous, research suggests that alterations of the usual asymmetries in conjunction with altered structural and functional connectivity might play an important role in this disease. Identification of unusual asymmetries might therefore be crucial for early intervention strategies. On the other hand, variations of the usual asymmetries also exist in the healthy population. Why altered hemispheric specialization does not always result in detrimental consequences is unclear but might be related to compensatory cognitive strategies or different individual combinations between functional lateralization and structural components, such as neuronal density and connectivity. The structure-function relationships underlying cerebral specialization in healthy individuals is therefore important for the understanding of the neuronal basis of diseases such as schizophrenia.

Future research

In future studies, it will be important to assess the interaction of different lateralized cognitive functions and its impact on structural connectivity. For example, four independent lateralised networks have been identified, which are related to speech, internal thought, attention and vision (Liu, Stufflebeam, et al., 2009). The current work did predominantly assess hemispheric specialization for speech so that the influence of the three other lateralized networks on structural connectivity remains to be determined.

As discussed in the General Introduction, cerebral specialization might not be controlled by one gene alone given that the observed variability could also be explained by a two gene model (Corballis et al., 2012). Thus, the genetic basis of hemispheric specialization warrants further investigation and novel approaches, such as the assessment of asymmetric gene expression and its influence on structural and functional connectivity, might produce a more in-depths understanding of the development of hemispheric dominance and the risks associated with aberrations of the usual lateralization patterns.

Summary and conclusions

The main aim of my thesis was to assess the relationship between inter- and intrahemispheric connectivity and hemispheric specialization. To this end, the degree and direction of functional hemispheric asymmetries was established in each participant using fMRI, and individual lateralization patterns were associated with differences in structural connectivity of interhemispheric and intrahemispheric fibre tracts, i.e., corpus callosum and arcuate fasciculus, respectively.

With regards to intrahemispheric connectivity, a close relationship between the asymmetric distribution of the language network and the white matter integrity of the arcuate fibres was observed, suggesting that the core language regions in the dominant hemisphere are more heavily interconnected, probably due to the increased need for linguistic information transmission. This relationship even existed within monozygotic twin pairs, suggesting that the efficiency of the arcuate fibres is closely related to the expression of hemispheric dominance and might not be genetically controlled.

The relationship between interhemispheric connectivity and hemispheric specialization on the other hand was more complex, at least partly due to the fact that it is influenced not only by one but by various lateralizing influences. In short, a low connectivity pattern in the corpus callosum was associated with right-handedness and left-cerebral language dominance. On the other hand, atypical functional asymmetries, such as a right-sided language network or crowding of various functions to the same hemisphere were associated with a high connectivity pattern. From these findings the conclusion can be drawn that unusual hemispheric specialization relies on a high amount of information transfer between the hemispheres, whereas the typical lateralization pattern can be sustained by both a high and a low connectivity pattern.

In Experiment 2, the lowest connectivity pattern was found for twin pairs whose members were both right-handed and left-cerebrally dominant for language and did not have any left-handers in the immediate family. On the other hand, twin pairs discordant for handedness and / or language dominance showed a high connectivity pattern. Given that results only indicated a genetic source in the former but not the latter group, the view of a genetically controlled process of callosal pruning in individuals with the putative lateralizing allele is supported. However, the lateralizing allele has not been identified yet, so that this hypothesis remains tentative. Nevertheless, the role of the corpus callosum in the development of hemispheric specialization and its genetic basis warrants further investigation.

In conclusion, this thesis indicates that the maintenance of asymmetrically distributed cognitive functions relies on the asymmetric distribution of intrahemispheric networks favouring the dominant hemisphere. Interhemispheric connectivity, on the other hand, might play a key role in the development of hemispheric specialization, at least in certain genotypes, without being linearly related to the expression of the individual hemispheric dominance pattern.

Appendix A: Handedness Questionnaire

Name:..Age:.....................Sex:...........

Please indicate which hand you habitually use for each of the following activities by writing R (for right), L (for left), or E (for either).

Which hand do you use:

1. To write a letter legibly? ....
2. To throw a ball to hit a target? ....
3. To hold a racquet in tennis, squash, or badminton? ....
4. To hold a match when striking it? ....
5. To cut with scissors? ....
6. To guide a thread through the eye of a needle (or guide a needle onto thread)? ....
7. At the top of a broom while sweeping? ....
8. At the top of a shovel, e.g. when moving sand? ....
9. To deal playing cards? ....
10. To hammer a nail into wood? ....
11. To hold a toothbrush when cleaning your teeth? ....
12. To unscrew the lid of a jar? ....

Appendix B: Participant Information Sheet

Subject ID:____________________ **Name:** _________________________

DOB: _____________________ **Gender:** male female

Word Generation Task:

P	
R	
W	

Handedness Inventory

Score:_____________

Familial Sinistrality: No mother father sibling

Medical history:

• Premature birth	no	yes (week ___)	not known
• Birth weight	< 2kg	> 2kg	not known
• Perinatal complications	no	yes	
• Head injury	no	yes	
• Epilepsy	no	yes	
• Other neurological conditions	no	yes	

Appendix C: Zygosity Assessment

1. Do you and your twin look:
    a. Like two ordinary siblings? Yes / No
    b. Like two peas in a pod? Yes / No
    c. Not very much alike? Yes / No

2. In school, is / was it difficult for your teachers and friends to tell you apart?

    Yes / No

3. Is / was it difficult for your family and friends to tell you apart?

    Yes / No

4. In childhood, did you and your twin both have the same eye colour and the same hair colour?

    Yes / No

(Christiansen et al., 2003)

References

Aboitiz, F., Lopez, J., & Montiel, J. (2003). Long distance communication in the human brain: timing constraints for inter-hemispheric synchrony and the origin of brain lateralization. *Biological Research, 36*(1), 89-99. doi: 10.4067/S0716-97602003000100007

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992a). Fiber composition of the human corpus callosum. *Brain Research, 598*(1-2), 143-153. doi: 10.1016/0006-8993(92)90178-C

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992b). Individual differences in brain asymmetries and fiber composition in the human corpus callosum. *Brain Research, 598*(1-2), 154-161. doi: 10.1016/0006-8993(92)90179-D

Aboitiz, F., Scheibel, A. B., & Zaidel, E. (1992). Morphometry of the Sylvian fissure and the corpus callosum, with emphasis on sex differences. *Brain, 115*(5), 1521-1541. doi: 10.1093/brain/115.5.1521

Adcock, J. E., Wise, R. G., Oxbury, J. M., Oxbury, S. M., & Matthews, P. M. (2003). Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. *NeuroImage, 18*(2), 423-438. doi: 10.1016/S1053-8119(02)00013-7

Afifi, M. (2007). Gender differences in mental health. *Singapore Medical Journal, 48*(5), 385-391. doi: Retrieved from *http://smj.sma.org.sg/4805/4805ra1.pdf*

Alexander, D. C., Hubbard, P. L., Hall, M. G., Moore, E. A., Ptito, M., Parker, G. J., & Dyrby, T. B. (2010). Orientationally invariant indices of axon diameter and density from diffusion MRI. *NeuroImage, 52*(4), 1374-1389. doi: 10.1016/j.neuroimage.2010.05.043

Alexander, M. P., Fischette, M. R., & Fischer, R. S. (1989). Crossed Aphasias Can Be Mirror-Image or Anomalous - Case-Reports, Review and Hypothesis. *Brain : a journal of neurology, 112,* 953-973. doi: 10.1093/brain/112.4.953

Anderson, B., Southern, B. D., & Powers, R. E. (1999). Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 12*(4), 247-254. Retrieved from *http://www.ovid.com*

Annett, M. (1991). Laterality and cerebral dominance. *Journal of Child Psychology and Psychiatry, 32*(2), 219-232. doi: 10.1111/j.1469-7610.1991.tb00303.x

Annett, M. (1996). In defence of the right shift theory. *Perceptual and Motor Skills, 82*(1), 115-137. doi: 10.2466/pms.1996.82.1.115

Annett, M. (1998). Handedness and cerebral dominance: the right shift theory. *The Journal of Neuropsychiatry and Clinical Neurosciences, 10*(4), 459-469. doi: Retrieved from *http://www.psychiatryonline.org*

Annett, M. (1999). The theory of an agnosic right shift gene in schizophrenia and autism. *Schizophrenia Research, 39*(3), 177-182. doi: 10.1016/S0920-9964(99)00072-9

Annett, M. (2002). *Handedness and brain asymmetry: the right shift theory.* East Sussex BN3 2FA: Psychology Press.

Annett, M. (2003). Cerebral asymmetry in twins: predictions of the right shift theory. *Neuropsychologia, 41*(4), 469-479. doi: S0028393202001379

Annett, M. (2004). Hand preference observed in large healthy samples: classification, norms and interpretations of increased non-right-handedness by the right shift theory. *British Journal of Psychology, 95*(3), 339-353. doi: 10.1348/0007126041528130

Annett, M. (2009). The genetic basis of lateralization. In I. E. C. Sommer & R. S. Kahn (Eds.), *Language lateralization and psychosis* (pp. 73-86). Cambridge: Cambridge University Press.

Artiges, E., Martinot, J. L., Verdys, M., Attar-Levy, D., Mazoyer, B., Tzourio, N., . . . Paillere-Martinot, M. L. (2000). Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophrenia Bulletin, 26*(3), 709-721. doi: 10.1093/oxfordjournals.schbul.a033488

Ashtari, M., Cervellione, K. L., Hasan, K. M., Wu, J., McIlree, C., Kester, H., . . . Kumra, S. (2007). White matter development during late adolescence in healthy males: a cross-sectional diffusion tensor imaging study. *NeuroImage, 35*(2), 501-510. doi: 10.1016/j.neuroimage.2006.10.047

Baare, W. F., Hulshoff Pol, H. E., Boomsma, D. I., Posthuma, D., de Geus, E. J., Schnack, H. G., . . . Kahn, R. S. (2001). Quantitative genetic modeling of variation in human brain morphology. *Cerebral Cortex, 11*(9), 816-824. doi: 10.1093/cercor/11.9.816

Badzakova-Trajkov, G., Haberling, I. S., & Corballis, M. C. (2010). Cerebral asymmetries in monozygotic twins: an fMRI study. *Neuropsychologia, 48*(10), 3086-3093. doi: 10.1016/j.neuropsychologia.2010.06.020

Badzakova-Trajkov, G., Haberling, I. S., Roberts, R. P., & Corballis, M. C. (2010). Cerebral asymmetries: complementary and independent processes. *PloS one, 5*(3), e9682. doi: 10.1371/journal.pone.0009682

Bailey, L. M., & McKeever, W. F. (2004). A large-scale study of handedness and pregnancy/birth risk events: implications for genetic theories of handedness. *Laterality, 9*(2), 175-188. doi: 10.1080/13576500342000013

Bakan, P. (1971). Handedness and birth order. *Nature, 229*(5281), 195. doi: 10.1038/229195a0

Banich, M. T. (1995). Interhemispheric processing: Theoretical considerations and empirical approaches. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 427-450). Cambridge, MA.: MIT Press.

Barrick, T. R., Lawes, I. N., Mackay, C. E., & Clark, C. A. (2007). White matter pathway asymmetry underlies functional lateralization. *Cerebral Cortex, 17*(3), 591-598. doi: 10.1093/cercor/bhk004

Barrick, T. R., Mackay, C. E., Prima, S., Maes, F., Vandermeulen, D., Crow, T. J., & Roberts, N. (2005). Automatic analysis of cerebral asymmetry: an exploratory study of the relationship between brain torque and planum temporale asymmetry. *NeuroImage*, *24*(3), 678-691. doi: 10.1016/j.neuroimage.2004.09.003

Bartley, A. J., Jones, D. W., & Weinberger, D. R. (1997). Genetic variability of human brain size and cortical gyral patterns. *Brain, 120*(2), 257-269. doi: 10.1093/brain/120.2.257

Beaton, A. A. (2003). The nature and determinants of handedness. In K. Hugdahl & R. J. Davidson (Eds.), *The Asymmetrical Brain* (pp. 105-158). Cambridge, MA: MIT Press.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine, 15*(7-8), 435-455. doi: 10.1002/nbm.782

Beaulieu, C. (2009). The biological basis of diffusion anisotropy. In H. Johansen-Berg & T. E. Behrens (Eds.), *Diffusion MRI* (pp. 105-126). Amsterdam: Elsevier.

Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., . . . Smith, S. M. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic Resonance in Medicine, 50*(5), 1077-1088. doi: 10.1002/mrm.10609

Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., & Ullen, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nature Neuroscience, 8*(9), 1148-1150. doi: 10.1038/nn1516

Berker, E. A., Berker, A. H., & Smith, A. (1986). Translation of Broca's 1865 report: localization of speech in the third left frontal convolution. *Archives of Neurology, 42*(12), 1210-1212. doi: 10.1001/archneur.1986.00520100069017

Bernal, B., & Altman, N. (2010). The connectivity of the superior longitudinal fasciculus: a tractography DTI study. *Magnetic Resonance Imaging, 28*(2), 217-225. doi: 10.1016/j.mri.2009.07.008

Bleich-Cohen, M., Sharon, H., Weizman, R., Poyurovsky, M., Faragian, S., & Hendler, T. (2012). Diminished language lateralization in schizophrenia corresponds to impaired inter-hemispheric functional connectivity. *Schizophrenia Research, 134*(2-3), 131-136. doi: 10.1016/j.schres.2011.10.011

Bloom, J. S., & Hynd, G. W. (2005). The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychology Review, 15*(2), 59-71. doi: 10.1007/s11065-005-6252-y

Bonzano, L., Tacchino, A., Roccatagliata, L., Abbruzzese, G., Mancardi, G. L., & Bove, M. (2008). Callosal contributions to simultaneous bimanual finger movements. *Journal of Neuroscience, 28*(12), 3227-3233. doi: 10.1523/Jneurosci.4076-07.2008

Bourne, V. J. (2008). Examining the relationship between degree of handedness and degree of cerebral lateralization for processing facial emotion. *Neuropsychology, 22*(3), 350-356. doi: 10.1037/0894-4105.22.3.350

Breier, J. I., Hasan, K. M., Zhang, W., Men, D., & Papanicolaou, A. C. (2008). Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. *American Journal of Neuroradiology, 29*(3), 483-487. doi: 10.3174/ajnr.A0846

Bryden, M. P., Hecaen, H., & DeAgostini, M. (1983). Patterns of cerebral organization. *Brain and Language, 20*(2), 249-262. doi: 10.1016/0093-934X(83)90044-5

Bryden, P. J., Bruyn, J., & Fletcher, P. (2005). Handedness and health: an examination of the association between different handedness classifications and health disorders. *Laterality, 10*(5), 429-440. doi: 10.1080/13576500442000193

Buchel, C., Raedler, T., Sommer, M., Sach, M., Weiller, C., & Koch, M. A. (2004). White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cerebral Cortex, 14*(9), 945-951. doi: 10.1093/cercor/bhh055

Carter-Saltzman, L., Scarr-Salapatek, S., Barker, W. B., & Katz, S. (1976). Left-handedness in twins: incidence and patterns of performance in an adolescent sample. *Behavior Genetics, 6*(2), 189-203. doi: 10.1007/BF01067148

Catani, M., Allin, M. P., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., & Jones, D. K. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America, 104*(43), 17163-17168. doi: 10.1073/pnas.0702116104

Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*(1), 8-16. doi: 10.1002/ana.20319

Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex, 44*(8), 1105-1132. doi: 10.1016/j.cortex.2008.05.004

Chance, S. A., Casanova, M. F., Switala, A. E., & Crow, T. J. (2006). Minicolumnar structure in Heschl's gyrus and planum temporale: Asymmetries in relation to sex and callosal fiber number. *Neuroscience, 143*(4), 1041-1050. doi: 10.1016/j.neuroscience.2006.08.057

Chang, E. F., Wang, D. D., Perry, D. W., Barbaro, N. M., & Berger, M. S. (2011). Homotopic organization of essential language sites in right and bilateral cerebral hemispheric dominance. *Journal of Neurosurgery, 114*(4), 893-902. doi: 10.3171/2010.11.JNS10888

Chang, S. E., Erickson, K. I., Ambrose, N. G., Hasegawa-Johnson, M. A., & Ludlow, C. L. (2008). Brain anatomy differences in childhood stuttering. *NeuroImage, 39*(3), 1333-1344. doi: 10.1016/j.neuroimage.2007.09.067

Chao, Y. P., Cho, K. H., Yeh, C. H., Chou, K. H., Chen, J. H., & Lin, C. P. (2009). Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. *Human Brain Mapping, 30*(10), 3172-3187. doi: 10.1002/hbm.20739

Chepuri, N. B., Yen, Y. F., Burdette, J. H., Li, H., Moody, D. M., & Maldjian, J. A. (2002). Diffusion anisotropy in the corpus callosum. *American Journal of Neuroradiology, 23*(5), 803-808. Retrieved from: *http://www.ajnr.org/*

Chi, J. G., Dooling, E. C., & Gilles, F. H. (1977). Left-right asymmetries of the temporal speech areas of the human fetus. *Archives of Neurology, 34*(6), 346-348. doi: 10.1001/archneur.1977.00500180040008

Chiang, M. C., Barysheva, M., Shattuck, D. W., Lee, A. D., Madsen, S. K., Avedissian, C., . . . Thompson, P. M. (2009). Genetics of brain fiber architecture and intellectual performance. *Journal of Neuroscience, 29*(7), 2212-2224. doi: 10.1523/JNEUROSCI.4184-08.2009

Chiang, M. C., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Hickie, I., Toga, A. W., . . . Thompson, P. M. (2011). Genetics of white matter development: a DTI study of 705 twins and their siblings aged 12 to 29. *NeuroImage, 54*(3), 2308-2317. doi: 10.1016/j.neuroimage.2010.10.015

Christiansen, L., Frederiksen, H., Schousboe, K., Skytthe, A., von Wurmb-Schwark, N., Christensen, K., & Kyvik, K. (2003). Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Research, 6*(4), 275-278. doi: 10.1375/136905203322296610

Christman, S. D., & Propper, R. E. (2001). Superior episodic memory is associated with interhemispheric processing. *Neuropsychology, 15*(4), 607-616. doi: 10.1037/0894-4105.15.4.607

Clarke, J. M., & Zaidel, E. (1994). Anatomical-behavioral relationships: corpus callosum morphometry and hemispheric specialization. *Behavioural Brain Research, 64*(1-2), 185-202. doi: 10.1016/0166-4328(94)90131-7

Conner, C. R., Ellmore, T. M., DiSano, M. A., Pieters, T. A., Potter, A. W., & Tandon, N. (2011). Anatomic and electro-physiologic connectivity of the language system: a combined DTI-CCEP study. *Computers in Biology and Medicine, 41*(12), 1100-1109. doi: 10.1016/j.compbiomed.2011.07.008

Cook, N. D. (1984a). Callosal inhibition: the key to the brain code. *Behavioral Science, 29*(2), 98-110. doi: 10.1002/bs.3830290203

Cook, N. D. (1984b). Homotopic callosal inhibition. *Brain and Language, 23*(1), 116-125. doi: 10.1016/0093-934X(84)90010-5

Corballis, M. C. (1993). *The Lopsided Ape*. New York: Oxford University Press.

Corballis, M. C. (1997). Mental rotation and the right hemisphere. *Brain and Language, 57*(1), 100-121. doi: 10.1006/brln.1997.1835

Corballis, M. C. (2003). From mouth to hand: gesture, speech, and the evolution of right-handedness. *The Behavioral and brain sciences, 26*(2), 199-208. doi: 10.1017/S0140525X03000062

Corballis, M. C. (2009). The evolution and genetics of cerebral asymmetry. *Philosophical Transactions of the Royal Society. B, Biological Sciences, 364*(1519), 867-879. doi: 10.1098/rstb.2008.0232

Corballis, M. C. (2012). Lateralization of the human brain. *Progress in Brain Research, 195*, 103-120. doi: 10.1016/B978-0-444-53860-4.00006-4

Corballis, M. C., Badzakova-Trajkov, G., & Haberling, I. S. (2012). Right hand, left brain: genetic and evolutionary bases of cerebral asymmetries for language and manual action. *Wiley Interdisciplinary Reviews: Cognitive Science, 3*(1), 1-17. doi: 10.1002/Wcs.158

Coren, S. (1995). Family Patterns in Handedness - Evidence for Indirect Inheritance Mediated by Birth Stress. *Behavior Genetics, 25*(6), 517-524. doi: 10.1007/BF02327575

Cornish, K. M. (1996). The geschwind and galaburda theory of cerebral lateralisation: an empirical evaluation of its assumptions. *Current Psychology, 15*(1), 68-76. doi: 10.1007/BF02686935

Crow, T. J. (1997). Schizophrenia as failure of hemispheric dominance for language. *Trends in Neurosciences, 20*(8), 339-343. doi: 10.1016/S0166-2236(97)01071-0

Crow, T. J. (2000). Schizophrenia as the price that Homo sapiens pays for language: a resolution of the central paradox in the origin of the species. *Brain Research Reviews, 31*(2-3), 118-129. doi: 10.1016/S0165-0173(99)00029-6

Crow, T. J. (2010). A theory of the origin of cerebral asymmetry: Epigenetic variation superimposed on a fixed right-shift. *Laterality, 15*(3), 289-303. doi: 10.1080/13576500902734900

Crow, T. J. (2012). Schizophrenia as variation in the sapiens-specific epigenetic instruction to the embryo. *Clinical Genetics, 81*(4), 319-324. doi: 10.1111/j.1399-0004.2012.01830.x

Davatzikos, C., & Resnick, S. M. (1998). Sex differences in anatomic measures of interhemispheric connectivity: correlations with cognition in women but not men. *Cerebral Cortex, 8*(7), 635-640. doi: 10.1093/cercor/8.7.635

Davis, S. W., Kragel, J. E., Madden, D. J., & Cabeza, R. (2012). The architecture of cross-hemispheric communication in the aging brain: linking behavior to functional and structural connectivity. *Cerebral Cortex, 22*(1), 232-242. doi: 10.1093/cercor/bhr123

De Schotten, M. T., Dell'Acqua, F., Valabregue, R., & Catani, M. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex, 48*(1), 82-96. doi: 10.1016/j.cortex.2011.10.001

De Weijer, A. D., Mandl, R. C. W., Diederen, K. M. J., Neggers, S. F. W., Kahn, R. S., Pol, H. E. H., & Sommer, I. E. C. (2011). Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. *Schizophrenia Research, 130*(1-3), 68-77. doi: 10.1016/j.schres.2011.05.010

Dehaene-Lambertz, G. (2000). Cerebral specialization for speech and non-speech stimuli in infants. *Journal of Cognitive Neuroscience, 12*(3), 449-460. doi: 10.1162/089892900562264

Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional neuroimaging of speech perception in infants. *Science, 298*(5600), 2013-2015. doi: 10.1126/science.1077066

Dehaene-Lambertz, G., Hertz-Pannier, L., & Dubois, J. (2006). Nature and nurture in language acquisition: anatomical and functional brain-imaging studies in infants. *Trends in Neurosciences, 29*(7), 367-373. doi: 10.1016/j.tins.2006.05.011

Di Virgilio, G., & Clarke, S. (1997). Direct interhemispheric visual input to human speech areas. *Human Brain Mapping, 5*(5), 347-354. doi: 10.1002/(SICI)1097-0193(1997)5:5<347::AID-HBM3>3.0.CO;2-3

Dorion, A. A., Chantome, M., Hasboun, D., Zouaoui, A., Marsault, C., Capron, C., & Duyme, M. (2000). Hemispheric asymmetry and corpus callosum morphometry: a magnetic resonance imaging study. *Neuroscience Research, 36*(1), 9-13. doi: 10.1016/S0168-0102(99)00102-9

Doron, K. W., & Gazzaniga, M. S. (2008). Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication. *Cortex, 44*(8), 1023-1029. doi: 10.1016/j.cortex.2008.03.007

Dorsaint-Pierre, R., Penhune, V. B., Watkins, K. E., Neelin, P., Lerch, J. P., Bouffard, M., & Zatorre, R. J. (2006). Asymmetries of the planum temporale and Heschl's gyrus: relationship to language lateralization. *Brain, 129*(5), 1164-1176. doi: 10.1093/brain/awl055

Dos Santos Sequeira, S., Woerner, W., Walter, C., Kreuder, F., Lueken, U., Westerhausen, R., . . . Wittling, W. (2006). Handedness, dichotic-listening ear advantage, and gender effects on planum temporale asymmetry--a volumetric investigation using structural magnetic resonance imaging. *Neuropsychologia, 44*(4), 622-636. doi: 10.1016/j.neuropsychologia.2005.06.014

Drachman, D. A. (2005). Do we have brain to spare? *Neurology, 64*(12), 2004-2005. doi: 10.1212/01.WNL.0000166914.38327.BB

Dragovic, M., & Hammond, G. (2005). Handedness in schizophrenia: a quantitative review of evidence. *Acta Psychiatrica Scandinavica, 111*(6), 410-419. doi: 10.1111/j.1600-0447.2005.00519.x

Dubois, J., Hertz-Pannier, L., Cachia, A., Mangin, J. F., Le Bihan, D., & Dehaene-Lambertz, G. (2009). Structural asymmetries in the infant language and sensori-motor networks. *Cerebral Cortex, 19*(2), 414-423. doi: 10.1093/cercor/bhn097

Duffau, H., Leroy, M., & Gatignol, P. (2008). Cortico-subcortical organization of language networks in the right hemisphere: an electrostimulation study in left-handers. *Neuropsychologia, 46*(14), 3197-3209. doi: 10.1016/j.neuropsychologia.2008.07.017

Eckert, M. A., Leonard, C. M., Molloy, E. A., Blumenthal, J., Zijdenbos, A., & Giedd, J. N. (2002). The epigenesis of planum temporale asymmetry in twins. *Cerebral Cortex, 12*(7), 749-755. doi: 10.1093/cercor/12.7.749

Eckert, M. A., Leonard, C. M., Possing, E. T., & Binder, J. R. (2006). Uncoupled leftward asymmetries for planum morphology and functional language processing. *Brain and Language, 98*(1), 102-111. doi: 10.1016/j.bandl.2006.04.002

Ellis, S. J., Ellis, P. J., Marshall, E., Windridge, C., & Jones, S. (1998). Is forced dextrality an explanation for the fall in the prevalence of sinistrality with age? A study in northern England. *Journal of Epidemiology and Community Health, 52*(1), 41-44. doi: 10.1136/jech.52.1.41

Ellmore, T. M., Beauchamp, M. S., Breier, J. I., Slater, J. D., Kalamangalam, G. P., O'Neill, T. J., . . . Tandon, N. (2010). Temporal lobe white matter asymmetry and language laterality in epilepsy patients. *NeuroImage, 49*(3), 2033-2044. doi: 10.1016/j.neuroimage.2009.10.055

Eluvathingal, T. J., Hasan, K. M., Kramer, L., Fletcher, J. M., & Ewing-Cobbs, L. (2007). Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. *Cerebral Cortex, 17*(12), 2760-2768. doi: 10.1093/cercor/bhm003

Fame, R. M., MacDonald, J. L., & Macklis, J. D. (2011). Development, specification, and diversity of callosal projection neurons. *Trends in Neurosciences, 34*(1), 41-50. doi: 10.1016/j.tins.2010.10.002

Fernandez, G., Specht, K., Weis, S., Tendolkar, I., Reuber, M., Fell, J., . . . Elger, C. E. (2003). Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. *Neurology, 60*(6), 969-975. doi: 10.1212/01.WNL.0000049934.34209.2E

Fink, G. R., Marshall, J. C., Shah, N. J., Weiss, P. H., Halligan, P. W., Grosse-Ruyken, M., . . . Freund, H. J. (2000). Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology, 54*(6), 1324-1331. doi: 10.1212/WNL.54.6.1324

Floel, A., Knecht, S., Lohmann, H., Deppe, M., Sommer, J., Drager, B., . . . Henningsen, H. (2001). Language and spatial attention can lateralize to the same hemisphere in healthy humans. *Neurology, 57*(6), 1018-1024. doi: 10.1212/WNL.57.6.1018

Foundas, A. L., Corey, D. M., Angeles, V., Bollich, A. M., Crabtree-Hartman, E., & Heilman, K. M. (2003). Atypical cerebral laterality in adults with persistent developmental stuttering. *Neurology, 61*(10), 1378-1385. doi: 10.1212/01.WNL.0000094320.44334.86

Foundas, A. L., Eure, K. F., Luevano, L. F., & Weinberger, D. R. (1998). MRI asymmetries of Broca's area: the pars triangularis and pars opercularis. *Brain and Language, 64*(3), 282-296. doi: 10.1006/brln.1998.1974

Foundas, A. L., Leonard, C. M., Gilmore, R., Fennell, E., & Heilman, K. M. (1994). Planum temporale asymmetry and language dominance. *Neuropsychologia, 32*(10), 1225-1231. doi: 10.1016/0028-3932(94)90104-X

Foundas, A. L., Leonard, C. M., & Hanna-Pladdy, B. (2002). Variability in the anatomy of the planum temporale and posterior ascending ramus: Do right- and left handers differ? *Brain and Language, 83*(3), 403-424. doi: 10.1016/S0093-934X(02)00509-6

Francks, C., DeLisi, L. E., Fisher, S. E., Laval, S. H., Rue, J. E., Stein, J. F., & Monaco, A. P. (2003). Confirmatory evidence for linkage of relative hand skill to 2p12-q11. *American Journal of Human Genetics, 72*(2), 499-502. doi: 10.1086/367548

Francks, C., Fisher, S. E., MacPhie, I. L., Richardson, A. J., Marlow, A. J., Stein, J. F., & Monaco, A. P. (2002). A genomewide linkage screen for relative hand skill in sibling pairs. *American Journal of Human Genetics, 70*(3), 800-805. doi: 10.1086/339249

Francks, C., Maegawa, S., Lauren, J., Abrahams, B. S., Velayos-Baeza, A., Medland, S. E., . . . Monaco, A. P. (2007). LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular Psychiatry, 12*(12), 1129-1139. doi: 10.1038/sj.mp.4002053

Friederici, A. D. (2009). Pathways to language: fiber tracts in the human brain. *Trends in Cognitive Sciences, 13*(4), 175-181. doi: 10.1016/j.tics.2009.01.001

Friederici, A. D., von Cramon, D. Y., & Kotz, S. A. (2007). Role of the corpus callosum in speech comprehension: Interfacing syntax and prosody. *Neuron, 53*(1), 135-145. doi: 10.1016/j.neuron.2006.11.020

Friston, K. J. (1998). The disconnection hypothesis. *Schizophrenia Research, 30*(2), 115-125. doi: 10.1016/S0920-9964(97)00140-0

Galaburda, A. M., Rosen, G. D., & Sherman, G. F. (1990). Individual variability in cortical organization: its relationship to brain laterality and implications to function. *Neuropsychologia, 28*(6), 529-546. doi: 10.1016/0028-3932(90)90032-J

Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., & Geschwind, N. (1985). Developmental Dyslexia - 4 Consecutive Patients with Cortical Anomalies. *Annals of Neurology, 18*(2), 222-233. doi: 10.1002/ana.410180210

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? *Brain, 123*(7), 1293-1326. doi: 10.1093/brain/123.7.1293

Geschwind, D. H., Miller, B. L., DeCarli, C., & Carmelli, D. (2002). Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *Proceedings of the National Academy of Sciences of the United States of America, 99*(5), 3176-3181. doi: 10.1073/pnas.052494999

Geschwind, N., & Galaburda, A. M. (1985a). Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of Neurology, 42*(5), 428-459. doi: 10.1001/archneur.1985.04060050026008

Geschwind, N., & Galaburda, A. M. (1985b). Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Archives of Neurology, 42*(6), 521-552. doi: 10.1001/archneur.1985.04060060019009

Geschwind, N., & Galaburda, A. M. (1985c). Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. *Archives of Neurology, 42*(7), 634-654. doi: 10.1001/archneur.1985.04060070024012

Geschwind, N., & Galaburda, A. M. (1987). *Cerebral lateralization*. Cambridge, MA: MIT Press.

Geschwind, N., & Levitsky, W. (1968). Human Brain - Left-Right Asymmetries in Temporal Speech Region. *Science, 161*(3837), 186-187. doi: 10.1126/science.161.3837.186

Gharabaghi, A., Kunath, F., Erb, M., Saur, R., Heckl, S., Tatagiba, M., . . . Karnath, H. O. (2009). Perisylvian white matter connectivity in the human right hemisphere. *BMC Neuroscience, 10*, 15. doi: 10.1186/1471-2202-10-15

Gilbert, A. N., & Wysocki, C. J. (1992). Hand preference and age in the United States. *Neuropsychologia, 30*(7), 601-608. doi: 10.1016/0028-3932(92)90065-T

Giorgio, A., Watkins, K. E., Douaud, G., James, A. C., James, S., De Stefano, N., . . . Johansen-Berg, H. (2008). Changes in white matter microstructure during adolescence. *NeuroImage, 39*(1), 52-61. doi: 10.1016/j.neuroimage.2007.07.043

Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex, 18*(11), 2471-2482. doi: 10.1093/cercor/bhn011

Good, C. D., Johnsrude, I., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage, 14*(3), 685-700. doi: 10.1006/nimg.2001.0857

Gootjes, L., Bouma, A., Van Strien, J. W., Van Schijndel, R., Barkhof, F., & Scheltens, P. (2006). Corpus callosum size correlates with asymmetric performance on a dichotic listening task in healthy aging but not in Alzheimer's disease. *Neuropsychologia, 44*(2), 208-217. doi: 10.1016/j.neuropsychologia.2005.05.002

Grimshaw, G. M., Bryden, M. P., & Finegan, J. (1995). Relations between prenatal testosterone and cerebral lateralization in children. *Neuropsychology, 9*(1), 68-79. doi: 10.1037/0894-4105.9.1.68

Grouios, G., Sakadami, N., Poderi, A., & Alevriadou, A. (1999). Excess of non-right handedness among individuals with intellectual disability: experimental evidence and possible explanations. *Journal of Intellectual Disability Research, 43,* 306-313. doi: 10.1046/j.1365-2788.1999.00217.x

Haberling, I. S., Badzakova-Trajkov, G., & Corballis, M. C. (2011). Callosal tracts and patterns of hemispheric dominance: a combined fMRI and DTI study. *NeuroImage, 54*(2), 779-786. doi: 10.1016/j.neuroimage.2010.09.072

Habib, M., Gayraud, D., Oliva, A., Regis, J., Salamon, G., & Khalil, R. (1991). Effects of handedness and sex on the morphology of the corpus callosum: a study with brain magnetic resonance imaging. *Brain and Cognition, 16*(1), 41-61. doi: 10.1016/0278-2626(91)90084-L

Habib, M., Robichon, F., Levrier, O., Khalil, R., & Salamon, G. (1995). Diverging Asymmetries of Temporo-Parietal Cortical Areas - a Reappraisal of Geschwind/Galaburda Theory. *Brain and Language, 48*(2), 238-258. doi: 10.1006/brln.1995.1011

Hagmann, P., Cammoun, L., Martuzzi, R., Maeder, P., Clarke, S., Thiran, J. P., & Meuli, R. (2006). Hand preference and sex shape the architecture of language networks. *Human Brain Mapping, 27*(10), 828-835. doi: 10.1002/hbm.20224

Halwani, G. F., Loui, P., Ruber, T., & Schlaug, G. (2011). Effects of practice and experience on the arcuate fasciculus: comparing singers, instrumentalists, and non-musicians. *Frontiers in Psychology, 2,* 156. doi: 10.3389/fpsyg.2011.00156

Hasan, K. M., Ewing-Cobbs, L., Kramer, L. A., Fletcher, J. M., & Narayana, P. A. (2008). Diffusion tensor quantification of the macrostructure and microstructure of human midsagittal corpus callosum across the lifespan. *NMR in Biomedicine, 21*(10), 1094-1101. doi: 10.1002/nbm.1286

Henze, R., Brunner, R., Thiemann, U., Parzer, P., Klein, J., Resch, F., & Stieltjes, B. (2012). White matter alterations in the corpus callosum of adolescents with first-admission schizophrenia. *Neuroscience Letters, 513*(2), 178-182. doi: 10.1016/j.neulet.2012.02.032

Herve, P. Y., Crivello, F., Perchey, G., Mazoyer, B., & Tzourio-Mazoyer, N. (2006). Handedness and cerebral anatomical asymmetries in young adult males. *NeuroImage, 29*(4), 1066-1079. doi: 10.1016/j.neuroimage.2005.08.031

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition, 92*(1-2), 67-99. doi: 10.1016/j.cognition.2003.10.011

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews. Neuroscience, 8*(5), 393-402. doi: 10.1038/nrn2113

Hines, M., Chiu, L., McAdams, L. A., Bentler, P. M., & Lipcamon, J. (1992). Cognition and the corpus callosum: verbal fluency, visuospatial ability, and language lateralization related to midsagittal surface areas of callosal subregions. *Behavioral Neuroscience, 106*(1), 3-14. doi: 10.1037/0735-7044.106.1.3

Hirnstein, M., Hausmann, M., & Gunturkun, O. (2008). The evolutionary origins of functional cerebral asymmetries in humans: does lateralization enhance parallel processing? *Behavioural Brain Research, 187*(2), 297-303. doi: 10.1016/j.bbr.2007.09.023

Hofer, S., & Frahm, J. (2006). Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *NeuroImage, 32*(3), 989-994. doi: 10.1016/j.neuroimage.2006.05.044

Hofer, S., Merboldt, K. D., Tammer, R., & Frahm, J. (2008). Rhesus monkey and human share a similar topography of the corpus callosum as revealed by diffusion tensor MRI in vivo. *Cerebral Cortex, 18*(5), 1079-1084. doi: 10.1093/cercor/bhm141

Huang, H., Zhang, J., Jiang, H., Wakana, S., Poetscher, L., Miller, M. I., . . . Mori, S. (2005). DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. *NeuroImage, 26*(1), 195-205. doi: 10.1016/j.neuroimage.2005.01.019

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., . . . Dierks, T. (2004). Pathways that make voices - White matter changes in auditory hallucinations. *Archives of General Psychiatry, 61*(7), 658-668. doi: 10.1001/archpsyc.61.7.658

Hugdahl, K. (2000). Lateralization of cognitive processes in the brain. *Acta Psychologica, 105*(2-3), 211-235. doi: 10.1016/S0001-6918(00)00062-7

Hulshoff Pol, H. E., Posthuma, D., Baare, W. F. C., De Geus, E. J. C., Schnack, H. G., van Haren, N. E. M., . . . Boomsma, D. I. (2002). Twin-singleton differences in brain structure using structural equation modelling. *Brain, 125*(2), 384-390. doi: 10.1093/brain/awf035

Hulshoff Pol, H. E., Schnack, H. G., Posthuma, D., Mandl, R. C., Baare, W. F., van Oel, C., . . . Kahn, R. S. (2006). Genetic contributions to human brain morphology and intelligence. *Journal of Neuroscience, 26*(40), 10235-10242. doi: 10.1523/JNEUROSCI.1312-06.2006

Hutsler, J., & Galuske, R. A. (2003). Hemispheric asymmetries in cerebral cortical networks. *Trends in Neurosciences, 26*(8), 429-435. doi: 10.1016/S0166-2236(03)00198-X

Innocenti, G. M., & Price, D. J. (2005). Exuberance in the development of cortical networks. *Nature Reviews. Neuroscience, 6*(12), 955-965. doi: 10.1038/nrn1790

Isaacs, K. L., Barr, W. B., Nelson, P. K., & Devinsky, O. (2006). Degree of handedness and cerebral dominance. *Neurology, 66*(12), 1855-1858. doi: 10.1212/01.wnl.0000219623.28769.74

Jancke, L., Schlaug, G., Huang, Y. X., & Steinmetz, H. (1994). Asymmetry of the Planum Parietale. *Neuroreport, 5*(9), 1161-1163. doi: 10.1097/00001756-199405000-00035

Jancke, L., Staiger, J. F., Schlaug, G., Huang, Y., & Steinmetz, H. (1997). The relationship between corpus callosum size and forebrain volume. *Cerebral Cortex, 7*(1), 48-56. doi: 10.1093/cercor/7.1.48

Jancke, L., & Steinmetz, H. (1993). Auditory Lateralization and Planum-Temporale Asymmetry. *Neuroreport, 5*(2), 169-172. doi: 10.1097/00001756-199311180-00019

Jancke, L., Wunderlich, G., Schlaug, G., & Steinmetz, H. (1997). A case of callosal agenesis with strong anatomical and functional asymmetries. *Neuropsychologia, 35*(10), 1389-1394. doi: 10.1016/S0028-3932(97)00068-7

Jansen, A., Floel, A., Deppe, M., van Randenborgh, J., Drager, B., Kanowski, M., & Knecht, S. (2004). Determining the hemispheric dominance of spatial attention: a comparison between fTCD and fMRI. *Human Brain Mapping, 23*(3), 168-180. doi: 10.1002/hbm.20055

Jansen, A., Floel, A., Menke, R., Kanowski, M., & Knecht, S. (2005). Dominance for language and spatial processing: limited capacity of a single hemisphere. *Neuroreport, 16*(9), 1017-1021. doi: 10.1097/00001756-200506210-00027

Jansen, A., Liuzzi, G., Deppe, M., Kanowski, M., Olschlager, C., Albers, J. M., . . . Knecht, S. (2010). Structural correlates of functional language dominance: a voxel-based morphometry study. *Journal of Neuroimaging, 20*(2), 148-156. doi: 10.1111/j.1552-6569.2009.00367.x

Jansen, A., Menke, R., Sommer, J., Forster, A. F., Bruchmann, S., Hempleman, J., . . . Knecht, S. (2006). The assessment of hemispheric lateralization in functional MRI--robustness and reproducibility. *NeuroImage, 33*(1), 204-217. doi: 10.1016/j.neuroimage.2006.06.019

Jarbo, K., Verstynen, T., & Schneider, W. (2012). In vivo quantification of global connectivity in the human corpus callosum. *NeuroImage, 59*(3), 1988-1996. doi: 10.1016/j.neuroimage.2011.09.056

Johansen-Berg, H., Della-Maggiore, V., Behrens, T. E., Smith, S. M., & Paus, T. (2007). Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *NeuroImage, 36* (Suppl 2), T16-21. doi: 10.1016/j.neuroimage.2007.03.041

John, J. P., Shakeel, M. K., & Jain, S. (2008). Corpus callosal area differences and gender dimorphism in neuroleptic-naive, recent-onset schizophrenia and healthy control subjects. *Schizophrenia Research, 103*(1-3), 11-21. doi: 10.1016/j.schres.2008.04.035

Josse, G., Kherif, F., Flandin, G., Seghier, M. L., & Price, C. J. (2009). Predicting Language Lateralization from Gray Matter. *Journal of Neuroscience, 29*(43), 13516-13523. doi: 10.1523/Jneurosci.1680-09.2009

Josse, G., Mazoyer, B., Crivello, F., & Tzourio-Mazoyer, N. (2003). Left planum temporale: an anatomical marker of left hemispheric specialization for language comprehension. *Brain research. Cognitive Brain Research, 18*(1), 1-14. doi: 10.1016/j.cogbrainres.2003.08.007

Josse, G., Seghier, M. L., Kherif, F., & Price, C. J. (2008). Explaining function with anatomy: language lateralization and corpus callosum size. *Journal of Neuroscience, 28*(52), 14132-14139. doi: 10.1523/JNEUROSCI.4383-08.2008

Kaplan, E., Naeser, M. A., Martin, P. I., Ho, M., Wang, Y., Baker, E., & Pascual-Leone, A. (2010). Horizontal portion of arcuate fasciculus fibers track to pars opercularis, not pars triangularis, in right and left hemispheres: a DTI study. *NeuroImage, 52*(2), 436-444. doi: 10.1016/j.neuroimage.2010.04.247

Karbe, H., Herholz, K., Halber, M., & Heiss, W. D. (1998). Collateral inhibition of transcallosal activity facilitates functional brain asymmetry. *Journal of Cerebral Blood Flow and Metabolism, 18*(10), 1157-1161. doi: 10.1097/00004647-199810000-00012

Karnath, H. O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature, 411*(6840), 950-953. doi: 10.1038/35082075

Kasprian, G., Langs, G., Brugger, P. C., Bittner, M., Weber, M., Arantes, M., & Prayer, D. (2011). The prenatal origin of hemispheric asymmetry: an in utero neuroimaging study. *Cerebral Cortex, 21*(5), 1076-1083. doi: 10.1093/cercor/bhq179

Keller, S. S., Crow, T., Foundas, A., Amunts, K., & Roberts, N. (2009). Broca's area: Nomenclature, anatomy, typology and asymmetry. *Brain and Language, 109*(1), 29-48. doi: 10.1016/j.bandl.2008.11.005

Keller, S. S., Highley, J. R., Garcia-Finana, M., Sluming, V., Rezaie, R., & Roberts, N. (2007). Sulcal variability, stereological measurement and asymmetry of Broca's area on MR images. *Journal of Anatomy, 211*(4), 534-555. doi: 10.1111/j.1469-7580.2007.00793.x

Keshavan, M. S., Diwadkar, V. A., DeBellis, M., Dick, E., Kotwal, R., Rosenberg, D. R., . . . Pettegrew, J. W. (2002). Development of the corpus callosum in childhood, adolescence and early adulthood. *Life Sciences, 70*(16), 1909-1922. doi: 10.1016/S0024-3205(02)01492-3

Knaus, T. A., Corey, D. M., Bollich, A. M., Lemen, L. C., & Foundas, A. L. (2007). Anatomical asymmetries of anterior perisylvian speech-language regions. *Cortex, 43*(4), 499-510. doi: 10.1016/S0010-9452(08)70244-2

Knaus, T. A., Silver, A. M., Kennedy, M., Lindgren, K. A., Dominick, K. C., Siegel, J., & Tager-Flusberg, H. (2010). Language laterality in autism spectrum disorder and typical controls: A functional, volumetric, and diffusion tensor MRI study. *Brain and Language, 112*(2), 113-120. doi: 10.1016/j.bandl.2009.11.005

Knecht, S., Deppe, M., Drager, B., Bobe, L., Lohmann, H., Ringelstein, E., & Henningsen, H. (2000). Language lateralization in healthy right-handers. *Brain, 123*(1), 74-81. doi: 10.1093/brain/123.1.74

Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., . . . Henningsen, H. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain, 123*(12), 2512-2518. doi: 10.1093/brain/123.12.2512

Knecht, S., Drager, B., Floel, A., Lohmann, H., Breitenstein, C., Deppe, M., . . . Ringelstein, E. B. (2001). Behavioural relevance of atypical language lateralization in healthy subjects. *Brain, 124*(8), 1657-1665. doi: 10.1093/brain/124.8.1657

Knecht, S., Floel, A., Drager, B., Breitenstein, C., Sommer, J., Henningsen, H., . . . Pascual-Leone, A. (2002). Degree of language lateralization determines susceptibility to unilateral brain lesions. *Nature Neuroscience, 5*(7), 695-699. doi: 10.1038/nn868

Knochel, C., Oertel-Knochel, V., Schonmeyer, R., Rotarska-Jagiela, A., van de Ven, V., Prvulovic, D., . . . Linden, D. E. J. (2012). Interhemispheric hypoconnectivity in schizophrenia: Fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. *NeuroImage, 59*(2), 926-934. doi: 10.1016/j.neuroimage.2011.07.088

Kochunov, P., Lancaster, J., Thompson, P., Toga, A. W., Brewer, P., Hardies, J., & Fox, P. (2002). An optimized individual target brain in the Talairach coordinate system. *NeuroImage, 17*(2), 922-927. doi: 10.1006/nimg.2002.1084

Laland, K. N., Kumm, J., Van Horn, J. D., & Feldman, M. W. (1995). A gene-culture model of human handedness. *Behavior Genetics, 25*(5), 433-445. doi: 10.1007/BF02253372

LaMantia, A. S., & Rakic, P. (1990a). Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. *Journal of Neuroscience, 10*(7), 2156-2175. Retrieved from *www.jneurosci.org*

LaMantia, A. S., & Rakic, P. (1990b). Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. *The Journal of Comparative Neurology, 291*(4), 520-537. doi: 10.1002/cne.902910404

Lebel, C., & Beaulieu, C. (2009). Lateralization of the arcuate fasciculus from childhood to adulthood and its relation to cognitive abilities in children. *Human Brain Mapping, 30*(11), 3563-3573. doi: 10.1002/hbm.20779

Lebel, C., Caverhill-Godkewitsch, S., & Beaulieu, C. (2010). Age-related regional variations of the corpus callosum identified by diffusion tensor tractography. *NeuroImage, 52*(1), 20-31. doi: 10.1016/j.neuroimage.2010.03.072

Lezak, M. D. (1995). *Neuropsychological assessment.* New York: Oxford University Press.

Lidzba, K., Staudt, M., Wilke, M., & Krageloh-Mann, I. (2006). Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: consequence of lesion or reorganization? *Neuropsychologia, 44*(7), 1088-1094. doi: 10.1016/j.neuropsychologia.2005.10.022

Liederman, J., Kantrowitz, L., & Flannery, K. (2005). Male vulnerability to reading disability is not likely to be a myth: a call for new data. *Journal of Learning Disabilities, 38*(2), 109-129. doi: 10.1177/00222194050380020201

Liu, H. S., Buckner, R. L., Talukdar, T., Tanaka, N., Madsen, J. R., & Stufflebeam, S. M. (2009). Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity Laboratory investigation. *Journal of Neurosurgery, 111*(4), 746-754. doi: 10.3171/2008.10.Jns08846

Liu, H. S., Stufflebeam, S. M., Sepulcre, J., Hedden, T., & Buckner, R. L. (2009). Evidence from intrinsic activity that asymmetry of the human brain is controlled by multiple factors. *Proceedings of the National Academy of Sciences of the United States of America, 106*(48), 20499-20503. doi: 10.1073/pnas.0908073106

Lovden, M., Bodammer, N. C., Kuhn, S., Kaufmann, J., Schutze, H., Tempelmann, C., . . . Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia, 48*(13), 3878-3883. doi: 10.1016/j.neuropsychologia.2010.08.026

Luders, E., Cherbuin, N., Thompson, P. M., Gutman, B., Anstey, K. J., Sachdev, P., & Toga, A. W. (2010). When more is less: associations between corpus callosum size and handedness lateralization. *NeuroImage, 52*(1), 43-49. doi: 10.1016/j.neuroimage.2010.04.016

Luders, E., Kurth, F., Mayer, E. A., Toga, A. W., Narr, K. L., & Gaser, C. (2012). The unique brainan atomy of meditation practitioners: alterations in cortical gyrification. *Frontiers in Human Neuroscience, 6*, 34. doi: 10.3389/fnhum.2012.00034

Luders, E., Phillips, O. R., Clark, K., Kurth, F., Toga, A. W., & Narr, K. L. (2012). Bridging the hemispheres in meditation: Thicker callosal regions and enhanced fractional anisotropy (FA) in long-term practitioners. *NeuroImage, 61*(1), 181-187. doi: 10.1016/j.neuroimage.2012.02.026

Luders, E., Thompson, P. M., & Toga, A. W. (2010). The development of the corpus callosum in the healthy human brain. *Journal of Neuroscience, 30*(33), 10985-10990. doi: 10.1523/JNEUROSCI.5122-09.2010

Luders, E., & Toga, A. W. (2010). Sex differences in brain anatomy. *Progress in Brain Research, 186*, 3-12. doi: 10.1016/B978-0-444-53630-3.00001-4

Lust, J. M., Geuze, R. H., Van de Beek, C., Cohen-Kettenis, P. T., Bouma, A., & Groothuis, T. G. (2011). Differential effects of prenatal testosterone on lateralization of handedness and language. *Neuropsychology, 25*(5), 581-589. doi: 10.1037/a0023293

Lust, J. M., Geuze, R. H., Van de Beek, C., Cohen-Kettenis, P. T., Groothuis, A. G., & Bouma, A. (2010). Sex specific effect of prenatal testosterone on language lateralization in children. *Neuropsychologia, 48*(2), 536-540. doi: 10.1016/j.neuropsychologia.2009.10.014

Lux, S., Keller, S., Mackay, C., Ebers, G., Marshall, J. C., Cherkas, L., . . . Gurd, J. M. (2008). Crossed cerebral lateralization for verbal and visuo-spatial function in a pair of handedness discordant monozygotic twins: MRI and fMRI brain imaging. *Journal of Anatomy, 212*(3), 235-248. doi: 10.1111/j.1469-7580.2008.00855.x

Madler, B., Drabycz, S. A., Kolind, S. H., Whittall, K. P., & MacKay, A. L. (2008). Is diffusion anisotropy an accurate monitor of myelination? Correlation of multicomponent T-2 relaxation and diffusion tensor anisotropy in human brain. *Magnetic Resonance Imaging, 26*(7), 874-888. doi: 10.1016/J.Mri.008.01.047

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage, 19*(3), 1233-1239. doi: 10.1016/S1053-8119(03)00169-1

Maldonado, I. L., Moritz-Gasser, S., & Duffau, H. (2011). Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study. *Brain Structure & Function, 216*(3), 263-274. doi: 10.1007/s00429-011-0309-x

Martino, J., De Witt Hamer, P. C., Berger, M. S., Lawton, M. T., Arnold, C. M., de Lucas, E. M., & Duffau, H. (2012). Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study. *Brain Structure & Function, Advance online publication*. doi: 10.1007/s00429-012-0386-5

Martino, J., De Witt Hamer, P. C., Vergani, F., Brogna, C., de Lucas, E. M., Vazquez-Barquero, A., . . . Duffau, H. (2011). Cortex-sparing fiber dissection: an improved method for the study of white matter anatomy in the human brain. *Journal of Anatomy, 219*(4), 531-541. doi: 10.1111/j.1469-7580.2011.01414.x

Matsumoto, R., Nair, D. R., LaPresto, E., Najm, I., Bingaman, W., Shibasaki, H., & Luders, H. O. (2004). Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain, 127*(10), 2316-2330. doi: 10.1093/brain/awh246

McGlone, J. (1980). Sex-Differences in Human-Brain Asymmetry - a Critical Survey. *Behavioral and Brain Sciences, 3*(2), 215-227. doi: 10.1017/S0140525X00004398

McManus, I. C. (1980). Handedness in twins: a critical review. *Neuropsychologia, 18*(3), 347-355. doi: 10.1016/0028-3932(80)90130-X

McManus, I. C. (1985a). Handedness, language dominance and aphasia: a genetic model. *Psychological Medicine. Monograph Supplement, 8*, 1-40. doi: 10.1017/S0264180100001879

McManus, I. C. (1985b). Right- and left-hand skill: failure of the right shift model. *British Journal of Psychology, 76*(1), 1-34. doi: 10.1111/j.2044-8295.1985.tb01926.x

McManus, I. C. (1995). Familial sinistrality: the utility of calculating exact genotype probabilities for individuals. *Cortex, 31*(1), 3-24. Retrieved from https://*www.ucl.ac.uk/medical-education/reprints/1995-Cortex-FamilialSinistrality.pdf*

McManus, I. C. (1999). Handedness, cerebral lateralization and the evolution of language. In M. C. Corballis & S. E. G. Lea (Eds.), *The descent of mind: Psychological perspectives on hominid evolution.* (pp. 194-217). Oxford: Oxford University Press.

McManus, I. C. (2002). *Right hand, left hand: the origins of asymmetry of brains, bodies, atoms and cultures.* Cambridge, MA, US: Harvard University Press.

McManus, I. C. (2010). Precisely wrong? The problems with the Jones and Martin genetic model of sex differences in handedness and language lateralisation. *Cortex, 46*(5), 700-702. doi: 10.1016/j.cortex.2009.08.008

McManus, I. C., & Bryden, M. P. (1992). The genetics of handedness, cerebral dominance and lateralization. In I. Rapin & S. J. Segalowitz (Eds.), *Handbook of neuropsychology* (Vol. 6, pp. 115-142). Amsterdam: Elsevier.

Medland, S. E., Duffy, D. L., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., . . . Boomsma, D. I. (2009). Genetic influences on handedness: data from 25,732 Australian and Dutch twin families. *Neuropsychologia, 47*(2), 330-337. doi: 10.1016/j.neuropsychologia.2008.09.005

Medland, S. E., Duffy, D. L., Wright, M. J., Geffen, G. M., & Martin, N. G. (2006). Handedness in twins: joint analysis of data from 35 samples. *Twin Research and Human Genetics, 9*(1), 46-53. doi: 10.1375/183242706776402885

Medland, S. E., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., Martin, N. G., & Duffy, D. L. (2003). Special twin environments, genetic influences and their effects on the handedness of twins and their siblings. *Twin Research, 6*(2), 119-130. doi: 10.1375/136905203321536245

Moffat, S. D., Hampson, E., & Lee, D. H. (1998). Morphology of the planum temporale and corpus callosum in left handers with evidence of left and right hemisphere speech representation. *Brain, 121*(12), 2369-2379. doi: 10.1093/brain/121.12.2369

Mulert, C., Kirsch, V., Whitford, T. J., Alvarado, J., Pelavin, P., McCarley, R. W., . . . Shenton, M. E. (2012). Hearing voices: A role of interhemispheric auditory connectivity? *World Journal of Biological Psychiatry, 13*(2), 153-158. doi: 10.3109/15622975.2011.570789

Nowicka, A., & Tacikowski, P. (2011). Transcallosal transfer of information and functional asymmetry of the human brain. *Laterality, 16*(1), 35-74. doi: 10.1080/13576500903154231

O'Kusky, J., Strauss, E., Kosaka, B., Wada, J., Li, D., Druhan, M., & Petrie, J. (1988). The corpus callosum is larger with right-hemisphere cerebral speech dominance. *Annals of Neurology, 24*(3), 379-383. doi: 10.1002/ana.410240305

Oertel, V., Knochel, C., Rotarska-Jagiela, A., Schonmeyer, R., Lindner, M., van de Ven, V., . . . Linden, D. E. J. (2010). Reduced Laterality as a Trait Marker of Schizophrenia-Evidence from Structural and Functional Neuroimaging. *Journal of Neuroscience, 30*(6), 2289-2299. doi: 10.1523/Jneurosci.4575-09.2010

Olivares, R., Michalland, S., & Aboitiz, F. (2000). Cross-species and intraspecies morphometric analysis of the corpus callosum. *Brain, Behavior and Evolution, 55*(1), 37-43. doi: 10.1159/000006640

Olivares, R., Montiel, J., & Aboitiz, F. (2001). Species differences and similarities in the fine structure of the mammalian corpus callosum. *Brain, Behavior and Evolution, 57*(2), 98-105. doi: 10.1159/000047229

Ordaz, S. J., Lenroot, R. K., Wallace, G. L., Clasen, L. S., Blumenthal, J. D., Schmitt, J. E., & Giedd, J. N. (2010). Are there differences in brain morphometry between twins and unrelated singletons? A pediatric MRI study. *Genes, Brain and Behavior*, *9*(3), 288-295. doi: 10.1111/j.1601-183X.2009.00558.x

Ota, M., Obata, T., Akine, Y., Ito, H., Ikehira, H., Asada, T., & Suhara, T. (2006). Age-related degeneration of corpus callosum measured with diffusion tensor imaging. *NeuroImage, 31*(4), 1445-1452. doi: 10.1016/j.neuroimage.2006.02.008

Papadatou-Pastou, M., Martin, M., Munafo, M. R., & Jones, G. V. (2008). Sex differences in left-handedness: A meta-analysis of 144 studies. *Psychological Bulletin, 134*(5), 677-699. doi: 10.1037/A0012814

Papoutsi, M., Stamatakis, E. A., Griffiths, J., Marslen-Wilson, W. D., & Tyler, L. K. (2011). Is left fronto-temporal connectivity essential for syntax? Effective connectivity, tractography and performance in left-hemisphere damaged patients. *NeuroImage, 58*(2), 656-664. doi: 10.1016/j.neuroimage.2011.06.036

Parker, G. J., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A., Ciccarelli, O., & Lambon Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage, 24*(3), 656-666. doi: 10.1016/j.neuroimage.2004.08.047

Paul, L. K., Brown, W. S., Adolphs, R., Tyszka, J. M., Richards, L. J., Mukherjee, P., & Sherr, E. H. (2007). Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nature Reviews Neuroscience, 8*(4), 287-299. doi: 10.1038/Nrn2107

Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., . . . Evans, A. C. (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science, 283*(5409), 1908-1911. doi: 10.1126/science.283.5409.1908

Pelletier, I., Paquette, N., Lepore, F., Rouleau, I., Sauerwein, C. H., Rosa, C., . . . Lassonde, M. (2011). Language lateralization in individuals with callosal agenesis: an fMRI study. *Neuropsychologia, 49*(7), 1987-1995. doi: 10.1016/j.neuropsychologia.2011.03.028

Penhune, V. B., Zatorre, R. J., MacDonald, J. D., & Evans, A. C. (1996). Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. *Cerebral Cortex, 6*(5), 661-672. doi: 10.1093/cercor/6.5.661

Perrin, J. S., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., Richer, L., . . . Paus, T. (2009). Sex differences in the growth of white matter during adolescence. *NeuroImage, 45*(4), 1055-1066. doi: 10.1016/j.neuroimage.2009.01.023

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M., & Buckner, R. L. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex, 16*(7), 907-915. doi: 10.1093/cercor/bhj036

Pfannkuche, K. A., Bouma, A., & Groothuis, T. G. (2009). Does testosterone affect lateralization of brain and behaviour? A meta-analysis in humans and other animal species. *Philosophical transactions of the Royal Society of London. B, Biological Sciences, 364*(1519), 929-942. doi: 10.1098/rstb.2008.0282

Pfefferbaum, A., Sullivan, E. V., & Carmelli, D. (2004). Morphological changes in aging brain structures are differentially affected by time-linked environmental influences despite strong genetic stability. *Neurobiology of Aging, 25*(2), 175-183. doi: 10.1016/S0197-4580(03)00045-9

Pfefferbaum, A., Sullivan, E. V., Swan, G. E., & Carmelli, D. (2000). Brain structure in men remains highly heritable in the seventh and eighth decades of life. *Neurobiology of Aging, 21*(1), 63-74. doi: 10.1016/S0197-4580(00)00086-5

Phillips, O. R., Clark, K. A., Woods, R. P., Subotnik, K. L., Asarnow, R. F., Nuechterlein, K. H., . . . Narr, K. L. (2011). Topographical relationships between arcuate fasciculus connectivity and cortical thickness. *Human Brain Mapping, 32*(11), 1788-1801. doi: 10.1002/hbm.21147

Poffenberger, A. T. (1912). *Reaction time to retinal stimulation with special reference to the time lost in conduction through nerve centers.* New York: The Science Press.

Porac, C. (1981). *Lateral Preferences and Human Behavior*. New York: Springer-Verlag.

Porter, J. N., Collins, P. F., Muetzel, R. L., Lim, K. O., & Luciana, M. (2011). Associations between cortical thickness and verbal fluency in childhood, adolescence, and young adulthood. *NeuroImage, 55*(4), 1865-1877. doi: 10.1016/j.neuroimage.2011.01.018

Powell, H. W., Parker, G. J., Alexander, D. C., Symms, M. R., Boulby, P. A., Wheeler-Kingshott, C. A., . . . Duncan, J. S. (2006). Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. *NeuroImage, 32*(1), 388-399. doi: 10.1016/j.neuroimage.2006.03.011

Powell, J. L., Kemp, G. J., & Garcia-Finana, M. (2012). Association between language and spatial laterality and cognitive ability: an fMRI study. *NeuroImage, 59*(2), 1818-1829. doi: 10.1016/j.neuroimage.2011.08.040

Powell, J. L., Parkes, L., Kemp, G. J., Sluming, V., Barrick, T. R., & Garcia-Finana, M. (2012). The effect of sex and handedness on white matter anisotropy: a diffusion-tensor magnetic resonance imaging study. *Neuroscience*. doi: 10.1016/j.neuroscience.2012.01.016

Preuss, U. W., Meisenzahl, E. M., Frodl, T., Zetzsche, T., Holder, J., Leinsinger, G., . . . Moller, H. J. (2002). Handedness and corpus callosum morphology. *Psychiatry Research, 116*(1-2), 33-42. doi: 10.1016/S0925-4927(02)00064-1

Previc, F. H. (1991). A general theory concerning the prenatal origins of cerebral lateralization in humans. *Psychological Review, 98*(3), 299-334. doi: 10.1037/0033-295X.98.3.299

Propper, R. E., O'Donnell, L. J., Whalen, S., Tie, Y., Norton, I. H., Suarez, R. O., . . . Golby, A. J. (2010). A combined fMRI and DTI examination of functional language lateralization and arcuate fasciculus structure: Effects of degree versus direction of hand preference. *Brain and Cognition, 73*(2), 85-92. doi: 10.1016/j.bandc.2010.03.004

Pujol, J., Deus, J., Losilla, J. M., & Capdevila, A. (1999). Cerebral lateralization of language in normal left-handed people studied by functional MRI. *Neurology, 52*(5), 1038-1043. doi: 10.1212/WNL.52.5.1038

Pujol, J., Lopez-Sala, A., Deus, J., Cardoner, N., Sebastian-Galles, N., Conesa, G., & Capdevila, A. (2002). The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging. *NeuroImage, 17*(2), 670-679. doi: 10.1106/nimg.2002.1203

Putnam, M. C., Wig, G. S., Grafton, S. T., Kelley, W. M., & Gazzaniga, M. S. (2008). Structural organization of the corpus callosum predicts the extent and impact of cortical activity in the nondominant hemisphere. *Journal of Neuroscience, 28*(11), 2912-2918. doi: 10.1523/JNEUROSCI.2295-07.2008

Qiu, D., Tan, L. H., Siok, W. T., Zhou, K., & Khong, P. L. (2011). Lateralization of the arcuate fasciculus and its differential correlation with reading ability between young learners and experienced readers: a diffusion tensor tractography study in a Chinese cohort. *Human Brain Mapping, 32*(12), 2054-2063. doi: 10.1002/hbm.21168

Rajagopalan, V., Scott, J., Habas, P. A., Kim, K., Corbett-Detig, J., Rousseau, F., . . . Studholme, C. (2011). Local Tissue Growth Patterns Underlying Normal Fetal Human Brain Gyrification Quantified In Utero. *Journal of Neuroscience, 31*(8), 2878-2887. doi: 10.1523/Jneurosci.5458-10.2011

Ramadhani, M. K., Koomen, I., Grobbee, D. E., van Donselaar, C. A., van Furth, A. M., & Uiterwaal, C. S. P. M. (2006). Increased occurrence of left-handedness after severe childhood bacterial meningitis: Support for the pathological left-handedness hypothesis. *Neuropsychologia, 44*(12), 2526-2532. doi: 10.1016/j.neuropsychosis.2006.03.026

Rasmussen, T., & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences, 299*, 355-369. doi: 10.1111/j.1749-6632.1977.tb41921.x

Reiss, M., Tymnik, G., Kogler, P., Kogler, W., & Reiss, G. (1999). Laterality of hand, foot, eye, and ear in twins. *Laterality, 4*(3), 287-297. doi: 10.1080/713754337

Rilling, J. K., Glasser, M. F., Preuss, T. M., Ma, X., Zhao, T., Hu, X., & Behrens, T. E. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nature Neuroscience, 11*(4), 426-428. doi: 10.1038/nn2072

Ringo, J. L., Doty, R. W., Demeter, S., & Simard, P. Y. (1994). Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay. *Cerebral Cortex, 4*(4), 331-343. doi: 10.1093/cercor/4.4.331

Rodrigo, S., Oppenheim, C., Chassoux, F., Hodel, J., de Vanssay, A., Baudoin-Chial, S., . . . Meder, J. F. (2008). Language lateralization in temporal lobe epilepsy using functional MRI and probabilistic tractography. *Epilepsia, 49*(8), 1367-1376. doi: 10.1111/j.1528-1167.2008.01607.x

Ross, D. C., Jaffe, J., Collins, R. L., Page, W., & Robinette, D. (1999). Handedness in the NAS/NRC twin study. *Laterality, 4*(3), 257-264. doi: 10.1080/713754342

Scamvougeras, A., Kigar, D. L., Jones, D., Weinberger, D. R., & Witelson, S. F. (2003). Size of the human corpus callosum is genetically determined: an MRI study in mono and dizygotic twins. *Neuroscience Letters, 338*(2), 91-94. doi: 10.1016/S0304-3940(02)01333-2

Schlaug, G., Jancke, L., Huang, Y. X., Staiger, J. F., & Steinmetz, H. (1995). Increased corpus callosum size in musicians. *Neuropsychologia, 33*(8), 1047-&. doi: 10.1016/0028-3932(95)00045-5

Schlegel, A. A., Rudelson, J. J., & Tse, P. U. (2012). White matter structure changes as adults learn a second language. *Journal of Cognitive Neuroscience, 24*(8), 1664-1670. doi: 10.1162/jocn_a_00240

Schulte, T., Sullivan, E. V., Muller-Oehring, E. M., Adalsteinsson, E., & Pfefferbaum, A. (2005). Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cerebral Cortex, 15*(9), 1384-1392. doi: 10.1093/cercor/bhi020

Shapleske, J., Rossell, S. L., Simmons, A., Davis, A. S., & Woodruff, P. W. R. (2001). Are auditory hallucinations the consequence of abnormal cerebral lateralization? A morphometric MRI study of the fissure and planum temporale. *Biological Psychiatry, 49*(8), 685-693. doi: 10.1016/S0006-3223(00)01006-4

Shapleske, J., Rossell, S. L., Woodruff, P. W., & David, A. S. (1999). The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain research. Brain Research Reviews, 29*(1), 26-49. doi: 10.1016/S0165-0173(98)00047-2

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., . . . et al. (1995). Sex differences in the functional organization of the brain for language. *Nature, 373*(6515), 607-609. doi: 10.1038/373607a0

Sicotte, N. L., Woods, R. P., & Mazziotta, J. C. (1999). Handedness in twins: a meta-analysis. *Laterality, 4*(3), 265-286. doi: 10.1080/713754339

Silva, D. A., & Satz, P. (1979). Pathological Left-Handedness - Evaluation of a Model. *Brain and language, 7*(1), 8-16. doi: 10.1016/0093-934X(79)90002-6

Simper, R., Walker, M. A., Black, G., Di Rosa, E., Crow, T. J., & Chance, S. A. (2011). The relationship between callosal axons and cortical neurons in the planum temporale: alterations in schizophrenia. *Neuroscience Research, 71*(4), 405-410. doi: 10.1016/j.neures.2011.08.007

Smiley, J. F., Rosoklija, G., Mancevski, B., Pergolizzi, D., Figarsky, K., Bleiwas, C., . . . Dwork, A. J. (2011). Hemispheric comparisons of neuron density in the planum temporale of schizophrenia and nonpsychiatric brains. *Psychiatry Research-Neuroimaging, 192*(1), 1-11. doi: 10.1016/j.pscychresns.2010.11.007

Smith, S. M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P. M., Federico, A., & De Stefano, N. (2002). Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *NeuroImage, 17*(1), 479-489. doi: 10.1006/nimg.2002.1040

Sommer, I. E., Aleman, A., Bouma, A., & Kahn, R. S. (2004). Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain, 127*(8), 1845-1852. doi: 10.1093/brain/awh207

Sommer, I. E., Aleman, A., Somers, M., Boks, M. P., & Kahn, R. S. (2008). Sex differences in handedness, asymmetry of the planum temporale and functional language lateralization. *Brain Research, 1206*, 76-88. doi: 10.1016/j.brainres.2008.01.003

Sommer, I. E., Ramsey, N. F., Mandl, R. C., & Kahn, R. S. (2002). Language lateralization in monozygotic twin pairs concordant and discordant for handedness. *Brain, 125*(12), 2710-2718. doi: 10.1093/brain/awf284

Sommer, I. E. C., Ramsey, N. F., Mandl, R. C. W., Van Oel, C. J., & Kahn, R. S. (2004). Language activation in monozygotic twins discordant for schizophrenia. *British Journal of Psychiatry, 184*, 128-135. doi: 10.1192/bjp.184.2.128

Sommer, M., Koch, M. A., Paulus, W., Weiller, C., & Buchel, C. (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet, 360*(9330), 380-383. doi: 10.1016/S0140-6736(02)09610-1

Spiegler, B. J., & Yeni-Komshian, G. H. (1983). Incidence of left-handed writing in a college population with reference to family patterns of hand preference. *Neuropsychologia, 21*(6), 651-659. doi: 10.1016/0028-3932(83)90063-5

Springer, J. A., Binder, J. R., Hammeke, T. A., Swanson, S. J., Frost, J. A., Bellgowan, P. S., . . . Mueller, W. M. (1999). Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain, 122*(11), 2033-2046. doi: 10.1093/brain/122.11.2033

Steinmetz, H. (1996). Structure, function and cerebral asymmetry: In vivo morphometry of the planum temporale. *Neuroscience and Biobehavioral Reviews, 20*(4), 587-591. doi: 10.1016/0149-7634(95)00071-2

Steinmetz, H., Herzog, A., Schlaug, G., Huang, Y., & Jancke, L. (1995). Brain (A) symmetry in monozygotic twins. *Cerebral Cortex, 5*(4), 296-300. doi: 10.1093/cercor/5.4.296

Steinmetz, H., Jancke, L., Kleinschmidt, A., Schlaug, G., Volkmann, J., & Huang, Y. (1992). Sex but no hand difference in the isthmus of the corpus callosum. *Neurology, 42*(4), 749-752. doi: 10.1212/WNL.42.4.749

Steinmetz, H., Rademacher, J., Huang, Y. X., Hefter, H., Zilles, K., Thron, A., & Freund, H. J. (1989). Cerebral asymmetry: MR planimetry of the human planum temporale. *Journal of Computer Assisted Tomography, 13*(6), 996-1005. doi: 10.1097/00004728-198911000-00011

Steinmetz, H., Volkmann, J., Jancke, L., & Freund, H. J. (1991). Anatomical Left-Right Asymmetry of Language-Related Temporal Cortex Is Different in Left-Handers and Right-Handers. *Annals of Neurology, 29*(3), 315-319. doi: 10.1002/ana.410290314

Strauss, E., Satz, P., & Wada, J. (1990). An examination of the crowding hypothesis in epileptic patients who have undergone the carotid amytal test. *Neuropsychologia, 28*(11), 1221-1227. doi: 10.1016/0028-3932(90)90057-U

Sun, T., Patoine, C., Abu-Khalil, A., Visvader, J., Sum, E., Cherry, T. J., . . . Walsh, C. A. (2005). Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science, 308*(5729), 1794-1798. doi: 10.1126/science.1110324

Szaflarski, J. P., Binder, J. R., Possing, E. T., McKiernan, K. A., Ward, B. D., & Hammeke, T. A. (2002). Language lateralization in left-handed and ambidextrous people: fMRI data. *Neurology, 59*(2), 238-244. doi: 10.1212/WNL.59.2.238

Takao, H., Abe, O., Yamasue, H., Aoki, S., Sasaki, H., Kasai, K., . . . Ohtomo, K. (2011). Gray and white matter asymmetries in healthy individuals aged 21-29 years: a voxel-based morphometry and diffusion tensor imaging study. *Human Brain Mapping, 32*(10), 1762-1773. doi: 10.1002/hbm.21145

Takao, H., Hayashi, N., & Ohtomo, K. (2011). White matter asymmetry in healthy individuals: a diffusion tensor imaging study using tract-based spatial statistics. *Neuroscience, 193*, 291-299. doi: 10.1016/j.neuroscience.2011.07.041

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., . . . Kawashima, R. (2010). Training of Working Memory Impacts Structural Connectivity. *Journal of Neuroscience, 30*(9), 3297-3303. doi: 10.1523/Jneurosci.4611-09.2010

Thiebaut de Schotten, M., Ffytche, D. H., Bizzi, A., Dell'Acqua, F., Allin, M., Walshe, M., . . . Catani, M. (2011). Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *NeuroImage, 54*(1), 49-59. doi: 10.1016/j.neuroimage.2010.07.055

Thompson, P. M., Giedd, J. N., Woods, R. P., MacDonald, D., Evans, A. C., & Toga, A. W. (2000). Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature, 404*(6774), 190-193. doi: 10.1038/35004593

Tomaiuolo, F., MacDonald, J. D., Caramanos, Z., Posner, G., Chiavaras, M., Evans, A. C., & Petrides, M. (1999). Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis. *European Journal of Neuroscience, 11*(9), 3033-3046. doi: 10.1046/j.1460-9568.1999.00718.x

Tovar-Moll, F., Moll, J., de Oliveira-Souza, R., Bramati, I., Andreiuolo, P. A., & Lent, R. (2007). Neuroplasticity in human callosal dysgenesis: A diffusion tensor imaging study. *Cerebral Cortex, 17*(3), 531-541. doi: 10.1093/cercor/bhj178

Tzourio-Mazoyer, N., Simon, G., Crivello, F., Jobard, G., Zago, L., Perchey, G., . . . Mazoyer, B. (2010). Effect of familial sinistrality on planum temporale surface and brain tissue asymmetries. *Cerebral Cortex, 20*(6), 1476-1485. doi: 10.1093/cercor/bhp209

Upadhyay, J., Hallock, K., Ducros, M., Kim, D. S., & Ronen, I. (2008). Diffusion tensor spectroscopy and imaging of the arcuate fasciculus. *NeuroImage, 39*(1), 1-9. doi: 10.1016/j.neuroimage.2007.08.046

Vallortigara, G. (2006). The evolutionary psychology of left and right: costs and benefits of lateralization. *Developmental Psychobiology, 48*(6), 418-427. doi: 10.1002/dev.20166

Van Agtmael, T., Forrest, S. M., Del-Favero, J., Van Broeckhoven, C., & Williamson, R. (2003). Parametric and nonparametric genome scan analyses for human handedness. *European Journal of Human Genetics, 11*(10), 779-783. doi: 10.1038/sj.ejhg.5201048

Van der Knaap, L. J., & van der Ham, I. J. (2011). How does the corpus callosum mediate interhemispheric transfer? A review. *Behavioural Brain Research, 223*(1), 211-221. doi: 10.1016/j.bbr.2011.04.018

Vernooij, M. W., Smits, M., Wielopolski, P. A., Houston, G. C., Krestin, G. P., & van der Lugt, A. (2007). Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. *NeuroImage, 35*(3), 1064-1076. doi: 10.1016/j.neuroimage.2006.12.041

Vogel, J. J., Bowers, C. A., & Vogel, D. S. (2003). Cerebral lateralization of spatial abilities: a meta-analysis. *Brain and Cognition, 52*(2), 197-204. doi: 10.1016/S0278-2626(03)00056-3

Vuoksimaa, E., Eriksson, C. J., Pulkkinen, L., Rose, R. J., & Kaprio, J. (2010). Decreased prevalence of left-handedness among females with male co-twins: evidence suggesting prenatal testosterone transfer in humans? *Psychoneuroendocrinology, 35*(10), 1462-1472. doi: 10.1016/j.psyneuen.2010.04.013

Vuoksimaa, E., Koskenvuo, M., Rose, R. J., & Kaprio, J. (2009). Origins of handedness: a nationwide study of 30,161 adults. *Neuropsychologia, 47*(5), 1294-1301. doi: 10.1016/j.neuropsychologia.2009.01.007

Wada, J. A., Clarke, R., & Hamm, A. (1975). Cerebral Hemispheric Asymmetry in Humans - Cortical Speech Zones in 100 Adult and 100 Infant Brains. *Archives of Neurology, 32*(4), 239-246. doi: 10.1001/archneur.1975.00490460055007

Wallentin, M. (2009). Putative sex differences in verbal abilities and language cortex: a critical review. *Brain and Language, 108*(3), 175-183. doi: 10.1016/j.bandl.2008.07.001

Watkins, K. E., Paus, T., Lerch, J. P., Zijdenbos, A., Collins, D. L., Neelin, P., . . . Evans, A. C. (2001). Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. *Cerebral Cortex, 11*(9), 868-877. doi: 10.1093/cercor/11.9.868

Wernicke, C. (1874, 1977). Der aphasische Symptomkomplex: eine psychologische Studie auf anatomischer Basis. In G. H. Eggert (Ed.), *Wernicke's work on aphasia: a sourcebook and review* (pp. 91-145). The Hague: Mouton.

Westerhausen, R., Gruner, R., Specht, K., & Hugdahl, K. (2009). Functional relevance of interindividual differences in temporal lobe callosal pathways: a DTI tractography study. *Cerebral Cortex, 19*(6), 1322-1329. doi: 10.1093/cercor/bhn173

Westerhausen, R., Kompus, K., Dramsdahl, M., Falkenberg, L. E., Gruner, R., Hjelmervik, H., . . . Hugdahl, K. (2011). A critical re-examination of sexual dimorphism in the corpus callosum microstructure. *NeuroImage, 56*(3), 874-880. doi: 10.1016/j.neuroimage.2011.03.013

Westerhausen, R., Kreuder, F., Dos Santos Sequeira, S., Walter, C., Woerner, W., Wittling, R. A., . . . Wittling, W. (2004). Effects of handedness and gender on macro- and microstructure of the corpus callosum and its subregions: a combined high-resolution and diffusion-tensor MRI study. *Brain Research. Cognitive Brain Research, 21*(3), 418-426. doi: 10.1016/j.cogbrainres.2004.07.002

Westerhausen, R., Kreuder, F., Dos Santos Sequeira, S., Walter, C., Woerner, W., Wittling, R. A., . . . Wittling, W. (2006). The association of macro- and microstructure of the corpus callosum and language lateralisation. *Brain and Language, 97*(1), 80-90. doi: 10.1016/j.bandl.2005.07.133

Whitehouse, A. J., & Bishop, D. V. (2009). Hemispheric division of function is the result of independent probabilistic biases. *Neuropsychologia, 47*(8-9), 1938-1943. doi: 10.1016/j.neuropsychologia.2009.03.005

Whitford, T. J., Kubicki, M., Ghorashi, S., Schneiderman, J. S., Hawley, K. J., McCarley, R. W., . . . Spencer, K. M. (2011). Predicting inter-hemispheric transfer time from the diffusion properties of the corpus callosum in healthy individuals and schizophrenia patients: a combined ERP and DTI study. *NeuroImage, 54*(3), 2318-2329. doi: 10.1016/j.neuroimage.2010.10.048

Wilke, M., & Lidzba, K. (2007). LI-tool: a new toolbox to assess lateralization in functional MR-data. *Journal of Neuroscience Methods, 163*(1), 128-136. doi: 10.1016/j.jneumeth.2007.01.026

Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., . . . Gorno-Tempini, M. L. (2011). Syntactic processing depends on dorsal language tracts. *Neuron, 72*(2), 397-403. doi: 10.1016/j.neuron.2011.09.014

Witelson, S. F. (1985). The brain connection: the corpus callosum is larger in left-handers. *Science, 229*(4714), 665-668. doi: 10.1126/science.4023705

Witelson, S. F. (1989). Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain, 112*(3), 799-835. doi: 10.1093/brain/112.3.799

Witelson, S. F., & Goldsmith, C. H. (1991). The relationship of hand preference to anatomy of the corpus callosum in men. *Brain Research, 545*(1-2), 175-182. doi: 10.1016/0006-8993(91)91284-8

Witelson, S. F., & Nowakowski, R. S. (1991). Left out axons make men right: a hypothesis for the origin of handedness and functional asymmetry. *Neuropsychologia, 29*(4), 327-333. doi: 10.1016/0028-3932(91)90046-B

Witelson, S. F., & Pallie, W. (1973). Left Hemisphere Specialization for Language in Newborn - Neuroanatomical Evidence of Asymmetry. *Brain, 96*(3), 641-646. doi: 10.1093/brain/96.3.641

Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., . . . Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology, 61*(5), 699-701. doi: 10.1212/01.WNL.0000078815.03224.57

Yang, M. J., Tzeng, C. H., Tseng, J. Y., & Huang, C. Y. (2006). Determination of twin zygosity using a commercially available STR analysis of 15 unlinked loci and the gender-determining marker amelogenin--a preliminary report. *Human Reproduction, 21*(8), 2175-2179. doi: 10.1093/humrep/del133

Yazgan, M. Y., Wexler, B. E., Kinsbourne, M., Peterson, B., & Leckman, J. F. (1995). Functional significance of individual variations in callosal area. *Neuropsychologia, 33*(6), 769-779. doi: 10.1016/0028-3932(95)00018-X

Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., & Ben-Shachar, M. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience, 23*(11), 3304-3317. doi: 10.1162/jocn_a_00061

Yetkin, F. Z., Swanson, S., Fischer, M., Akansel, G., Morris, G., Mueller, W., & Haughton, V. (1998). Functional MR of frontal lobe activation: comparison with Wada language results. *American Journal of Neuroradiology, 19*(6), 1095-1098. Retrieved from *www.ajnr.org*

Zarei, M., Johansen-Berg, H., Smith, S., Ciccarelli, O., Thompson, A. J., & Matthews, P. M. (2006). Functional anatomy of interhemispheric cortical connections in the human brain. *Journal of Anatomy, 209*(3), 311-320. doi: 10.1111/j.1469-7580.2006.00615.x

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging, 20*(1), 45-57. doi: 10.1109/42.906424