AN INVESTIGATION OF THE ASSOCIATION BETWEEN HANDEDNESS, COGNITION, BRAIN STRUCTURE & FUNCTION

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ACKNOWLEDGEMENTS

It is widely known in academia that any PhD, unique in its own right, will observe its fair share of teething troubles and technical hitches, and this PhD has been no exception. In fact those who have crossed paths with this particular PhD might go as far as to say that this PhD has seen more than its fair share of difficulties. Indeed the voyage was fraught with obstacles and complications, but like any epic saga this was one journey not travelled alone. It is to that end that I would like to express my gratitude and thanks to those that have hoisted the sails, scrubbed the decks, read the compass and brought us to dock.

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ABSTRACT

An investigation of the association between handedness, cognition, Brain structure and function

Joanne L. Powell

Left- and right-handers show functional and structural brain differences. However, the literature on the relationship between handedness and cognitive ability is inconsistent. Moreover, possible differences in the neuroanatomical correlates of cognitive ability, including regional grey matter (GM) volume, between left- and right-handers have not been explored. This thesis describes work with two main aims: (i) to explore differences in brain structure and function between left- and right-handers using MRI on a sample of left- (n=40) and right- (n=42) handers, and (ii) to explore the effect of handedness on the neuroanatomical correlates of cognitive capacity on the same cohort.

The effect of sex and handedness on pars opercularis (PO) and pars triangularis (PTR) volume and the sulcal contours defining these regions are described in Chapter 5. PO volume asymmetry is leftward (left-greater-than-right) in right-handed males, non-asymmetrical in right-handed females and rightward in left-handed males and females. PTR volume is rightward in right-handers and non-asymmetrical in left-handers. The inferior frontal sulcus is discontinuous more often in the right than left hemisphere in right-handers and discontinuous more often in the left than right hemisphere in left-handers. The probability of presence of diagonal sulcus is higher in the right than the left hemisphere for left-handers. A second part to this study found a significant effect of handedness on foot preference for kicking and parental handedness. In Chapter 6 fractional anisotropy (FA) asymmetry across the whole brain is explored using voxel-wise statistics on FA maps obtained from diffusion weighted images: increased FA is found in right-handers, and FA asymmetry along the uncinate fasciculus and arcuate fasciculus in both groups. Chapter 7 shows significantly greater leftward language laterality in right-handers and greater activation in right IFG in response to a language production task in left- compared to right-handers. Working memory score is higher in right-handers is associated with increased leftward language laterality. Subjects with opposed language and spatial laterality perform better in tests assessing verbal comprehension and perceptual organization. Next, relationships between GM volume and cognitive ability is explored for fluid and crystallised intellectual functioning using voxel-based morphology (Chapter 8). Significant differences in the GM correlates of fluid and crystallised intelligence were found between the handedness groups. Lastly, Chapter 9 explores the relationship between prefrontal cortex (PFC) volume and intentionality in left- and right-handers using stereological volume estimates from T_1-weighted MR images. Although no significant difference in intentionality score was found between the handedness groups, higher scores of intentionality were associated with larger orbital PFC volume in right-handers, but with larger dorsal PFC volume in left-handers.

This research extends the literature demonstrating differences in brain structure and function between left- and right-handers. Overall, the results suggest that individuals may achieve similar cognitive ability scores with different brain designs. Future research should consider the effect of group differences in the population and how this might influence brain ‘design’ and cognitive ability.

LIST OF ABBREVIATIONS AND GLOSSARY

ABBREVIATION	DESCRIPTION
AC-PC	**Anterior commissure-posterior commissure**: The AC-PC plane is used to correct for head tilt following MRI structural acquisition. A horizontal line is used to connect the anterior commissure with the posterior commissure. Re-aligning structural images to the AC-PFC plane is one vital pre-processing step performed prior to demarcating the T_1-weighted MR images.
ADC	**Apparent Diffusion Coefficient** (*also referred to as mean diffusivity*): A measure of the diffusion within a voxel in the brain and the method used to collect this data is DTI. Water molecules diffuse more freely in regions where it is relatively unconstrained, such as CSF, and the diffusion is more restricted in regions such as WM where the alignment of myelinated axons hinder water motion. An ADC map shows diffusion within each voxel.
AF	**Arcuate fasciculus**: The bundle of WM fibres connecting anterior language regions located on IFG and posterior language associated cortex located on superior temporal lobe.
AIR	**Automatic image registration**: Corrects for motion distortion induced by the MR scanner including eddy current correction. This technique is used in this thesis on diffusion-weighted images.
AR	**Anterior ascending ramus**: Present on the lateral surface of the IFG, anterior to the DS, used to demarcate PO from PTR. It is commonly located where the temporal lobe turns downwards to form the temporal pole.
BA	**Brodmann area**: Regions of the brain defined based on their cytoarchitectonic structure. These areas are used to associate brain function with brain structure and provide a way of cross referencing regional functional activation within the brain across studies.
BOLD	**Blood oxygen level-dependent**: The signal obtained from fMRI associated with neuronal activity. Briefly it represents the change in signal which accompanies changes in blood oxygenation levels as a result of neural activity.
CSF	**Cerebrospinal fluid**: This clear fluid liquid is contained within the subarachnoid space and ventricular system. It surrounds the brain acting as a cushion and provides immunological stability in the brain.
DL PFC	**Dorsolateral prefrontal cortex:** A region of the prefrontal cortex, located in the lateral-anterior portion of the frontal lobe.
DM PFC	**Dorsomedial prefrontal cortex:** A region of the prefrontal cortex, located in the medial-anterior portion of the frontal lobe.
DTI	**Diffusion tensor imaging:** A recently developed MR imaging technique used to measure the translational displacement of water molecules in the brain. DTI can be used to measure both diffusion and anisotropy. The former is a measure of water diffusion and the latter is measure of the directionality of water molecules (*see ADC and FA*).
DS	**Diagonal sulcus**: This sulcus when present in the brain is located on

	the lateral surface of pars opercularis. It may connect with either: IFS, IPCS< AR or a connection may not be present.
EF	**Executive functioning:** Refers to a set of skills such as, working memory, mathematical ability, verbal comprehension and visuospatial ability. EF can be considered one aspect of intellectual capacity and is typically the skills that are being referred to when somebody uses the term general intelligence. Standard psychometric tests such as the WAIS or Raven's progressive matrices are used to measure EF skills.
EHI	**Edinburgh Handedness Inventory**: Developed by Oldfield (1971) as an assessment of hand preference. It is the most widely used measure of hand preference in the literature. It consists of a series of questions. The outcome of this questionnaire is a measure of handedness degree i.e. the extent to which an individual uses one hand more than the other. This can then be used to place the individual into a handedness category e.g. left-, right-, mixed-handed.
FA	**Fractional anisotropy**: A measure of the anisotropy in a voxel. Anisotropy corresponds to directionality of fibres within WM. Water motion is isotropic in CSF where water diffuses freely and anisotropic in WM where water is highly directional due to axonal membranes and myelin sheaths. Water motion is measured during an MR scan in different directions and a tensor ellipsoid is imposed to establish the directionality (anisotropy) in the voxel.
FDR	**False discovery rate**: This is one approach used to correct for multiple comparisons when tests are performed using the GLM in SPM. It takes into account that multiple tests are performed during one contrast in SPM as a result of the thousands of voxels in the brain and it corrects for these multiple tests to reduce the risk of Type II error (*see FWE*).
fMRI	**functional Magnetic Resonance Imaging**: Detects the BOLD changes in the MR signal which result from an increase in neuronal activity in a region of cortex following a change in brain state, which may be produced by a stimulus or task.
fTCD	**functional Transcranial Doppler sonography**: A technique used to measure changes in event-related cerebral perfusion that are related to neuronal activation. Cerebral perfusion is assessed within the whole territory of the insonated artery.
FWE	**Family wise error**: Similar to FDR this is one approach used to correct for multiple comparisons when tests are performed using the GLM in SPM. This approach is more conservative than the FDR correction, however, is less often used as it may increase the risk of making Type II errors.
FWHM	**Full-width half maximum:** (*see IGK*)
GLM	**General linear model:** A flexible framework which incorporates many different statistical models (e.g. ANOVA's and regression) and therefore allows many different tests to be applied.
GM	**Grey matter:** Neural tissue in the brain covering WM. It consists almost entirely of neurons and glial cells.
HR	**Anterior horizontal ramus**: Present on the lateral-orbital frontal lobe. It demarcates the PTR from pars opercularis, forming the anterior-inferior boundary of the PTR. When present it may share a common trunk with the AR.

ICV	**Intra-cranial volume:** The sum of GM, WM and CSF volumes.
IFG	**Inferior frontal gyrus:** A region of cortex is located anterior to the IPCS, inferior to the middle frontal gyrus. Three regions known to reside within this region of cortex are PO, PTR and part of pars orbitalis.
IFS	**Inferior frontal sulcus:** Located between inferior and middle frontal gyri. The first ventral horizontal frontal sulcus extending from the IPCS (either connected or separated by a bridge of cortex) is used to identify the posterior portion of the IFS. This provides the superior boundary of the PO and part of the superior boundary of the PTR.
IGK	**Isotropic Gaussian Kernal**: Used in MR data analysis to smooth images by multiplying every data point with a curve the shape of a 3D normal distribution. An IGK is defined by its FWHM, which is typically 2-3 times the voxel size.
IMT	**Imposing Memory Task:** A questionnaire used to assess intentionality, a social cognitive competence.
IPC	**Information processing capacity**: It is the ability to receive, store, integrate, retrieve and use information. In other words "the amount [of information] that can be processed simultaneously" (Ramsey *et al.*, 2004, p.517).
IPCS	**Inferior pre-central sulcus**: Used as the posterior boundary of the PO. It is identified as the first descending sulcus anterior to the central sulcus.
IQ	**Intelligence quotient:** A measure obtained from a standardised intelligence tests designed to have a mean score of 100 and a standard deviation of 15. One example is the WAIS.
LI	**Laterality index:** A measure of the extent to which one hemisphere or region of the brain is involved in a particular task compared to the opposite hemisphere or corresponding region in the opposite hemisphere.
MD	**Mean diffusivity**: *see ADC*
MNI	**Montreal Neurological Institute**: MNI space is a template developed by the Montreal Neurological Institute. This template is used to normalise images to when analysing MR data and is performed to ensure that all images are in the same space so corresponding brain regions can be compared.
MRI	**Magnetic resonance imaging**: An imaging technique based on the magnetic properties of hydrogen protons in brain tissue. This technique can be used to produce images of different tissues in the body including the brain e.g. GM, WM and CSF. The gradients used in an MR scan can be adjusted to collect structural MR images, functional MR images (*see fMRI*) and diffusion-weighted images (*see DTI*).
OL PFC	**Orbitolateral prefrontal cortex:** A region of the prefrontal cortex, located in the lateral-inferior anterior portion of the frontal lobe.
OM PFC	**Orbitomedial prefrontal cortex:** A region of the prefrontal cortex, located in the medial-inferior anterior portion of the frontal lobe.
P-FIT	**Parieto-frontal integration theory of intelligence**: A theory of intelligence developed by Jung and Haier (2007). They combined results from many previous studies to show which regions in the brain

	are associated with increases in general intelligence.
PFC	**Prefrontal cortex:** The anterior portion of the frontal lobe. The last brain region to develop in evolution and ontogeny. It shows a high degree of connectivity both within itself and other regions of the cortex. WM fibres in the prefrontal lobe exhibit a prolonged developmental time course, not fully developing in the individual until approximately 30 years of age.
PO	**Pars opercularis**: Part of the posterior IFG. Located posterior to PTR, known to be involved in language.
PTR	**Pars triangularis**: Part of the posterior IFG. Located anterior to PO and is known to be involved in language. The PO and PTR are referred to collectively as Broca's area.
ROI	**Region of interest:** In brain imaging a ROI refers to a region of neural tissue under investigated. MR imaging data is collected at the voxel level and the brain contains many voxels. When testing research hypothesis it is often better to reduce the number of voxels being explored due to correction for multiple comparisons (*see FDR and FWE*).
SF	**Sylvian fissure:** This fissure runs horizontally along the lateral surface of the brain. Anteriorly it separates temporal lobe from frontal lobe. The posterior portion extends upwards into parietal cortex.
SLF	**Superior longitudinal fasciculus:** A bundle of WM fibres that can be sub-divided into four parts, which connect anterior and posterior regions of cortex, particularly dorsal and medial regions of the frontal lobe and superior and inferior regions of the parietal cortex. The AF is considered to be one part of the SLF.
SPM	**Statistical parametric mapping**: This is essentially a statistical technique developed to test hypothesis about functional imaging data. A software package called SPM was developed incorporating these statistical processes.
SPSS	**Statistical Package for the Social Sciences**
ToM	**Theory of Mind:** Theory of mind is closely related to the "Social Brain Hypothesis" which proposes that ecological problems are solved socially. It is essentially the ability to explain and predict the behaviour of others by attributing to them mental states, beliefs or intentions.
UF	**Uncinate fasciculus:** WM fibre tract connecting limbic system in the temporal pole with orbitofrontal cortex.
VBM	**Voxel based morphometry**: A fully-automated computerized image analysis technique developed to detect brain differences *in vivo* between two groups of participant's. Differences in the local composition of brain tissue are identified, while discounting large scale differences in gross anatomy and position.
WAIS-III	**Wechsler Adult Intelligence Scale–version III**: A measure of different EF skills and general intelligence. Developed by Wechsler it can be used to produce a number of different index scores or measures of executive functioning such as working memory, verbal comprehension, perceptual organisation and speed processing ability.
WM	**White matter**: Neural tissue underlying GM. It consists almost entirely of myelinated axons which transfer signals between cortex.

CHAPTER 1: INTRODUCTION

Despite a wealth of research on hemispheric brain asymmetry and laterality, unanswered questions remain about its significance for cognitive functioning (intelligence). For instance, how does it manifest itself in behaviour, and what is its significance for higher cognitive functioning? The most obvious behavioural manifestation of cerebral laterality is handedness, which is usually central to discussion on hemispheric lateralization and anatomical asymmetry. This motor property is closely related to perhaps the most prominent lateralized brain function reported – language. Since Paul Broca (1861a,b, 1863, 1865) first discovered, over 150 years ago, that a lesion to the posterior portion of the inferior frontal gyrus (IFG), located within the frontal lobe, resulted in impaired language production, but only when the lesion occurred in the left hemisphere, interest in hemispheric specialisation has burgeoned. Now even a casual reading of the clinical neuroscience literature shows that hemispheric specialisation has a role in most of the theories and models proposed to explain neurological and psychiatric disorders. The development of new imaging techniques, particularly functional Magnetic Resonance Imaging (fMRI) has catalysed a great expansion in this research (Ogawa *et al*., 1990).

Anatomical connections between distant brain regions or modules of postulated functional significance can now be explored with the use of diffusion tensor imaging (DTI), whose popularity has increased strikingly over the last 5 years. DTI is used to measure the microstructural properties of white matter (WM) e.g. fractional anisotropy (FA) which is a measure of the directionality of water motion. DTI provides a useful technique for understanding the group and individual differences in WM integrity in healthy and patient populations.

There is also potential to use these different imaging techniques, namely fMRI, DTI and structural MRI, in a complementary fashion to explore inter- and intra-individual differences in neuroanatomy and function associated with cognitive abilities. For instance, imaging studies demonstrate an effect of sex on brain asymmetry, function (Sommer, 2010) and neuroanatomical correlates of intelligence (Haier *et al*., 2004). Haier *et al.* (2005) report strong correlations between intelligence and fronto-parietal grey matter (GM) volume in males, whereas in females, intelligence showed stronger correlations with WM volume and GM volume in Broca's area. The effect of individual differences on task performance has been shown in other studies (e.g. Hausmann and Bayer, 2010) suggesting that the effects of brain structure and function on individual differences in cognitive functioning (e.g. working memory, verbal comprehension) should be explored in other populations of individuals known to differ in brain organisation and/or cognitive ability measures, such as left- and right-handed populations. This thesis utilises MR imaging techniques to investigate brain anatomy, function and the neuroanatomical correlates of intelligence in a sample of left- and right-handed individuals.

Approximately 10% of the population are left-handed, while 90% are right-handed, a figure which has remained relatively stable for centuries and is observed across populations in different geographical locations (Coren and Porac, 1977; Gilbert and Wysocki, 1992; Perelle and Ehrman, 1994). Handedness clearly reflects a cerebral asymmetry and is the most obvious functionally lateralized behaviour seen in humans (Corballis, 2009). The interest in handedness that is ubiquitous throughout the neuroscience literature partially stems from the observed association between handedness, structural asymmetries and functional lateralities in the brain. The most robust functional laterality observed in the human brain is the widely reported left hemisphere dominance for language, which is seen in 96% of right-handers and 76% of left-handed individuals (Flöel *et al*., 2005; Pujol *et al*., 1999). Language is widely considered uniquely human, at least with respect to the grammatical component (e.g. Chomsky, 2006; Corballis, 2009; Hauser *et al*., 2002; Pinker and Jackendoff, 2005).

Whilst a number of studies have examined asymmetries in anterior speech regions in right- and left-handers (e.g. Foundas *et al*., 1995; Foundas *et al*., 1998), they have not addressed the interacting effects of handedness and sex on these asymmetries. Such interaction is important, as handedness (e.g. Habib *et al*., 1995; Steinmetz *et al*., 1989) and sex (e.g. Good *et al*., 2001a; Jäncke *et al*., 1994; Kertesz *et al*., 1990; Paus *et al*., 1996; Steinmetz *et al*., 1995) differences in anatomical measures of asymmetry (e.g. surface area or volume) have been described for several regions including the corpus callosum, anterior speech regions, planum parietale and planum temporal.

Less attention is given in the literature to the association between handedness and hemispheric dominance of other functions, such as spatial processing. Visuospatial processing takes place predominantly in the right-hemisphere in most individuals (Dupont *et al*., 1998; Faillenot *et al*., 2001; Marshall and Fink, 2001; Ng *et al*., 2001; Orban *et al*., 1997; Vandenberghe *et al*., 1996). To my knowledge, no study has explored the interaction between language and spatial laterality in a large sample of left- and right-handed individuals using fMRI, which would enable the investigation of specific language and spatial associated regions of interest (ROIs) i.e. IFG and parietal lobe respectively.

Throughout history left-handers have been stigmatised, evoking fear and suspicion because they are essentially “different from the rest of us” (Perelle and Ehrman, 2005). Because of this, many studies have sought to investigate what the fundamental differences are between left- and right-handed individuals. An area of dispute concerns the association between handedness and cognitive ability. Heilman (2005) suggests that left- and/or mixed-handedness have been associated with cognitive abilities that can have both advantageous and disadvantageous outcomes. Differences have been found between left- and right-handers for specific measures of cognitive ability and overall measures of general intelligence. For example, the proportion of left-handers is found to be greater in gifted children (intelligence quotient (IQ)>131) than in non-gifted children (Ehrman and Perelle, 1983; Granville *et al*., 1979; Hicks and Dusek, 1980). However, left-handers are also overrepresented in populations of mentally challenged individuals i.e. individuals exhibiting learning and developmental impairments and left-handers are reported to perform worse than right-handers on various measures of intelligence (Gregory and Paul, 1980; McBurney and Dunn, 1976; Pirozzolo and Rayner, 1979; Ross *et al*., 1992; Springer and Eisenson, 1977). The effect of individual differences on intellectual functioning is important because general intelligence test scores are associated with important life outcomes (Deary *et al*., 2007; Gottfredson, 1997; Johnson *et al*., 2006; Strenze, 2007). This thesis explores the effect of handedness on brain structure, brain function and cognitive ability as well as the neuroanatomical correlates of cognitive ability.

THESIS OUTLINE:

Chapter 2: *Handedness, cognition, cerebral anatomy and function.* This chapter provides an in-depth review of the literature underpinning this thesis. Areas of research that this thesis will focus on are outlined.

Chapter 3: *Principles of MR image acquisition.* This chapter briefly introduces the principles of MR physics including how the signal is obtained to produce structural, functional and diffusion weighted MR images.

Chapter 4: *Materials, methods and participants*. The cohort of participants used in this study is described along with a description of the neuropsychological tests used. The methodological approach used to analyse the MR images and neuropsychological tests is also given.

Chapter 5: *Broca's area, Sex, handedness and other behavioural literalities.* This chapter investigates the effect of sex and handedness on pars opercularis and pars triangularis volume and the sulcal contours surrounding these regions. The relationship between handedness and other behavioural lateralities is also explored along with the relationship between parental and offspring hand preference.

Chapter 6: *Handedness and white matter anisotropy.* The effect of handedness and sex on WM anisotropy and FA asymmetry across the whole brain is explored here.

Chapter 7: *Handedness, language laterality, spatial laterality and executive function.* This study investigates the effect of handedness and sex on language and spatial laterality and neuronal activation in response to a language task. The interaction between language and spatial laterality on verbal comprehension, working memory and perceptual organisation is also explored.

Chapter 8: *Handedness, grey matter volume and intelligence.* The relationship between GM volume with fluid and crystallised intelligence is explored along with the effect of handedness on this relationship.

Chapter 9: *Handedness, prefrontal volume and intentionality.* This study explores the effect of handedness on the association between intentionality competence and prefrontal cortex volume.

Chapter 10: *Discussion.* An overview of the findings is presented here. The advantages and limitations of the methodological approach used are given along with suggestions for future research. Finally the interpretation of the findings presented in this thesis is given along with the overall conclusion.

CHAPTER 2:

HANDEDNESS, COGNITION, CEREBRAL ANATOMY AND FUNCTION

2.1 HANDEDNESS

2.1.1 Handedness in the population

Handedness in ancient humans has been inferred by analysis of archaeological samples from skeletons (Trinkaus *et al*., 1994), stone tools (Bermúdez de Castro *et al*., 1988; Fox and Frayer, 1997; Rugg and Mullanne, 2001), and various other artefacts (Phillipson, 1997) (see Steele and Uomini (2005) for review). All of these studies clearly show a polymorphism of hand use in Hominid populations during prehistoric and historic times, with an overall dominance of right-handers. Geographical variation in the proportion of left-handedness however is evident (Perelle and Ehrman, 1994; Peters *et al*., 2006) and may be a result of the tasks used to assess handedness (Raymond and Pontier, 2004) or social pressures within that particular culture (Teng *et al*., 1976). The exact percentage of a country's population that is reported as left-handed depends upon the era and method of assessment, but typically the figure is around 10%. Interestingly this figure is the same whether right-handedness is classified as a reported preference for the right hand (McManus, 1985, 2002) or greater skill or strength in the right hand (Annett, 2002).

Raymond and Pontier (2004) reviewed 81 studies on handedness that examined throwing or hammering in 14 countries in America, Africa, Europe, Asia and Australia and found a range of 5-26% suggesting an important geographical variation in hand preference. This geographical variation has also been observed for writing hand preference. For instance, in a survey of 12,000 subjects from 17 different countries, 2.5-12.8% were left-handed for writing, with an overall proportion of 9.5% (Perelle and Ehrman, 1994). A separate study found that among seven ethnic groups based on 255,100 answers to a BBC internet study 7.0-11.8% were left-handed (Peters *et al*., 2006). In most populations studied, the proportion of left-handers among women was lower than in men (reviewed in Raymond and Pontier, 2004), suggesting that the determinism of hand preference is influenced by sex and/or stronger cultural influences exerted in the female population.

Given that the frequency of left-handedness in the population is much lower than that of right-handedness logic would dictate that a disadvantage to left-handedness must be evident. Indeed this is suggested to be the case by a number of authors (e.g. Annett and Manning, 1989; Coren and Halpern, 1991; Crow, 1997; Shan-Ming *et al.*, 1985). Some authors have suggested that left-handedness and/or mixed-handedness may predispose individuals to certain psychiatric conditions (Klar, 1999; Satz and Green, 1999), choice of profession (Halpern *et al.*, 1998), epilepsy (Rasmussen and Milner, 1977) and decreased life expectancy (Coren, 1995; Coren and Halpern, 1991; Graham and Cleveland, 1995; Halpern and Coren, 1988; Hugdahl *et al.*, 1993). Additionally an excess of non-right-handedness has been found in individuals with schizophrenia (Crow, 1997; Shan-Ming *et al.*, 1985). This disadvantage is thought to arise as a result of atypical laterality (e.g. Crow, 1997).

2.1.2 Handedness assessments and classification

Individuals are generally classified as being left- or right-handed based on their skill or preferred use of one hand over the other, although a handedness classification does not rule out the use of the non-dominant hand. Whilst the majority of people use their right-hand for most tasks, many will also use their left-hand to some extent more than others (Annett, 1996, 1998, 2002). One fundamental question is, “what is the best way to define handedness?” Handedness may be assessed through self-reported questionnaires such as the Edinburgh Handedness Inventory (EHI: Oldfield, 1971), Annett’s hand preference questionnaire (Dragovic and Hammond, 2007), or the Waterloo Handedness questionnaire (Steenhuis and Bryden, 1989). Handedness may also be assessed based on performance (or proficiency) using measures designed to assess hand skill, such as the Purdue Pegboard task (Tiffin and Asher, 1948), Annett’s Peg-Placing task (Annett, 1992), Tapley-Bryden’s dot-filling task (Tapley and Bryden, 1985), and the Wathand Box (Bryden *et al.*, 2000). One criticism of handedness inventories is that individuals may avoid an extreme response to inventory items thus confounding the measurement (Beaton and Moseley, 1984). Handedness can be seen as both a continuous or categorical variable and is most often assessed using self-reported questionnaires. The EHI is perhaps the most popular brief measure of hand preference used and allows for the classification of handedness as both a continuous or categorical variable based on the strength to which the individual uses one hand more than the other.

Handedness has been grouped in a number of ways, for instance, some studies have grouped handedness into three categories: left-handers, mixed-handers and right-handers (e.g. Crow *et al*., 1998). Some of the neurologic and neurobehavioural literature suggests handedness should be divided into two populations, those who are strong right-handed (i.e. those who use the right hand for almost all activities) and those who are nonright-handed (who may prefer the left hand for some, or the majority, of fine motor activities) (Geschwind and Galaburda, 1985). Whether non-right-handedness or only strong left-handedness is the most biologically relevant trait is a matter of controversy (Annett, 2002; Geschwind and Galaburda, 1985; McManus, 2001).

The only task that most people cannot learn to perform equally well with either hand, even after considerable training, is writing. Most individuals will categorise their handedness based on their writing hand (Perelle and Ehrman, 2005). Ambidextrous individuals are those who are equally comfortable and can write equally well with both hands: Perelle and Ehrman (1994) found that only 0.9% of individuals considered themselves to be ambidextrous for writing. Writing should be considered a unilateral task, it is the single behaviour humans do not change during their lifetime unless forced (Perelle and Ehrman, 2005).

Whilst most individuals will show a preference for using either the left- or the right-hand, the majority of individuals will also use the non-dominant hand to a degree (Annett, 1996, 1998, 2002). For this reason, Annett (2002) has suggested that handedness lies on a continuum with strong left- and right-hand categories lying at the two extremes and a mixture of preferences in between. This continuous distribution of hand preference takes the form of a single normal (Gaussian) curve, which for humans is displaced in a dextral direction (Annett, 1972, 2002; Annett and Alexander, 1996; Annett and Kilshaw, 1983). When individuals are classified into hand category based on their handedness degree, Annett concludes that the proportions of consistent left-, mixed- and right-handers are approximately 4, 30, and 66%, respectively, in human samples (Annett, 1996; Annett and Turner, 1974; Annett *et al*., 1974).

One debate is whether measures of hand performance and hand preference yield similar results. Handedness figures obtained from self-reported hand preference questionnaires are very similar to preference observed when the behaviour is carried out (Coren and

Porac, 1978; Raczkowski *et al.*, 1974) and test-retest reliability is reasonable (McMeekan and Lishman, 1975; Raczkowski *et al.*, 1974). Steenhuis and Bryden (1999) measured hand preference and hand proficiency in a sample of 52 right- and 48 left-handers. Results showed that self-reported right-handers and left-handers showed superior performance with the preferred hand on a dot-filling task. This suggests high agreement between the different measures of handedness. A strong correlation has been shown between strength of hand preference and hand performance on a peg-moving task (Annett, 1970, 1976, 1985) and between hand preference and proficiency in finger tapping (Peters and Durding, 1979). Although this work has been challenged by Porac and Coren (1981) who suggest that, whilst such relationships between hand preference and performance do exist associations are only modest, the reviewed evidence supports a high agreement between proficiency and preference measures.

Bishop *et al* (1996) tested the agreement between measures of hand preference and hand performance in a sample of right-handed subjects. Three handedness groups were identified using the EHI: strong right-handers, predominant right-handers and weak right-handers. Results showed that the groups did not differ on three measures of hand skill of the two hands: peg-moving, finger tapping and dotting. They concluded that there is no difference in relative hand skill when right-handers are grouped based on self-reported preference. This might suggest that, although there is agreement between preference and performance measures of handedness, tests of hand performance are unable to detect subtle differences in hand preference between groups of right-handers varying on self-reported hand strength. Preference measures may be superior at assessing subtle differences in handedness. Hand skill may not be very stable over time due to exposure to tasks requiring varying levels of hand skill. For instance, Reddon *et al* (1988), assessed 26 healthy subjects (12 males) with a Purdue Pegboard test 5 times at weekly intervals. All were self-reported dextrals. Test-retest reliability for men/women averaged .63/.76 for the right-hand and .64/.79 for the left-hand. These results show that the correlation between hand skill over time is relatively weak due to exposure to the task and show that there may be a small effect of sex on the stability of hand skill over time, with females showing greater consistency in hand skill than males.

Preference measures of handedness generally yield a bimodal distribution of handedness (i.e. two distinct handedness groups) which is J-shaped, whereas performance measures generally produce no clear division between the groups, instead the result is a unimodel distribution with a slight rightward shift (Corey *et al.*, 2001). However, not all proficiency tasks show this distribution, for example, studies using a dot-filling task (McManus, 1985; Tapley and Bryden, 1985) found distinct groups of right-handers and left-handers. Similarly D'Elia *et al* (1998) showed a strong relationship between the preferred hand and hand skill for inserting a pin in a series of bots. This suggests that the type of task used to measure hand performance is important to consider, as some may be more strongly correlated with hand skill than others. It also suggests that when wanting to define groups of handedness, preference measures are better.

The J-shaped distribution of hand preference is shown to be effected by at least two factors (i) the length of the questionnaire: with longer questionnaires resulting in a less skewed distribution (Provins *et al.*, 1982; Steenhuis and Bryden, 1987, 1988, 1989) and (ii) the type of activity. For example, Steenhuis and Bryden (1989) characterised activities as either, those that were "skilled" (e.g. writing, throwing darts) or those that were "unskilled" (e.g. picking up objects, petting a cat or dog). Only 25% of subjects reported strong preferences for one hand for the unskilled activities whereas 80% of right- and left-handers reported a strong hand preference for the skilled activities. Additionally, preference scores for the skilled activities yielded a J-shaped distribution whereas the scores for the unskilled activities was right-biased model. Peters (1998) provides further support to this by showing that handedness questionnaires should include both skilled and unskilled activities. This suggests that those measures assessing hand performance that require a high degree of hand skill will affect reported handedness proportions: a questionnaire containing largely questions on unskilled activities is likely to result in a higher proportion of right-handers.

Collectively this literature suggests that when handedness is assessed using self-reported questionnaires two distinct handedness groups emerge. This is important when exploring differences between the handedness groups. The results also suggest that there may be concordance among the different measures of handedness i.e. hand preference and hand performance, however some caution should be taken as the skill required for each activity on a performance measure can produce quite different results. Also some skills may show greater test-retest reliability than others. As the aim of thesis is to explore group differences between left- and right-handers the EHI was chosen to select participants. One advantage of this is that it is easy to administer, understand and response category is binary requiring the individual to assign crosses to one of two hand preferences. Further information on the EHI can be found in Section 4.2.1.

2.1.3 Other behavioural lateralities

Overall the research on behavioural laterality suggests that approximately one in three individuals show a left-eye preference and one in ten show a left-hand preference (Bourassa, 1996). Researchers have investigated the relationship between different lateralized behaviours such as hand, foot and eye preference in order to determine a common lateral dominance (Dargent-Paré *et al*., 1992; Gabbard, 1992; Nachshon *et al*., 1983). The commonality of lateral dominance is thought by many to be a marker for cerebral dominance (e.g. Nachshon *et al*., 1983). Nachshon *et al* (1983) explored the association between hand, foot and eye laterality in a sample of 7364 children. Overall 80% of the children reported a right-hand/right-foot preference: an overall right-eye preference was reported in approximately 50% of individuals. Consistent lateralities i.e. same hand, foot and eye preference, were reported in 40% of subjects: of the total sample of subjects 37% were right-handed and 3% were left-handers. The results were interpreted as suggesting an effect of cerebral dominance on laterality, with a stronger influence on hand and foot laterality than eye laterality. This thesis assesses foot preference for kicking and eye preference using the two questions presented on the EHI (for questions see Section 4.2.1).

2.1.4 Genetic models of handedness

Multiple factors are believed to affect handedness, including maternal handedness and family history of left-handedness (Annett, 1998, 1999), sex (Gilbert and Wysocki, 1992), age (Ellis *et al*., 1998), testosterone level (Tan, 1991), and history of early brain injury (Rasmussen and Milner, 1977). The persistence of the dominant right-hand preference observed throughout history and across populations distributed in different geographical locations suggests the involvement of some evolutionary mechanisms. However, for selection of this trait to take place, hand laterality should also be heritable (Llaurens *et al*., 2009). A full explanation of the causes of handedness is beyond the scope of this thesis. Although genetic theories can explain at least some of the variability in handedness, no single genetic theory of handedness can fully explain the handedness data in the published literature, indicating that other factors must be involved in its global prevalence and historical persistence.

One feature of the genetic theories proposed to explain the proportion of right-handers in the population is that the genetic influence is towards right-handedness with no such influence towards left-handedness. This idea was first proposed by Annett (1972) in her right-shift theory of handedness. Annett has since revised her initial theory (Annett, 2002) based on the observed association between handedness and hemispheric dominance for language. Annett’s right shift (RS) theory suggests that individual differences in cerebral organization arise from natural variation associated with the presence or absence of a single gene with two alleles, a right shift allele RS+ and an allele without directional specification RS-. In the human population, handedness follows a normal distribution curve that ranges from strong left-handedness to strong right-handedness. However, the mean of this distribution curve is located to the right. The normal distribution in handedness is thought to be attributed to chance, and its displacement towards dextrality is attributed to the influence of a gene for left cerebral advantage (Annett and Alexander, 1996). Annett (2002) suggests that the left hemisphere speech inducing RS+ factor could be inherited and that the “gene(s) involved would be “for” left hemisphere speech, not handedness” (p.70). Thus, the gene does not determine right handedness, but increases its probability by displacing a random distribution in a dextral direction (Annett, 2002). For those individuals homozygous for the RS+ allele, designated RS++, the shift is about two standard deviations to the right of neutrality. For heterozygotes designated RS+- the shift is about one standard deviation to the right and for those homozygous for the RS- allele (designated RS--) cerebral asymmetry and handedness are likely to occur at random.

Researchers have attempted to locate the genes involved in handedness. The involvement of a gene called LRRTM1 in handedness and schizophrenia has been proposed (Francks *et al*., 2007), however, evidence supporting its involvement as a single gene theory for handedness has been criticized (Crow *et al*., 2009) leaving the genetic debate in the air (Francks, 2009). Heritability estimates for handedness are in the range of 0.23 to 0.66 (Annett, 1985; Hicks and Kinsbourne, 1976; Longstreth, 1980; McKeever, 2000; McManus and Bryden, 1991; Porac and Coren, 1981; Risch and Pringle, 1985; Warren *et al*., 2006). A higher prevalence of left-handedness has been found in children from right-handed fathers and left-handed mothers (RxL pair) than from left-handed fathers and right-handed mothers (LxR pair) (Annett, 1973; Ashton, 1982; McKeever, 2000; McManus, 1991; Risch and Pringle, 1985; Spiegler and Yeni-Komshian, 1983). For instance, McManus (1991) reported the frequency of left handedness to be 22.1% in sons and 21.7% in daughters in the RxL pair and 18.2% in sons and 15.3% in daughters for the LxR pair. This suggests stronger maternal effects on offspring handedness, which may be the result from a sex-linked genetic effect or from a greater social influence likely to be exerted by the mother on the child. Two right-handed parents produced the fewest number of left-handed and two left-handed parents produced the highest proportion of left-handed children i.e. approximately 30-40% (McManus, 1991; McKeever, 2000).

The genetic contribution to the heritability of handedness is difficult to infer from the studies presenting handedness proportions. Llaurens *et al* (2009) suggests that three major problems have arisen for determining a genetic aetiology of handedness: (i) cultural biases influence the practice of hand usage, (ii) despite identical genotypes, approximately 18% of monozygotic twins are discordant for handedness (McManus, 1991) and (iii) only 30-40% of children from LxL couples are left-handed (McKeever, 2000; McManus, 1991). Additional factors such as maternal handedness may influence the infant’s exposure to hand use for various tasks which the infant then mirrors as they learn and practice performing the task e.g. using a knife and fork, writing, pouring a drink, brushing hair. It should be noted that even if a gene is found to be involved in the expression of handedness it is unlikely that such a gene will underlie all of the variability in human cognition, behaviour and emotion (Franks, 2009, Franks *et al*., 2007).

2.2 COGNITIVE ABILITY

2.2.1 Handedness and cognitive ability

The effect of individual differences on intellectual functioning is important because general intelligence test scores are associated with important life outcomes, including school achievement (Deary *et al*., 2007; Johnson *et al*., 2006), occupational attainment, social mobility (Strenze, 2007) and job performance (Gottfredson, 1997). In a study involving 70,000+ children, general intelligence at age 11 years had a correlation of over 0.8 with scores on national tests of educational achievement 5 years later (Deary *et al.*, 2007). Longitudinal studies showing the association between more specific cognitive domains and important life outcomes are currently lacking.

Understanding the association between handedness and cognitive ability is important because, approximately 10% of the population is left-handed (Coren and Porac, 1977; Perelle and Ehrman, 1994). Non-right-handedness i.e. left- or mixed-handedness has been associated with both positive and negative cognitive outcomes (Heilman, 2005). For instance, differences in manual skill have been found between the two handedness groups: left-handers have less pronounced lateralities in hand skill (Curt *et al.*, 1992; Judge and Stirling, 2003; Peters and Servos, 1989) and greater inter-manual coordination (Gorynia and Egenter, 2000; Judge and Stirling, 2003) than right-handers. Creativity is reported to be linked with left-handedness (Newland, 1981), more specifically in men (Coren, 1995). Left-handers have also been considered to have special talents that could lead to benefits, such as enhanced musical (Aggleton *et al.*, 1994; Kopiez *et al.*, 2006) or mathematical (Casey *et al.*, 1992; Crow *et al.*, 1998) capacities.

The frequency of left-handedness in interactive sports (such as fencing, boxing, tennis, baseball, and cricket) appears to be higher when compared with the frequency of left-handers in non-interactive sports (such as gymnastics, swimming, and bowling), which does not differ to the frequency of left-handers in the general population (Aggleton and Wood, 1990; Goldstein and Young, 1996; Grouios *et al.*, 2000; Raymond *et al.*, 1996). One potential explanation for the strategic advantage of left-handedness is that, left-handers are more used to the right-handers' way of playing whereas right-handers are more likely to be confronted by a right-handed opponent. Left-handers have a surprise advantage, which increases when their frequency in the population is lower (Raymond *et al.*, 1996). The left-handed advantage in interactive sports only holds because they remain proportionately lower than that of right-handers despite the frequency of left-handedness being higher than that seen at the population level.

The proportion of left-handers is also shown to be greater in gifted (IQ>131; note this is approximately 2 standard deviations above the average which is 100) than in non-gifted children (Ehrman and Perelle, 1983; Granville *et al.*, 1979; Hicks and Dusek, 1980).

Scores from a Scholastic Aptitude Test showed that left-handed children were overrepresented in the extremely gifted population (Benbow, 1986; O'Boyle and Benbow, 1990). Investigations into the members of the Mensa Society, whose membership requirements include possessing an IQ in the top 2% of the world's population, showed that approximately 20% of the members of Mensa were left-handed, double the proportion of left-handers in the general population (Ehrman and Perelle, 1983; Granville *et al*., 1979, 1980).

Left-handers are overrepresented in populations of the mentally challenged i.e. individuals exhibiting learning and developmental impairments, children with learning deficits, and those with reading difficulties, and it has been found that the proportion of left-handers increases as IQ decreases (Geschwind and Behan, 1982; Gregory and Paul, 1980; McBurney and Dunn, 1976; Pirozzolo and Rayner, 1979; Springer and Eisenson, 1977). The fact that left-handers are found to be over-represented in the gifted and mentally challenged populations and yet do not differ from right-handers in their average scores presents no contradiction. The distribution of cognitive ability scores may simply be wider for left-handers. This is not a completely new concept as males show similar mean scores to that of females but present a greater distribution of scores than females, being over-represented at both extremes of the normal distribution curve (Johnson *et al*., 2008a).

Studies of schoolchildren however, show no difference in cognitive ability between left- and right-handers (Hardyk and Petrinovich, 1977), nor were there any differences between left- and right-handers in articulation, stammering, speech, writing productivity, or syntactic maturity among a "nationally representative" population of 11-year-olds (Calnan and Richardson, 1976). Johnston *et al* (2009) using a large sample of (approximately 5,000) 4- and 5-year-olds, investigated the impact of handedness on children's cognitive development. Skills assessed included: vocabulary, reading, writing, social development and motor skills. The results showed that left- and mixed-handed children perform significantly worse in nearly all measures of development than right-handed children, the relative disadvantage being larger for boys than girls.

Mascie-Taylor (1980) obtained verbal and performance IQ scores from a sample of 687 individuals. Left-handers' overall verbal IQ score was significantly higher than their performance IQ score; whereas the opposite was found in right-handers i.e. performance IQ was significantly greater than verbal IQ. Additionally, left-handers scored higher than right- and mixed-handers on verbal IQ but lower on performance IQ. This could reflect an advantage of right-hemispheric language dominance for verbal IQ and an advantage of left hemispheric visuospatial processing for performance IQ. The association between handedness and cognitive ability may therefore relate to laterality rather than handedness per se.

No study to date has considered the effect of handedness on functions that show no clear lateralization between the hemispheres such as Theory of Mind (ToM). Whilst emotional processing such as the processing of emotional facial expressions indicate a rightward laterality (Badzakova-Trajkov *et al*., 2010), laterality of the social/emotional function ToM has not been clearly established. Additionally the effect of handedness on social processing has not yet been investigated. This thesis explores the effect of handedness on intentionality in a sample of left- and right-handers (Chapter 9).

Collectively these studies show that, despite the proposed advantages and disadvantages of left-handedness, the association between handedness and cognitive ability remains largely unclear. The inconsistency in these findings may be related to the specific cognitive ability tests used, the way in which handedness is assessed and the frequency of hemispheric lateralization for language in the samples studied. This thesis explores the effect of handedness and brain laterality for different functions on cognitive ability. Overall the literature suggests that if there is a disadvantage to being left-handed this difference is likely to be small, highly variable across the left-handed population and applicable only to certain cognitive domains (Corballis *et al*., 2008).

2.2.2 General Intelligence or cognitive domains

The term cognitive ability is often used as a synonym to mental ability, intelligence, and IQ (intelligence quotient). The term ‘cognitive ability’ is primarily used throughout this thesis when referring to scores obtained from psychometric assessments, and mental ability in general; however there are instances in which the term “intelligence” is used, as it is deemed to be more appropriate, for instance, when referring to literature which has used this term. The term general intelligence ‘*g*’ is used to describe the strong common core that cognitive tests share. Individual differences in intelligence are usually measured using psychometric tests, which assess cognitive domains such as working memory, verbal reasoning and spatial ability. However, it is worth noting that the full range of human capabilities is not covered by psychometric tests (Sternberg, 1999).

Psychometric tests designed to assess intelligence include the British Abilities Scales-II (BAS: Elliot, 1996), Cattell's Culture Fair test (Cattell and Cattell, 1973), the Stanford-Binet Intelligence Scale-IV (Thorndike et al., 1986), Raven's Progressive Matrices (Raven et al., 2003), Wechsler Adult Intelligence Scale-III (WAIS-III: Wechsler, 1997a,b), and Wechsler Intelligence Scale for Children (WISC: Wechsler, 2004). Some of these tests place greater emphasis on assessing fluid intelligence e.g. Raven's Progressive Matrices which is a non-verbal test of inductive reasoning. Other tests such as the California Verbal Learning Test (CVLT: Delis et al., 2000) have been designed to assess verbal learning and memory. The CVLT involves auditorily presented lists of words which can be used to assess recall, recognition, learning rate and primacy and recency effects. The Benton Visual Retention test (Benton, 1992), in contrast, is used to assess visual perception, visual memory and visuoconstructive abilities. The WAIS comprises a battery of tasks that require different kinds of cognitive performance, which collectively yield a score which is believed to represent general intelligence. Tasks in this test involve providing definitions of words or visualising three-dimensional objects from two-dimensional diagrams. The WAIS battery of tasks can also be used to produce four index scores: verbal comprehension, working memory, processing speed and perceptual organisation each of which represent different cognitive component. Additionally WAIS-III subtests can be combined to assess both fluid and crystallised intelligence.

Intelligence has been defined in many ways and none is universally accepted. It may be defined as a measure of the individual's ability to react and respond to problems in order to survive in their natural and social environment (Roth and Dicke, 2006). This involves the appraisal of a particular stimulus, task or situation, and choosing the appropriate response, involving mental or behavioural flexibility. A definition of intelligence has been proposed by 52 prominent researchers in the field:

> *"Intelligence is a very general capacity that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather, it reflects a broader and deeper capacity for comprehending our surroundings-'catching on', 'making sense' of things, or 'figuring out' what to do. Intelligence, so defined, can be measured, and intelligence tests measure it well"* (Gottfredson, 1997, p.13).

Given this general definition of intelligence it is easy to understand why many experts in the field of intelligence argue that the full potential of an individual's intellectual capacity cannot be fully captured by any single score of intellectual ability (e.g. Gardner, 2006). Much of the focus in cognitive neuroscience has been on the specific cognitive domains themselves. This raises an important and long discussed dispute regarding how to conceptualise intelligence.

The fact that people who perform well on one cognitive domain also tend to perform well in another provides evidence for the existence of a general intellectual capacity (*g*). About half of the variation across these cognitive tests is contained in *g*, and *g* is the locus of most of the genetic variance in cognitive ability tests (see Deary *et al*., 2010 for a review of genetic influences on intelligence). The positive correlation between scores on cognitive ability tasks is referred to as the "positive manifold". Much less of the variance in cognitive test scores is therefore, contained within the broad cognitive domains (Deary *et al*., 2010). Indeed Deary *et al* (2010) indicate "it is inappropriate to assume that performing any cognitive task involves only one relevant mental module" (p. 202). Cognitive tasks draw on multiple abilities, some of which are unique to the specific task and others which can also be applied to other tasks. This poses a challenge for cognitive neuroscientists who seek to localize brain activities that are specific to the task at hand.

Cattell and Horn conceptualised intelligence as consisting of two distinct functions (Horn, 1989): fluid intelligence and crystallised intelligence. Fluid intelligence refers to analytical intelligence. It is typically assessed using tests that require abstract reasoning and on-the-spot processing i.e. situations in which past education and knowledge can be of no assistance (Deary *et al*., 2010). Fluid intelligence is often not considered psychometrically distinct from *g* (Carroll, 1993; Jensen, 1980). In contrast crystallised intelligence is concerned more with over-learned skills and static knowledge such as vocabulary (Kane and Engle, 2002) and is not as closely related to *g*.

The WAIS-III is one of the most widely used measures of *g* (Deary *et al*., 2006) and factor analysis (Deary, 2001a) of the WAIS-III data obtained (from a sample of 2450 adults) by Wechsler (1997a,b) identified four different cognitive domains i.e. verbal comprehension, perceptual organisation, processing speed and working memory. Deary has suggested in a number of reviews on intelligence (Deary, 2001a,b; Deary and Caryl, 1997; Deary *et al*., 2006, 2010), that intelligence can be viewed as a hierarchical structure with *g* at the top, the various cognitive domains underneath and the sub-tests that make up these domains at the bottom. Within this model verbal comprehension may be considered the best measure of crystallised intelligence and is made up of the sub-test vocabulary, comprehension and information on the WAIS-III. The cognitive domains perceptual organisation, processing speed and working memory in contrast are considered to be better measures of fluid intelligence. The factor loadings of each sub-test on each index scale and the factor loading of each index scale on *g* is shown by Deary (2001a). Processing speed shows the weakest factor loading with *g* whereas perceptual organisation and working memory show the strongest factor loadings with *g*.

The distinction between fluid and crystallised intelligence becomes apparent when age is considered. Evidence suggests that crystallised intelligence remains relatively stable over time (Deary *et al*., 2000; Schwartzman *et al*., 1987) whereas fluid intelligence declines with age (Baltes *et al*., 1999; Gold *et al*., 1995; Salthouse, 1996). Importantly when it comes to defining the neuroanatomical correlates of intelligence it is better to consider the different dimensions of intelligence. For instance, Duncan *et al* (1995) suggest that the frontal lobes are involved more in fluid intelligence than crystallised intelligence. Their study showed that patients with frontal lobe damage present impairments in measures of fluid intelligence but not crystallised intelligence. A study by Roca *et al* (2010) support this finding by showing a deficit in general fluid intelligence in a separate sample of patients with lesions to the frontal lobe. Following a review of the neuroimaging literature Gray and Thompson (2004) suggest there is strong evidence that dorsolateral PFC in particular supports intelligent behaviour.

Working memory and *g* are considered (by some) to be closely related (Engle *et al.*, 1999; Kyllonen, 1996; Kyllonen and Christal, 1990; Stauffer *et al*., 1996). For instance, Engle *et al* (1999) argued that fluid intelligence and working memory reflect “the ability to keep a representation active, particularly in the face of interference and distraction” (p. 309). Working memory has traditionally been divided into two types of processes: executive control (governing the encoding, manipulation and retrieval of information in working memory) and active maintenance (keeping information available ‘online’) (Cohen *et al*., 1997). The central executive is aided by the phonological loop and visuospatial sketchpad: subsidiary slave systems which ensure the temporary maintenance of information. The phonological loop is involved in verbal storage and according to Baddeley’s model of working memory (Baddeley, 1986) can be decomposed into a phonological buffer for short-term maintenance of phonological information and a subvocal rehearsal process that refreshes its contents (see also Baddeley, 2003). Following a review of the literature Conway *et al* (2003) conclude that working memory capacity and *g* are highly related but are not the same construct. Neuroimaging studies indicate a distinction between tasks requiring storage versus those that require storage plus manipulation of information (Smith and Jonides, 1999). For instance, tasks requiring only storage recruit regions of cortex related to the task in question e.g., Broca’s area for verbal material. In contrast tasks requiring storage and manipulation involve regions of the frontal lobe including dorsolateral PFC and anterior cingulate cortex (Conway *et al*., 2003; Fiez *et al*., 1996; Jonides *et al*., 1998; Smith and Jonides, 1999). Overall the literature indicates that working memory capacity and *g* are heavily reliant upon the dorsolateral PFC (Duncan, 1995; Kane and Engle, 2002).

Cattell’s Culture Fair test and the WAIS-III are measures of both crystallised and fluid intelligence. Of these tests Cattell’s Culture Fair test can be seen as a reliable measure of fluid intelligence. In contrast the WAIS-III consists of 13 subtests that can be divided into measures of fluid and crystallised intelligence. Raven’s Progressive Matrices is used as a measure of non-verbal reasoning and mental arithmetic skill. The majority of the standardised tests of intelligence such as Ravens Progressive Matrices and the WAIS-III are designed to assess what Ardilla (2008) referred to as “metacognitive executive functions”. These abilities include, inductive reasoning, perceptual or organisational ability, attention and working memory. Ardilla (2008) distinguishes this type of executive function (EF) from “emotional/motivational EFs” which involve coordinating cognition and emotion/motivation. Examples of emotional/motivational EFs include the ability to choose the most socially acceptable response during a social interaction whilst inhibiting an unsociable response and Theory of Mind (ToM) (or intentionality).

The difficulty with many of the standardised psychometric tests is that while they are very good at assessing EFs they do not incorporate measures of social cognition (i.e. emotional/motivational EFs) such as theory of mind (ToM) or intentionality. Intentionality allows an individual to explain and predict the behaviour of others by attributing to them mental states and is an essential skill for understanding the behaviour of others which is crucial for normal social functioning. However, whilst intentionality is thought to be more closely related to social cognitive skills such as social reward, which is not usually assessed on standard psychometric tests, a number of EFs which are assessed on standardised psychometric tests may support intentionality competence e.g. memory. Whilst intentionality in this respect is considered to be a separate domain (Ardilla, 2008), the cognitive processes involved are similar to that in fluid intelligence as described above i.e. past education and knowledge can be of no assistance, instead abstract reasoning and problem are involved.

Intentionality is the ability to explain and predict the behaviour of others by attributing to them mental states, beliefs or intentions, and is frequently referred to in the literature as ‘theory of mind’ (ToM) (Bull *et al*., 2008; Frith and Frith, 1999, 2003, 2006; Gobbini *et al*. 2007; Leslie, 1987, 1994). There is potentially an unlimited hierarchy of mind states (e.g. beliefs, intentions, wants) which can be reflexively attributed to other individuals (“I know that you believe that Hilary wants me to think....) (Kinderman *et al*. 1998; Stiller and Dunbar, 2007). Intentionality skills are essential for understanding the behaviour of others, which is in turn crucial for normal social functioning. ToM is closely related to the “Social Brain Hypothesis” which proposes that ecological problems are solved socially and that the need for mechanisms, like intentionality, that enhance social cohesion, drives brain size evolution (Barton and Dunbar, 1997; Dunbar and Shultz, 2007).

Evidence for the distinction between EF’s and ToM comes from neuroimaging and patient studies, which demonstrate an association between each category of EF (i.e.

metacognitive EFs and emotional/motivational EFs) and distinct regions of the PFC. Specifically, associations have been found between metacognitive EFs and dorsal PFC, and between emotional/motivational EFs and orbital PFC (also see Ardilla, 2008 for a review on the literature). For instance, deficits in metacognitive EFs such as the ability to organise a behavioural response to novel or complex stimuli (Cummings, 1993) and decision-making (Manes *et al.*, 2002) have been reported following damage to dorsal regions of the PFC, whereas damage to orbitofrontal and medial frontal cortex is associated with deficits in emotional/motivational EFs such as an inability to respond to social cues, tactlessness, personality change and inappropriate behaviours (Stuss and Knight, 2002).

The development of the human PFC was rapid and recent in comparison to other brain regions (Huey *et al.,* 2006). It is one of the last regions to develop in evolution as well as ontology (Fuster, 2001, Gogtay *et al.*, 2004), not attaining full maturity until adolescence (Chugani *et al*., 1987; Paus *et al*., 1999; Sowell *et al*., 1999). The PFC exhibits more complex cortical convolutions than any other brain region (Fuster, 2001; Gogtay *et al*., 2004) and has a high degree of interconnectivity, not only within itself (Elston, 2003) but also to the rest of the cortex (Fuster, 1997, 2001) including more posterior brain structures (Wood and Grafman, 2003). This suggests that those cognitive skills such as intentionality (ToM) which are thought to be uniquely human processes would be more closely related to the PFC which is a more recently developed structure in humans.

The neuropsychological literature supports a distinction between dorsal regions of the PFC that mediate higher order cognitive functions, and orbital regions (medial-orbital regions in particular) of the PFC that mediate mood, affective behaviour and social aspects of cognition (Ardila, 2008). Dorsal PFC supports the widely acknowledged ‘metacognitive’ executive functions (EFs) (Ardila, 2008), such as planning (Damasio and Anderson, 1985), working memory (Goldman-Rakic, 1996), attention (Vendrell *et al*., 1995), and delayed judgements (Curtis and D’Esposito, 2003). Studies of individuals with damage to orbital PFC have shown impulsive aggressive behaviour (Davidson *et al*., 2000), and impairments to social cognition (Anderson *et al*., 1999) and risk judgment (Bechara *et al*., 2000a,b; Tranel *et al*., 2000). A previous study showed an association between orbital PFC volume and intentionality competence using stereological volume estimates in a sample of right-handed subjects, aged 18 – 47 years (Powell *et al*., 2010). This association is argued to reflect the role of the orbital PFC in social cognition, including functions which support social cohesion such as social reward (Cohen *et al*., 2009) and response inhibition (Elliott *et al*., 2000).

2.2.3 Neuroanatomical correlates of cognitive ability

With the advancement of image acquisition and analysis methods in recent decades, unique opportunities have emerged to study the neuroanatomical correlates of intelligence. Previous studies that have explored the neuroanatomical correlates of intelligence (Andreasen *et al*., 1993; Flashman *et al*., 1997; Gong *et al*., 2005; Gray and Thompson, 2004; MacLullich *et al*., 2002; Toga and Thompson, 2005) highlight an association between total and regional brain volume and increased executive functioning (see Luders *et al*., 2009 for review). Increased global brain volumes observed in more intelligent individuals may be accounted for by selectively enlarged volumes in brain regions especially relevant for higher cognitive function (Andreasen *et al*., 1993). However, this does not mean that the basis of this correlation is understood.

Greater skill at specific cognitive competences is assumed to reflect various task demands (Andreasen *et al*., 1993; Flashman *et al*., 1997), which have been attributed to different brain regions (e.g. verbal task demands to the left IFG and posterior temporal lobe; spatial demands to the parietal lobe). An interesting study was reported by Maguire *et al* (2000) who using MRI compared the brains of licensed London taxi drivers and a group of control subjects who did not drive taxis. Differences in hippocampal volume were found between the two groups with significantly larger posterior hippocampus volume in taxi drivers compared to controls. Moreover hippocampal volume was correlated with the amount of time spent in a taxi. This association was explained by the idea that the posterior hippocampus stores a spatial representation of the environment and can expand regionally to accommodate elaboration of this representation in people with a high dependence on navigational skills.

A recent study by Lebreton *et al* (2009), using a voxel-based morphometry (VBM) approach and a measure of social Reward Dependence (RD), provided evidence for a structural disposition towards social cognition. Higher social RD in men was associated with increased GM density in the orbitofrontal cortex, basal ganglia and temporal poles. According to Lebreton *et al* (2009), social RD is a stable pattern of attitudes and behaviour hypothesised to represent a favourable disposition towards social relationships and attachment as a personality dimension. In this respect, social cognitive mechanisms supporting social cohesion or favourable social interaction would be more rewarding to those reporting a high disposition to social relationships and attachment. Importantly this study also accounted for total GM volume in their model indicating that the association was between relative GM density and social RD.

Recent studies using VBM have demonstrated correlations between IQ and some specific brain regions which involve frontal (Colom *et al.*, 2006; Frangou *et al.*, 2004; Gong *et al.*, 2005; Haier *et al.*, 2004, 2005), parietal (Colom *et al.*, 2006; Haier *et al.*, 2004, 2005), temporal (Colom *et al.*, 2006; Haier *et al.*, 2004, 2005) and occipital (Colom *et al.*, 2006; Haier *et al.*, 2004, 2005) lobes. An additional way to test whether a brain area is crucially involved in intelligence differences is to study people with brain lesions. Gläscher *et al* (2009) collected data from a large sample of 241 patients with brain lesions. Using voxel-based lesion mapping, they found highly specific lesion-deficit relations in left frontal and parietal cortex for working memory efficiency, in the left inferior frontal cortex for verbal comprehension and in right parietal cortex for perceptual organisation, all metacognitive EFs.

These studies clearly demonstrate a biological basis to cognitive competences, indicating that certain structures are selectively altered in individuals with greater skill in specific cognitive competences. They also suggest that specific cognitive abilities including spatial skills and social cognition are related to differences in brain structure. This indicates that in addition to understanding the neuroanatomical correlates of *g*, the different cognitive components constituting *g* and the cognitive skills not typically measured on standardised ability tests, namely social cognition, should also be considered separately.

There is mounting evidence that the integrity of WM tract pathways, as measured by DTI, is related to individual differences in performance across a wide range of cognitive skills (e.g. Madden *et al.*, 2009; Nagy *et al.*, 2004; Schmithorst *et al.*, 2005; Yu *et al.*, 2008). Loss of WM integrity due to demyelination has been implicated as an anatomical contributor to a number of neurological disorders associated with loss of cognitive function including schizophrenia, Alzheimer's disease and amyotrophic lateral sclerosis (Ciccarelli *et al*., 2003; Duan *et al*., 2006; Kanaan *et al*., 2005; Nestor *et al*., 2004; Stricker *et al*., 2009). Moderate to strong correlations have been reported between the severity of working memory deficits in Alzheimer patients and the severity of deficits in FA of specific WM tracts (Fellgiebel *et al*., 2005; Rose *et al*., 2000).

Moreover, individual differences in WM integrity account for significant inter-individual variation in cognitive performance within healthy populations. For example, FA in fronto-parietal WM correlates with performance during working memory tasks, as well as with the magnitude of corresponding brain activations, showing strongest correlations in the anterior corona radiate (Olesen *et al*., 2003; Nagy *et al*., 2004). Niogi and McCandliss (2006) found a strong correlation between FA values in a left temporo-parietal WM region and standardised reading scores of typically developing children. FA values in this same region accounted for differences between children scoring in the average range and children scoring in the reading disorder range. This suggests an important role for WM anisotropy development in cognitive functions even within typically developing populations. Yu *et al* (2008) examined the integrity of WM tracts and intelligence in patients with "mental retardation" and healthy adults using voxel-wise statistics on FA images. Results showed that FSIQ scores (assessed using the WAIS-III) were significantly correlated with the average FA of the right uncinate fasciculus in healthy adults. Collectively these studies, outlined above, suggest that variation in the association between GM volume, WM integrity and cognitive ability exists within humans. A review of the contribution of WM to learning, cognition and psychiatric disorders is given in Fields (2008).

The association between measures of GM, WM and intelligence has been summarised by Jung and Haier (2007) in their parieto-frontal integration theory of intelligence (P-FIT). After an extensive review of the literature (available at the time) existing results were assigned to Brodmann Areas. Jung and Haier (2007) concluded that a network of brain regions relate to individual differences in intelligence, including areas in the dorsolateral PFC, anterior cingulate cortex and regions of the parietal, temporal and occipital lobes (see Figure 2.1). Deary *et al* (2010) argues that this theory is the best available description of how intelligence is distributed in the brain.

Each region is thought to be involved in intelligence test performance due to its particular involvement in brain function. For instance, according to the P-FIT, the extrastriate cortex (BA18 and BA19) and fusiform gyrus (BA37) are involved in intelligence test performance because they contribute to the recognition, imagery, and elaboration of visual input, just as Wernicke's area (BA22) does for syntactic auditory input. This information, is then processed in the supramarginal (BA40), superior parietal (BA7) and angular (BA39) gyri of the parietal lobe. These regions are thought to subserve structural symbolism, abstraction and elaboration. A working memory network may then be established when these parietal regions interact with frontal lobe regions (especially BA6, BA9, BA10, BA45, BA46 and BA47). This will allow the individual to compare different possible task responses. Following response selection the anterior cingulate cortex (BA32) supports response engagement and inhibition of alternative responses. The interactions among brain regions communicate via WM fibres such as the AF, and therefore the importance of WM fibres in transferring information from one region to the next are pivotal in intellectual performance. The left hemisphere seems to be more important to cognitive task performance than the right hemisphere for most of these brain regions (Deary *et al.*, 2010).

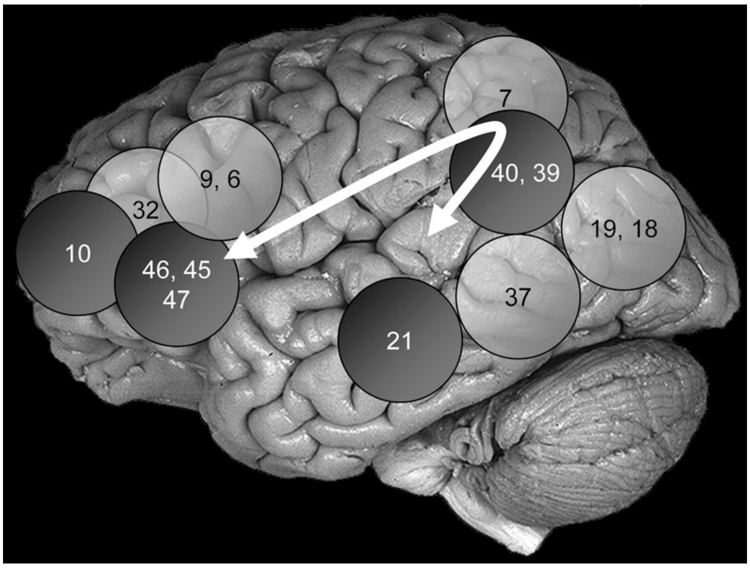


Figure 2.1. Regions involved in intelligence proposed by Jung and Haier (2007) in their parieto-frontal integration theory (P-FIT) of intelligence. The circles represent Brodmann Areas associated with intelligence: dark circles represent predominantly left and light circles represent predominantly right hemisphere associations. The white arrow represents the AF (a WM pathway). Figure is taken from Jung and Haier (2007).

The neuroanatomical correlates of intelligence (mostly metacognitive EFs) have largely been investigated in the population as a whole. Little consideration has been given to the neuroanatomical correlates of intelligence of different populations/groups of individuals, with the notable exception of sex. Haier *et al* (2005), for instance, found that in males, intelligence was more strongly correlated with fronto-parietal GM volume whereas, in females, intelligence showed stronger correlations with WM volume and GM volume in Broca's area. Based on these findings Haier *et al* (2005) suggested that there is no single underlying neuroanatomical structure to general intelligence and that different types of brain design may manifest equivalent intellectual performance. Narr *et al* (2007) found that cortical thickness in frontal regions correlated more strongly with intelligence in females, whereas temporal-occipital cortical thickness showed a stronger correlation with intelligence in males. The results of Haier *et al* (2005) and Narr *et al* (2007) suggest that males and females achieve similar IQ results with different brain regions. This principle might apply to other groups known to differ in brain structure and organisation such as left- and right-handers. Identical intelligence test scores in two healthy individuals may be evident, however, such scores may be achieved through different neuronal mechanisms as a result of differences in brain structure and organisation, expertise and training or the cognitive strategies used (Deary *et al*., 2010; Haier *et al*., 2005; Johnson and Bouchard, 2007; Johnson *et al*., 2008a,b). Differences in the neuroanatomical correlates of intelligence in different groups of individuals need to be addressed in order to clarify the normal variation in brain organisation.

2.2.4 Cerebral asymmetry, laterality and cognitive ability

The relationship between functional lateralization (e.g. language, spatial processing) and cognitive performance (e.g. verbal ability, visuospatial functions and memory) is still unclear. Some suggest a cognitive advantage when language is lateralized to the right hemisphere (e.g. Everts *et al*., 2010), when there is a symmetrical distribution of language associated WM pathways (Catani *et al*., 2007) and when there is increased leftward asymmetry of the planum temporale (e.g. Schlaug *et al*., 1995). Recent studies have reported a link between cognitive performance and language lateralization in healthy subjects (Everts *et al*., 2009; van Ettinger-Veenstra *et al*., 2010) and patients with epilepsy (Everts *et al*., 2010). Atypical (bilateral or right-sided) language lateralization has been related to weaker language performance in healthy children

(Everts *et al*., 2009) and worse visuospatial memory performance in children (Gleissner *et al*., 2003) and adults (Loring *et al*., 1999) with left hemisphere epilepsy. Everts *et al* (2010) found in patients with left-sided epilepsy a correlation between language lateralization and verbal memory performance, with bilateral or right-sided language lateralization being correlated with better verbal memory performance. They suggest that atypical language lateralization is advantageous for verbal memory performance as a result of transfer of verbal memory function between neocortical language and hippocampal memory regions.

van Ettinger-Veenstra *et al* (2010) found further support for the advantage of rightward laterality in increased cognitive performance. They used a sentence-completion paradigm in an fMRI study to determine region-specific lateralization indices, in addition to a dichotic listening task. Decreased right ear advantage, which indicates decreased left-hemisphere language dominance, correlated to higher performance in most administered language tasks, including reading, language ability, fluency and non-word discrimination. Performance in the cognitive task measuring subtle language dysfunctions correlated negatively with laterality indices in the inferior frontal cortex (Broca’s area), indicating that increased involvement of the right hemisphere is associated with increased cognitive performance. This finding may be due to the involvement of Broca’s area in many functions on which that particular task depends. For instance, Broca’s area is involved in subtle grammatical decisions (Damasio, 1992; Rodd *et al*., 2005; Ullman *et al*., 2005) and may be recruited in working memory tasks (Huang *et al*., 2002).

Other studies have not however, observed an association between language lateralization and cognitive ability. For example, Knecht *et al* (2001) established language lateralization using fTCD and found that individuals with right, left and bilateral language representation did not differ significantly with respect to mastery of foreign languages, academic achievement, artistic talents, verbal fluency or intelligence. However, because of the relatively poor spatial resolution of fTCD which assesses changes in CBFV over the whole vascular territory of the insonated artery this approach (see Section 2.3.3) does not distinguish between more focal ROIs known to be associated with language functioning, such as the IFG or Wernicke’s area. Neuroimaging techniques like fMRI are required to further clarify the association by exploring in detail specific ROIs and cognitive ability. Differences in findings between these studies may also be due to the laterality index (LI) used or the cognitive functions assessed, much of which has focused on the laterality of a single function, namely language. Further details on how LIs may be calculated when using fMRI are given in Section 4.5.5.

Some reports also indicate exaggerated asymmetry in language associated cortex to be related to increased cognitive ability (Toga and Thompson, 2003). For example, Schlaug *et al* (1995) found leftward planum temporale asymmetry to be twice as great in musicians as in non-musicians, and greatest of all in those with perfect pitch. Exaggerated asymmetries might therefore, indicate increased capabilities in processing certain auditory features (Steinmetz, 1996). A follow up study (Keenan *et al.*, 2001) revealed that the pronounced asymmetry in the perfect-pitch group was attributable to a smaller right (rather than enlarged left) planum temporale compared with non-musician controls or musicians without perfect pitch. Furthermore, decreased planum temporale volume asymmetries have been reported in some subjects with reading disorders and developmental dyslexia (Hynd *et al.*, 1990; Larsen *et al.*, 1990). Hynd *et al* (1995) reported reversed planar asymmetry (that is, larger right planum temporale) in nine out of ten right-handed dyslexic children. Dyslexic individuals with phonological processing deficits also show reduced planum temporale asymmetry (Larsen *et al.*, 1990).

The interactions of the laterality of language and spatial processing with handedness are still unclear. Some assume that language and spatial laterality dissociate between the hemispheres (Knecht *et al.*, 2001, 2002; Lezak, 1995). As most right-handers (>95%) show left-hemispheric language dominance, most right-handers are expected to display right-hemispheric spatial dominance. However, other studies suggest that language and spatial laterality are largely independent (Badzakova-Trajkov *et al.*, 2010; Bryden *et al.*, 1983; Whitehouse and Bishop, 2009). Badzakova-Trajkov *et al.* (2010) measured three functions showing a predominant laterality: leftward dominance for language (assessed in the frontal lobes using the word generation task) and rightward dominance for emotional (face-processing, temporal lobe) and spatial processing (parietal lobe). They found that left-frontal, right-temporal and right-parietal dominance was intercorrelated.

While handedness was associated with left-frontal laterality for language, no association was found between handedness and parietal laterality for spatial processing.

2.2.5 Cognitive advantages of an asymmetric brain

A number of theories have been proposed to explain hemispheric specialisation in the brain. One advantage of hemispheric specialisation is that it avoids unnecessary duplication of expensive neural tissue and this may be especially important in complex functions, such as language, which requires extensive neural circuitry. Complementary specialisation in the two hemispheres is thought to result in a gain in overall computational efficiency. Most individuals for instance, demonstrate left-hemisphere dominance for language and right-hemispheric dominance for spatial attention (see Section 2.3.3).

A second advantage of lateralization is that dominance by one side of the brain is a convenient way of preventing simultaneous initiation of incompatible responses. This is particularly important in organisms with laterally placed eyes for instance (Andrew, 1991; Cantalupo *et al*., 1995; Vallortigara, 2000). Duplication of programming in the two hemispheres might lead to interhemispheric conflict also referred to by Crow *et al* (1998) as "hemispheric indecision". Stuttering, for example, is a complex motor speech disorder which has been associated with bilateral language lateralization (Nil *et al.,* 2000; Sussman, 1982), atypical prefrontal and occipital lobe asymmetries (Foundas *et al.*, 2003) and reduced planum temporale asymmetry (Foundas *et al.*, 2001).

Another advantage of lateralization is related to the transfer of information within the hemisphere. Bilateral control of information is constrained by the relatively slow conduction time between hemispheres, whereas unilateral computations i.e. computations taking place within a single hemisphere, can be carried out with greater speed (Ringo *et al*., 1994). It has been speculated that during language development functional clustering in one hemisphere allows faster linguistic processing because transmission times between brain regions within one hemisphere are shorter than when signals have to cross the corpus callosum i.e. transhemispheric operations (Nowicka and Tacikowski., 2011). Signals sent between anterior and posterior language associated cortex within the same hemisphere is likely to result in increased connectivity between the regions resulting in faster transmission of signals. Increased connectivity is reflected in greater WM anisotropy (a measure of WM integrity) as assessed with DTI techniques. The fact that language is lateralized to the left hemisphere in the majority of people and there is increased WM integrity in the AF in the left hemisphere (the language associated WM tract) provides some support for this claim.

Ringo *et al* (1994) suggest that hemispheric specialisation may depend on the size of the brain. In larger brains signals being sent from one brain region to another must cover larger distances in comparison to that of smaller brains. As explained in Section 2.2 the speed in which information is passed from one brain region to another is an important factor for IPC and efficient processing of information. To increase conduction speed in larger brains they suggest that the distance the signals travel may have been limited by way of a more local, intrahemispheric organisation of information processing. This has been used to explain the sex differences in functional and structural lateralization for language (Josse and Tzourio-Mazoyer, 2004). Since men have larger brains than women (Amunts *et al*., 2000; Good *et al*., 2001a; Gur *et al*., 1999) and smaller brains have larger corpus callosum's as compared to the size of their brain (Jäncke *et al*., 1997), the less marked hemispheric lateralization in females is reflected in the weaker anatomical asymmetries and a larger corpus callosum (Luders *et al*., 2002). Studies of sex difference support the view that a smaller brain size goes along with a less marked hemispheric specialisation for language as seems to be the case in women (Jäncke *et al*., 1997; Luders *et al*., 2002; Ringo *et al*., 1994). Understanding the way in which the brain is organised to send and receive signals is important as the speed with which information is sent from one region to the next is an important factor for intelligence (Deary *et al*., 2010).

Overall these theories suggest hemispheric specialisation may be advantageous for a number of reasons including, the speed of information transfer, the sparing of neural tissue and reducing the possibility of inter-hemispheric conflict. While these theories are difficult to test empirically there does appear to be a consensus that laterality for the individual proposes a number of distinct advantages. To my knowledge no study to date has looked at the combined effect of language and spatial lateralization on cognitive ability. This thesis investigates the association between handedness, cognitive ability and laterality of both language and spatial processing using fMRI in focal ROIs. The interactive effect of these lateralities on cognitive ability is explored in Chapter 7.

2.3 CEREBRAL ASYMMETRY, LATERALITY AND HANDEDNESS

2.3.1 Grey matter asymmetry and handedness

The brain is asymmetric in structure. In the majority of cases the frontal lobe is larger in the right hemisphere and the occipital lobe is larger in the left hemisphere. This clockwise twist in brain morphology is called the "*Yakovlevian* torque". Structural neuroimaging studies have shown this torque to be more prominent in right-handers (Kertesz *et al*., 1986; Le May and Kido, 1978).

The relationship between structure and function was first discovered over 150 years ago by Paul Broca, who observed that expressive aphasia results from damage to the posterior inferior frontal gyrus (IFG), which corresponds to pars opercularis (PO) and pars triangularis (PTR) in the left hemisphere, now known as Broca's area. Damage in the right hemisphere homologue does not produce the same deficit in language production. A wealth of functional neuroimaging, electrical stimulation and lesion studies confirm that the left hemisphere is specialised for language, and specifically that these cortical regions (PO in particular) are crucial for speech production (Costafreda *et al*., 2006; Geschwind and Galaburda, 1985; Geschwind and Levitsky, 1968; Hutsler and Galuske, 2003; Stephan *et al*., 2003; Toga and Thompson, 2003). A review of the literature on language (and spatial) laterality is given in Section 2.3.3.

The functional lateralization for language has prompted many researchers to determine leftward asymmetry by exploring the left hemisphere Broca area and the right hemisphere homologue (Keller *et al*., 2009a). For example, a post-mortem study has shown leftward asymmetry in the cortical surface area of the PO and PTR (Falzi *et al*., 1982). Geschwind and Miller (2001) point out how the functional language lateralization is correlated with the structural asymmetry of Broca's area in the IFG and the planum temporale in the posterior temporal lobe (Wernicke's area) (Foundas *et al*., 1995; Galaburda, 1980; Geschwind and Levitsky, 1968; Witelson, 1977). These two regions are located on the anterior and posterior boundaries of the Sylvian fissure in the left hemisphere of most individuals and are known to be involved in language production and language perception, respectively.

The literature exploring asymmetry of the IFG is inconsistent. Whilst some studies have found asymmetry of the posterior IFG (Albanese *et al*., 1989; Amunts *et al*., 1999, 2003; Falzi *et al*., 1982; Foundas *et al*., 1998, 2001; Keller *et al*., 2007; Uylings *et al*., 2006) others have not (Good *et al*., 2001a; Herve *et al*., 2006; Luders *et al*., 2004; Tomaiuolo *et al*., 1999; Wada *et al*., 1975; Watkins *et al*., 2001). This discrepancy might be due to: methodological differences in region of interest (ROI) boundary definitions; variability in morphology of the ROI, for instance, lateralized presence of the diagonal sulcus within the PO has been associated with increased PO volume (Keller *et al*., 2007); or differences in handedness and/or sex, both of which influence regional brain asymmetries (for review see Toga and Thompson, 2003).

Handedness is a particularly important factor to consider when exploring anatomical asymmetries of the language-associated regions (Steinmetz *et al.*, 1989, 1991). For example handedness is shown to be related to planum temporale asymmetry (Habib *et al*., 1995; Steinmetz *et al*.1989). However it should also be noted that studies based on large samples of subjects have failed to detect an effect of handedness on brain structure including anatomical asymmetry (e.g. Good et al., 2001a).

Although a number of studies have examined asymmetries in anterior speech regions in right- and left-handers (e.g. Foundas *et al*., 1995; Foundas *et al*., 1998), they have not addressed the interaction of handedness and sex on this asymmetry, perhaps because of small sample sizes used. Such interaction is important, as sex differences in anatomical measures of asymmetry (e.g. surface are or volume) have been described for several regions including the corpus callosum, anterior speech regions, and perisylvian regions such as the Sylvian fissure and planum parietale (Amunts *et al*., 2000; Beaton, 1997; Berrebi *et al*., 1988; Geschwind and Galaburda, 1985; Good *et al*., 2001a; Ide *et al*., 1996; Jäncke *et al*., 1994; Kertesz *et al*., 1990; Paus *et al*., 1996; Steinmetz *et al*., 1995; Wisniewski, 1998; Witelson and Kigar, 1992). Good *et al* (2001a) for example, using voxel-based morphometry (VBM) report increased leftward GM volume asymmetry within Heschl’s gyrus (HG) and the planum temporale in males compared to females. However, several studies failed to detect sex differences in brain structure (Foundas *et al*., 1999; Watkins *et al*., 2001).

The interaction between sex and handedness may be affecting the differences in asymmetry observed in separate groups of left- and right-handers and males and females. An interaction between the effects of handedness and sex on anatomical differences in the brain is supported by planimetric studies of the corpus callosum (Cowell *et al*., 1993; Witelson, 1989), anatomical measurements of the Sylvian fissure (Witelson and Kigar, 1992), diffusion tensor imaging studies (Hagmann *et al*., 2006) and studies using patients with quadrant lesions (Gur *et al*., 1982). The effect of handedness seems to be greater for males, this is supported by VBM studies on structural images (Pujol *et al*., 2002; Watkins *et al*., 2001), morphology (Witelson and Kigar, 1992), morphometry (Witelson, 1989) and DTI (Hagmann *et al*., 2006) studies using healthy subjects. For instance, Witelson (1989) found that handedness was a factor in corpus callosum size for males but not females. Witelson and Kigar (1992) documented anatomical details of the Sylvian fissure as a measure of language lateralization in 67 post-mortem brains (24 males), and found that these correlated with handedness in males but not females: specifically, right-handed males had longer horizontal Sylvian fissure segments in both hemispheres than males who were not consistently right-handed, while the direction and magnitude of asymmetry did not differ between these two groups. This thesis considers the interaction between handedness and sex on PO and PTR volume asymmetry (see Chapters 5).

Few studies have examined the sulco-gyral anatomy of the anterior speech regions (Keller *et al*., 2007; Keller *et al*., 2009b; Ono *et al*., 1990; Tomaiuolo *et al*., 1999). Keller *et al* (2007) found great variation in the morphology and sulcal connection patterns between the inferior frontal sulcus, inferior precentral sulcus and diagonal sulcus in 50 subjects of which 13 were left-handed. The sulcal contours defining the PO and PTR were not however, explored in relation to handedness. This thesis considers the effect of handedness and sex on the sulcal contours defining the PO and PTR (see Chapter 5).

2.3.2 White matter asymmetry and handedness

Traditionally research on structural asymmetries has focussed on grey matter (GM) volume using region-of-interest measurements of the cerebral cortex (e.g. Amunts *et al*., 2003; Keller *et al*., 2007) or voxel-based statistics on large data sets (e.g. Good *et al*., 2001a,b; Watkins *et al*., 2001). Cortical regions in isolation cannot, however, perform all language processing. Rather, it is the active network of regions, connected by white matter (WM) fibre bundles, that is required (Frederici, 2009). Given the structural asymmetries and functional lateralities reported in language-associated cortical regions, similar asymmetries in WM structure particularly language-associated cortical fibres are thought to exist. Voxel based morphometry (VBM) studies performed on GM and WM densities have shown differences between the two hemispheres (e.g. Barrick *et al*., 2005; Good *et al*., 2001a, Luders *et al*., 2004; Watkins *et al*., 2001). These studies however, found no significant effect for handedness. Hervé *et al* (2006) examined cerebral anatomical asymmetry in 56 right- and 56 left-handed males using VBM and observed leftward WM asymmetry in both groups. Their study found that only two small WM asymmetry clusters differed between the left- and right-handed groups ($P<0.001$) in the cerebellum and middle frontal gyrus, however results were uncorrected for multiple comparisons. Whilst studies using VBM on structural MR images have found no clear effect of handedness on GM or WM asymmetries Watkins *et al* (2001) in a sample of 142 subjects, found variations in T-statistics for WM volume (with greater T-statistics in males and right-handers for leftward WM volume asymmetry) when processing, separately, groups of either men or right-handed subjects. The suggestion here is that a significant effect for sex and/or handedness may be detected in a larger sample of subjects balanced for sex and handedness.

Recent years have seen a growth in voxel-based studies exploring diffusion anisotropy (Barnea-Goraly *et al*., 2003; Büchel *et al*., 2004; Burns *et al*., 2003; Eriksson *et al*., 2001; Foong *et al*., 2002; Park *et al*., 2004; Rugg-Gunn *et al*., 2001). Using a voxel-based approach Büchel *et al* (2004) found leftward fractional anisotropy (FA) asymmetry in a C-shaped structure connecting temporal and frontal cortex. This C-shaped structure was thought to represent the arcuate fasciculus (AF), the main WM pathway connecting frontal (Broca's area) and parieto-temporal language areas and is thought to play a major role in language functioning (e.g. Catani *et al*., 2007; Friederici, 2009; Glasser and Rilling, 2008). An image of the AF can be seen in Figure 2.2. Takao *et al* (2010) explored FA asymmetry by performing VBM on asymmetric FA images in a sample comprising only right-handed subjects. Results revealed a significant leftward FA asymmetry in the AF, cingulate fasciculus and cortico-spinal tract. Additionally cognitive abilities have been correlated with measures of WM such as FA to explain some of the variance in performance within samples of healthy subjects and clinical populations, such as schizophrenic patients (e.g. Karlsgodt *et al*., 2008).

Findings using FA maps obtained from DTI show asymmetries in similar anatomical regions to those observed when exploring WM volume asymmetries using WM segments from T_1-weighted images (e.g. Good *et al*., 2001a; Paus *et al*., 1999; Pujol *et al*., 2002). Good *et al* (2001a) for instance, observed WM asymmetry in occipital, frontal, and temporal lobes, including Heschl's gyrus, planum temporale (PT) and the hippocampal formation and there was no significant effect for handedness. Additionally diffusion tensor (DT) tractography studies provide supporting evidence for a structural asymmetry of the AF (Catani *et al*., 2007; Glasser and Rilling, 2008; Hagmann *et al*., 2006; Nucifora *et al*., 2005; Parker *et al*., 2005; Powell *et al*., 2006) and suggest that language networks represent a more likely anatomical substrate for lateralization of language function than cortical areas alone. It should be noted however, that there are discrepant findings in the literature regarding the existence of the AF in the right hemisphere. While Catani *et al* (2007) report a right hemispheric AF representation in around 40% of their right-handed subjects Gharabarghi *et al* (2009) using a similar identification approach to that of Catani *et al* (2005, 2007), were able to identify both direct and indirect language pathways in the right hemisphere in all 12 of their right-handed subjects. Vernooij *et al* (2007) were able to identify a right hemisphere AF in their 20 subjects and additionally report leftward asymmetry of the AF in 80% of individuals. Moreover subjects comprised 13 left- and 7 right-handers.

What is evident from the literature is leftward laterality of WM language tracts whether this is assessed using volumetric measures such as VBM on WM images, voxel-wise statistical analysis of FA maps or asymmetry calculations of WM fibres as obtained using DT-tractography. What is unclear from the literature is whether differences in WM anisotropy asymmetry or WM volume asymmetry between left- and right-handed groups exist. To date the research provides no compelling evidence to suggest any significant effect of handedness on WM language tracts.

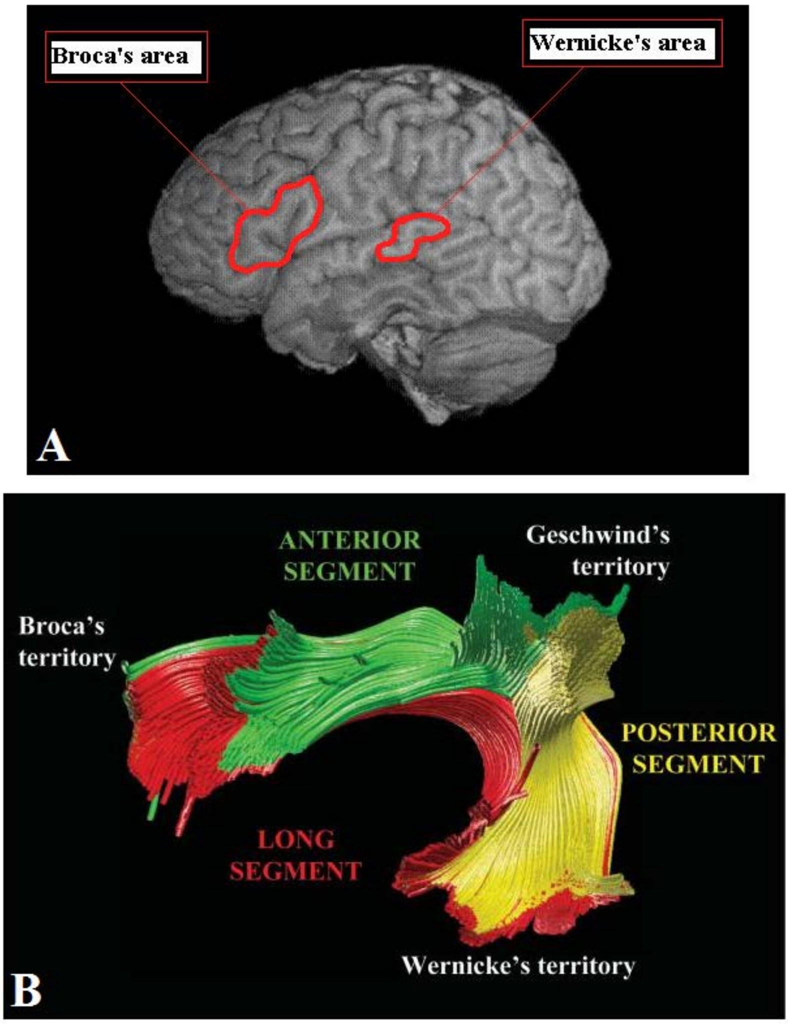


Figure 2.2. Broca's area, Wernicke's area and the arcuate fasciculus (AF). Broca's area and Wernicke's can be seen in the top image, these regions are located in the frontal and temporal lobe respectively. The AF can be seen in the bottom image extending from Broca's area to Wernicke's area. The long segment connects these regions directly. However another pathway connecting these regions is thought to exist. This pathway is broken and is composed of two pathways: an anterior and a posterior pathway which goes through Geschwind's territory. The top image was created from the T_1-weighted MR image of a subject used in this thesis and the bottom image is taken directly from Catani *et al* (2005).

Most diffusion asymmetry studies have focused exclusively on right-handers (Barrick *et al*., 2007; Catani *et al*., 2005, 2007; Gharabaghi *et al*., 2009; Glasser and Rilling, 2008; Nucifora *et al*., 2005; Powell *et al*., 2006; Xiang *et al*., 2009; Yu *et al*., 2008) and the few studies that have considered left-handers (Büchel *et al*., 2004; Hagmann *et al*., 2006; Saur *et al*., 2008; Vernooij *et al*., 2007) have examined only small numbers (i.e. between 9-16 left-handed subjects). Hagmann *et al* (2006) also studied the interaction between sex and handedness on fibre tract connectivity and observed left hemisphere fibre tract differences between right and left-handers in men to a much greater extent than in women. Takao *et al* (2011) showed in a sample of 109 right-handers aged 21-29 years GM and WM asymmetries using voxel-based analysis of FA maps derived from DTI. Leftward WM anisotropy asymmetries were observed in the AF, cingulum and corticospinal tract. However, no effect of sex on GM or WM asymmetry was observed. No study to my knowledge, has examined differences in WM integrity across the whole brain between left and right-handers.

2.3.3 Cerebral laterality and handedness

A wealth of functional neuroimaging, electrical stimulation and lesion studies confirm that the left hemisphere is specialised for language, and specifically that these cortical regions (left hemisphere PO in particular) are crucial for speech production (Costafreda *et al*., 2006; Geschwind & Galaburda, 1985; Geschwind & Levitsky, 1968; Stephan *et al*., 2003; Toga & Thompson, 2003).

Neuroimaging and neuropsychological research indicates that language and spatial attention are subserved by large scale cognitive networks which are lateralized to one hemisphere (Bookheimer, 2002; Nobre and Plunkett, 1997; Ojemann, 1991), with the left hemisphere implicated in the processing of language, and the right hemisphere implicated in spatial processing. The proportion of individuals with left and right hemispheric language and spatial dominances has now been examined in large groups of healthy subjects using various non-invasive functional imaging techniques including fMRI and functional Transcranial Doppler sonography (fTCD) (a sample of these studies can be seen in Table 2.1). Handedness has been assessed, in these studies using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), allowing easy comparison across studies. The majority of these studies have examined handedness as a dichotomous variable (i.e. left- and right-handers). Of those presented two studies (Flöel *et al*., 2005; Jansen *et al*., 2004) also report spatial lateralization in addition to language lateralization. fTCD measures changes in event-related cerebral perfusion that are related to neuronal activation in a way comparable with fMRI (Deppe *et al*., 2000).

Because fTCD integrates and averages repeated activations within the whole territory of the insonated artery, which in the case of language would be the middle cerebral artery (MCA) (van der Zwan *et al*., 1993), it provides a reliable measure of hemispheric language lateralization (Knecht *et al*., 1996, 1998a, 2000a,b; Deppe *et al*., 1997). All the fTCD studies outlined in Table 2.1 have assessed the activity-related perfusion changes in the vascular territories of the left and right MCA's.

The spatial resolution of fTCD is limited, however, because cerebral blood flow velocity (CBFV) changes are integrated over the whole vascular territory of the insonated artery (i.e. the MCA) (van der Zwan *et al*., 1993). fTCD does not therefore allow the investigation of brain laterality in smaller ROIs. fMRI provides much better spatial resolution (in the region of 2-3mm) allowing the investigator to more precisely define ROIs known to be involved in a particular task, for instance, the IFG during word production. The application of fTCD has been cross-validated with fMRI (Deppe *et al*., 2000; Jansen *et al*., 2004; Knecht *et al*., 2003) and the WADA test (Knecht *et al*., 1998b) indicating that large cohorts can be scanned for language and spatial hemispheric dominance using fTCD, which will provide consistent results to that of fMRI. The use of fMRI is then applicable for in-depth assessment of the specific patterns of activation within smaller ROIs.

Research on the association between handedness and language lateralization spans at least the last four decades and is thought to comprise over 10,000 studies (Sommer, 2010). The general consensus to emerge from these studies is a difference in language lateralization between left- and right-handers (e.g. Annett & Alexander, 1996; Cabeza and Nyberg, 2000; Cabeza *et al*., 2004; Corballis, 2003; Deppe *et al*., 2000; Flöel *et al*., 2005; Knecht *et al*., 2001; Pujol *et al*., 1999). For instance, Pujol *et al*. (1999) found that 76% of left-handers demonstrate left-hemisphere language dominance, 14% show bilateral language dominance, and 10% show right-hemisphere language, while 96% of right-handers demonstrate left hemisphere dominance for language and 4% show bilateral language dominance. Similar findings were reported by Flöel *et al*. (2005). The proportion of left-handers with right-hemisphere language dominance is clearly far greater than that observed in right-handers. This is a robust finding which has been demonstrated using different methodologies, including: the WADA test (Rasmussen and Milner, 1977; Zatorre, 1989); fMRI (Deppe *et al*., 2000; Pujol *et al*., 1999;

Szaflarski *et al*., 2002); and fTCD (Deppe *et al*., 2000; Flöel *et al*., 2005; Knecht *et al*., 2000a, 2001). Quantitative studies with large subject samples also suggest the existence of a continuum of language lateralization patterns ranging from strongly left dominant to strongly right dominant (Frost *et al*., 1999; Knecht *et al*., 2000a; Pujol *et al*., 1999; Springer *et al*., 1999; Tzourio *et al*., 1998).

The fact that handedness and language laterality are related has aroused considerable debate as to their evolutionary origins and the causality of this association (for a review on this association see Corballis, 2003). There appears to be some consensus that language may have evolved from manual gestures not from vocal calls (e.g. Arbib, 2005; Armstrong *et al*., 1995; Armstrong and Wilcox, 2007; Corballis, 2003; Pollock and de Waal, 2007; Rizzolatti and Sinigaglia, 2008; Tomasello, 2008).

Other research has attempted to localise characteristics of language to regions within the dominant hemisphere. A large proportion of these studies assessing hemispheric dominance for language have established language lateralization using language production tasks. Language production and some aspects of semantic processing (Binder *et al.*, 2000; Dapretto and Bookheimer, 1999) are localised primarily to areas of the anterior left hemisphere, including the PO and PTR of the IFG (Broca’s area). Lesions to this area have effects including inability to generate word lists (Binder *et al*., 1997). By contrast, language comprehension, such as understanding spoken words (Price, 2000), is confined primarily to the posterior temporal-parietal region, including Wernicke’s area (Brodmann Areas (BA’s) 39 and 40, posterior BA21, BA22, and part of BA37).

Table 2.1. A sample of studies assessing language and spatial laterality using fTCD, fMRI or the Wada test. Left = left hemispheric laterality; Right = right hemispheric laterality; LH = Left-handers; RH = Right-handers.

Authors	fTCD/fMRI/ Wada	Number of subjects (sex)	Handedness	Laterality assessed	Hemispheric laterality (%)
Knecht *et al* (1998a)	fTCD	11 (7 male)	*not reported*	Language	Left: 60; Right:10; Bilateral: 30
Knecht *et al* (1998b)	fTCD/Wada	19 (12 male)	13RH, 6LH	Language	Left: 73.3; Right: 20; Bilateral: 6.7
Pujol *et al* (1999)	fMRI	100 (50 male)	50LH, 50RH	Language	**RH**: Left: 96; Bilateral: 4 **LH**: Left: 76; Right: 10; Bilateral: 14
Knecht *et al* (2000a)	fTCD	326 (128 male)	*not reported*	Language	Left: 80; Right: 10; Bilateral: 10
Deppe *et al* (2000)	fTCD/fMRI	13 (7 male)	9RH, 4LH	Language	**RH**: Left: 67; Right: 33 **LH**: Left: 25; Right: 75
Knecht *et al* (2001)	fTCD	326 (128 male)	*not reported*	Language	Left: 80; Right: 10; Bilateral: 10
Szaflarski *et al* (2002)	fMRI	50 (sex not stated)	50 non-right handers	Language	Left: 78; Right: 8; Bilateral: 14
Knecht *et al* (2003)	fTCD/fMRI	14 (7 male)	9RH, 5LH	Language	**RH**: Left: 67; Right: 33 **LH**: Left: 20; Right 80
Jansen *et al* (2004)	fTCD/fMRI	15 (7 male)	9RH, 6LH	Language Spatial	Language: Left: 67; Right: 33 Spatial: Left: 20; Right: 80
Flöel *et al* (2005)	fTCD	75 (33 male)	37RH, 38LH	Language Spatial	**RH:** Language: Left: 97; Right: 3 **RH:** Spatial: Left: 5; Right: 95 **LH:** Language: Left: 74; Right: 26 **LH:** Spatial: Left: 19; Right: 81

Note: All studies except Szaflarski et al (2002) used the word generation to establish language laterality. Spatial laterality was assessed using the landmark task. Studies which selected participants based on their language laterality were: Deppe et al., 2000; Knecht et al., 2003; Jansen et al., 2004.

In an fMRI study using the word generation task Deppe *et al* (2000) indicate the main foci of activity for the word generation task to be in the IFG and middle frontal gyrus, corresponding to BA44, BA45, and BA46 (Broca area) and BA9. Knecht *et al* (2003) found in their study of 14 subjects that word generation leads to a unilateral activation of the posterior middle frontal gyrus and IFG, including classical Broca's area, as well as premotor cortex. Additionally, BA22 and BA38 in the superior temporal gyrus were found activated, regions known to be involved in language comprehension (Vandenberghe *et al*., 1996; Wise *et al*., 1991). Bilateral activation was seen in BA32, BA38 and BA47, supporting previous studies (e.g. Lurito *et al*., 2000). Knecht *et al* (2003) found no increased activation in the subdominant hemisphere in subjects with typical or atypical language laterality, and observed similar variability in the pattern of activation in both groups. Furthermore, a mirror reversed pattern of activation in right- compared to left-hemisphere dominant subjects was demonstrated. The use of the word generation task constitutes an essential feature in the production of language and is proven to be a robust task in eliciting language laterality. The word generation task was used in this thesis to activate language associated cortex.

Although language-related activation in healthy right-handed subjects is predominantly left hemispheric, almost all subjects activate right hemisphere areas to some extent during functional imaging studies (Buckner *et al*., 1995; Pujol *et al*., 1999; Springer *et al*., 1999; Tzourio *et al*., 1998). Some aspects of linguistic function such as processing the prosodic, emotional and melodic aspects of language are thought to be performed by the non-dominant hemisphere. Rather than processing the literal meanings of words, the right hemisphere is thought to interpret the figurative meanings in language, conveyed by humour and metaphor, as well as hesitations and tone of voice (Toga and Thompson, 2003). Whether the right hemisphere continues to take on these roles, even in those individuals with language highly lateralized to the right remains unknown.

Sex differences are reported in brain structure and function (for a review see Cosgrove *et al*., 2007). The literature on the influence of sex on language laterality is inconsistent. Results tend to indicate that hemispheric specialisation is less marked in females (Baxter *et al*., 2003; Gur *et al*., 2000; Jaeger *et al*., 1998; Kansaku *et al*., 2000; Shaywitz *et al*., 1995). For instance, Shaywitz *et al* (1995) used fMRI during a phonological rhyming task in 19 males and 19 females and observed leftward lateralization in males but no clear lateralization in females. Other studies however, report no difference between men and women (Frost *et al*., 1999; Hund-Georgiadis *et al*., 2002), and show a leftward lateralization in both sexes. A meta-analysis of the fMRI data from 2,151 subjects from 26 studies found no effect of sex of language lateralization (Sommer, 2010). Using data from a sample of 3,822 subjects the effect of sex on dichotic listening tasks was investigated (Sommer, 2010). The effect of sex was not significant with both sexes demonstrating a right ear advantage (REA). Additionally the inclusion of non-right-handed subjects had no major influence on the sex difference in language lateralization. Inconsistent findings related to the effect of sex on language lateralization suggest that the difference, if any, in the functional organisation of language functioning is small.

Studies which have focused on visuospatial lateralization suggest preferential processing of the right hemisphere (Dupont *et al*., 1998; Faillenot *et al*., 2001; Marshall and Fink, 2001; Ng *et al*., 2001; Orban *et al*., 1997; Vandenberghe *et al*., 1996), with activation observed in the right occipito-temporal cortex, prefrontal cortex (Ng *et al*., 2001; Vandenberghe *et al*., 1996), and parietal cortex (Faillenot *et al*., 2001; Vandenberghe *et al*., 1996). The landmark task is frequently used in the assessment of hemispheric spatial dominance. Jansen *et al* (2004) using fMRI found that the landmark task activates a large neurocognitive network, with the main activation centres located in the anterior cingulate cortex (BA24/BA32), lateral parietal cortex (BA7/BA40) and frontal cortex (BA45/BA10). Consistently studies show activation predominantly within parietal cortex during the landmark task (e.g. Fink *et al*., 2000, 2001; Marshall *et al*., 1997). The landmark task was used in this thesis to activate spatial associated cortex.

Little is known about the association between handedness and visuospatial processing and even less is known about the effect of handedness on the interaction between language and spatial lateralization. Those studies that have investigated spatial lateralization in conjunction with that of language using fTCD report a distribution for spatial lateralization with handedness, similar to that of language lateralization and handedness (Flöel *et al*., 2001; Flöel *et al*., 2005; Jansen *et al*., 2004). Using fTCD in a sample of 37 right- and 38 left-handers Flöel *et al* (2005) showed that a greater proportion of right-handers display right hemispheric spatial dominance than left-handers. However, this research whilst able to demonstrate proportions of hemispheric dominance for a given task is limited as the functional organisation of these lateralized processes within the dominant hemisphere cannot be explored using fTCD. Thus the question of concomitant left hemisphere activation for visuospatial processing within specific ROIs requires elucidation as does the interaction between language and spatial lateralities within specified ROIs.

Since it is generally assumed that lateralization of language and spatial attention dissociate between the hemispheres (Knecht *et al.*, 1998a, 2001, 2002; LeDoux, 2003 Lezak, 1995) right-handed subjects are expected to display right-hemispheric attentional dominance. Indeed, for right-handed subjects, this pattern of lateralization has been found in the majority of cases in lesion (Alexander and Annett, 1996) and functional imaging studies (Cabeza and Nyberg, 2000; Fink *et al.*, 2000; Flöel *et al.*, 2001, 2002; Gitelman *et al.*, 1999; Jansen *et al.*, 2004). However, reports based on small number of subjects using lesion studies (Alexander and Annett, 1996; Osmon *et al.*, 1998; Trojano *et al.*, 1994; Weintraub and Mesulam, 1987) and activation studies (Flöel *et al.*, 2001, 2005; Jansen *et al.*, 2004) indicate that a dissociation of language and attention is not an invariable principle of brain organisation (see Flöel *et al.*, 2005 and Jansen *et al.*, 2004 in Table 2.1). For instance, Flöel *et al* (2005) reported using a sample of 75 subjects an association of language and visuospatial attention within the left hemisphere in 5 subjects and within the right hemisphere in 8 subjects.

Other studies have suggested that left- and right-hemisphere dominances are largely independent (Badzakova-Trajkov *et al.*, 2010; Bryden *et al.*, 1983; Whitehouse and Bishop, 2009). Badzakova-Trajkov *et al.* (2010) measured three functions showing a predominant laterality: leftward dominance for language (assessed in the frontal lobes using the word generation task) and rightward dominance for emotional (face-processing, temporal lobe) and spatial processing (parietal lobe). They found left-frontal, right-temporal and right-parietal dominance to be intercorrelated. While handedness was associated with left-frontal laterality for language, no association was found between handedness and parietal laterality for spatial processing.

2.4 QUANTIFICATION OF GREY AND WHITE MATTER

The human brain corresponds to roughly 2% of body mass (Roth and Dicke, 2005). Relative brain size is an important measure, as mammals with relatively larger brains are often assumed to be more intelligent (Jerison, 1973). As body size increases, brain size (i.e. brain volume) increases in a negatively allometric way following a power function with an exponent of 0.6-0.8 (Hofman, 2003; Jerison, 1973). This means that with increasing body size, brains become absolutely larger, but relatively smaller. It is assumed that animals with both larger and relatively larger brains are more intelligent than those with smaller ones (Deaner *et al*., 2007; Gibson *et al*., 2001). Quantifying brain size within species is important in the field of intelligence because larger total brain volume (McDaniel, 2005; Rushton and Ankney, 2009) and regional brain volume (Andreasen *et al*., 1993; Flashman *et al*., 1997; Witelson *et al*., 2006) have been associated with increased intelligence in humans.

The mechanisms underlying the association between brain size and cognitive ability remains unclear. An increase in neuronal number is associated with larger brains, greater GM volumes and thicker cortices (Pakkenberg and Gundersen, 1997), however why this is advantageous to intellectual performance is unclear. One suggestion may relate to a greater number of synaptic connections however, given that brain development involves substantial neuronal pruning (Luo and O’Leary, 2005) and enlarged brains are associated with decreased rather than increased cognitive functions (Deary *et al*., 2010) this hypothesis is likely inadequate in explaining the observed associations. However, it should also be pointed out here that an increase in neuronal number and an increase in axons are not contradictory. One (albeit unsubstantiated) explanation might be that efficient synaptic connections are associated with increased cognitive capacity, but that thicker and/or more GM is also associated with increased intellectual capacity within regional brain areas due to an abundance of multipolar interneurons (i.e. neurons without axons). In this respect the efficient myelinated axons transfer signals to regions where multipolar interneurons integrate these signals. This of course is just conjecture and further research would be required to substantiate this hypothesis.

Information processing capacity (IPC) is defined by Ramsey *et al* (2004) as “the amount [of information] that can be processed simultaneously” (p. 517). It is essentially the extent to which an individual: receives, stores, integrates, retrieves and uses information. IPC is closely related to efficient processing, which is thought to be an important factor for intelligence as more intelligent people react to and inspect visual and auditory stimuli more rapidly than less intelligent people (Deary *et al.*, 2010). An important factor for IPC is conduction velocity of cortical fibres, which is chiefly determined by the diameter of myelinated fibres (Roth and Dicke, 2005). Myelinated cortical fibres are particularly thick in primates (Changizi, 2001; Zhang and Sejnowski, 2000) and thinner fibres have a much lower conduction velocity. The speed with which signals pass from one brain region to the next is an important factor for IPC.

While humans do not have the largest brain or cortex either in absolute or relative terms, they do have the largest number of cortical neurons, owing to the thickness and relatively high cell density in the cortex (for review see Roth and Dicke, 2005). Given the higher conduction velocity and smaller distances between neurons Roth and Dicke (2005) suggest that the human cortex probably has the greatest IPC, which may partially explain the increased intelligence seen in this species.

The human cortex however, is not a homogenous structure. There is variability in the intra-cortical organization in mammals regarding density, size and shape of the pyramidal cells and spine density (de Felipe *et al.*, 2002; Elston, 2002). For instance, dendrites are more branched in the prefrontal cortex (PFC) than the primary visual area and neurons in the PFC of macaque monkeys and humans carry up to 16 and 23 times more spines respectively than neurons in the primary visual area (de Felipe *et al.*, 2002; Elston *et al.*, 2001). These differences are interpreted as indicating a greater IPC of the PFC (de Felipe *et al.*, 2002). It may therefore, be more fruitful to consider the association between regional brain structures such as the PFC and measures of intellectual capacity than the association between intelligence and global brain volume, particularly for specific cognitive abilities.

Quantifying the amount of GM gives an estimate of the density and number of neuronal bodies and dendritic expansions whereas quantifying WM helps to approximate the number of axons and their degree of myelination (Luders *et al.*, 2009). While the amount of GM might reflect the capacity of information processing centres, the amount of WM might mirror the efficiency of inter-neuronal communication. Thus, individual intelligence might be related to global and/or regional tissue volumes or concentrations (Luders *et al.,* 2009). A better assessment of the contribution of WM to cognitive capacity can be gained by assessing the integrity of WM fibres within the brain. This is a measure of the strength of the connections between distant and adjacent cortical regions, and is thought to reflect the speed of information transfer within the brain.

Previous studies have shown associations between GM volume and increased intellectual functioning (for review see Jung and Haier, 2007). However, the most appropriate measure for quantifying GM (as a measure reflecting IPC), is highly contended. Various methods have been proposed such as quantifying GM volume (Im *et al*., 2008), or cortical thickness (Fischl and Dale, 2000; Im *et al*., 2008) and quantifying cortical surface area (Herculano-Houzel *et al.,* 2008; Im *et al*., 2008; Rockel *et al*., 1980). This increase in GM volume is thought to reflect an increase in neuronal number which is considered a measure of IPC as neurons reflect brain activity. Rockel *et al* (1980) demonstrated a direct association between unit area of cortical surface and neuron number in a sample of five mammalian species. Specifically they demonstrated approximately 147,000 neurons underneath a surface area of 1mm^2. This is important because a post-mortem study, for instance, has shown leftward asymmetry in the cortical surface area of the PO and PTR (Falzi *et al*., 1982). This would imply a greater number of neurons in the left PO and PTR than the right which might therefore explain the leftward lateralization of language. The association between cortical surface area, cortical volume and cortical thickness is not always linear. For instance, Pakkenberg and Gundersen (1997) have shown that a large cortical volume is accompanied by a major increase in cortical surface area but a smaller increase in cortical thickness. Cortical thickness also varies between brain regions (Fischl and Dale, 2000) suggesting no linear relationship between these three measures. Additionally Im *et al* (2008) demonstrated the ratio of cortical GM volume to ICV decreases as brain size increased. Their study also showed that the cortex thickened only slightly but the area increased greatly as brains enlarged indicating that the increases in cortical GM volume in larger brains are driven more by increases in cortical surface area than by cortical thickening.

Roth and Dicke (2005) argue that number of cortical neurons combined with a high conduction velocity of cortical fibres, which are an important parameter for IPC, correlates best with intelligence. This explanation seems entirely plausible given the involvement of both GM and WM in intellectual performance and the differences in the neuroanatomical correlates of intelligence in males and females. Further studies exploring the neuroanatomical correlates of intelligence should take into account both GM and WM in intellectual functioning. It remains to be established whether WM-specific correlations with intelligence are a secondary consequence of GM-specific correlations (or vice versa) or whether there is no general rule but instead, region-specific mechanisms apply. In the absence of this information, the significant positive correlations between GM/WM volumes and intelligence underscore that the structural integrity of particular brain regions is important to support higher cognitive functions (Luders *et al*., 2009) as has been shown in those studies demonstrating associations between GM and WM volumes and higher performance on intelligence tests.

One unexplored area of research is the composition of brain cells within GM. The literature suggests that GM also consists of glia, specifically astrocytes which may also have a functional role in brain activity, and also communicate with neurons bidirectionally. Additionally the literature which has sought to quantify glial cells (a nonneuronal cell) suggests that the ratio of nonneuronal/neuronal cells in the brain differs between regions. This may affect the brain's IPC and reported GM density associated with intellectual functioning. Thus, the increase in GM volume may be associated with increased cognitive ability; however the composition of nonneuronal/neuronal cells is unclear. This thesis quantifies GM volume within predefined brain regions which are located by an expert in brain morphology. Brains are not normalised into standardised stereotaxic space in order to maintain individual variability in gyri and sulcal contours. GM volume is taken here to reflect an increase in neuronal number (although the composition of neuronal and non-neuronal number cannot be established).

2.5 RESEARCH PROBLEMS

Whilst studies continue to demonstrate differences between handedness groups in language associated cortex and language function, particularly language production, there are gaps within the literature. In particular, no study has explored the effect of handedness on the sulcal contours defining language associated cortex. Few studies have considered the interaction between sex and handedness on the PO and PTR. No study has explored the effect of handedness on WM anisotropy or WM anisotropy asymmetry across the whole brain on a voxel-wise level This thesis aims to address these gaps in the literature using functional, structural and diffusion weighted MR images in a group composed of 42 right- and 40 left-handers. These areas are explored in Chapters 5, 6 and 7.

Studies of the relationship between handedness and cognitive performance have reported conflicting results. Left-handed children are overrepresented in the extremely gifted population defined by a Scholastic Aptitude Test (Benbow, 1986; O'Boyle and Benbow, 1990). Some research indicates an advantage for left-handers in musical ability (Aggleton *et al*., 1994; Kopiez *et al*., 2006) and interactive sports (Annett, 1985; Voracek *et al*., 2006). Left-handers are also reportedly overrepresented among individuals exhibiting learning and developmental impairments, and their proportion reportedly increases as IQ decreases (Gregory and Paul, 1980; Pirozzolo and Rayner, 1979). In a study of 687 individuals Mascie-Taylor (1980) found that overall verbal IQ was higher than performance IQ in left-handers, the opposite in right-handers; additionally, left-handers scored higher than right- and mixed-handers on verbal IQ but lower on performance IQ. Mascie-Taylor (1980) suggested that this may reflect an advantage of right-hemispheric language dominance for verbal IQ and of left-hemispheric visuospatial dominance for performance IQ. However, while a greater proportion of right-handers present left-hemispheric language dominance than left-handers, handedness cannot itself be taken as a measure of laterality. The association between handedness and cognitive ability may be influenced by hemisphere dominance rather than being explained entirely by handedness *per se*.

Direct studies of the relationship between brain laterality and cognitive performance are few and the results are inconsistent. For instance, atypical (bilateral or right-sided) language laterality is related to weaker language performance in healthy children (Everts *et al*., 2009) and poorer visuospatial memory performance in children (Gleissner *et al*., 2003) and adults (Loring *et al*., 1999) with left hemisphere epilepsy. Moreover, a rightward language laterality advantage for cognitive ability has been found (Everts *et al*., 2010; van Ettinger-Veenstra *et al*., 2010). Everts *et al* (2010) found a correlation between language laterality and verbal memory performance in patients with left-sided epilepsy, with bilateral or right-sided language laterality being correlated with better verbal memory. A cognitive advantage has also been found in relation to structural asymmetries in the brain, for instance, when there is a symmetrical distribution of language associated WM pathways (Catani *et al*., 2007) and when there is increased leftward asymmetry of the planum temporale (e.g. Schlaug *et al*., 1995). A number of theories (outlined in Section 2.2.5) have been proposed to explain hemispheric specialisation in the brain including, the speed of information transfer, the sparing of neural tissue and reducing the possibility of inter-hemispheric conflict. While these theories are difficult to test empirically, there does appear to be a consensus that laterality for the individual poses a number of distinct advantages.

Crucially, it appears that no study has looked at the interaction between language and spatial laterality on cognitive ability, and this is the aim in this thesis. This is particularly important as the cerebral hemispheres are typically shown to be dominant for language and spatial laterality, the left hemisphere (in particular the inferior frontal gyrus (IFG)) being dominant for language, the right hemisphere (particularly the parietal lobe) for spatial processing. Furthermore, the fact that the majority of individuals show this pattern of laterality suggests it must confer some cognitive advantage. To my knowledge no study to date has looked at the interaction between language and spatial lateralization on cognitive ability. The association between laterality and the cognitive abilities, verbal comprehension, perceptual organisation and working memory as assessed using the WAIS-III is explored in Chapter 7.

The neuroanatomical correlates of intelligence have previously been explored (Andreasen *et al*., 1993; Flashman *et al*., 1997; Gong *et al*., 2005; Gray and Thompson, 2004; MacLullich *et al*., 2002; Toga and Thompson, 2005). Results show associations between both total and regional brain volume and increased cognitive performance (see Luders *et al*., 2009 for review). Typically larger cortical volume is associated with an increase in cognitive performance. The GM correlates of *g*, as assessed on standard psychometric tests, have received considerably more attention when compared with other cognitive functions such as social/emotional cognitive skills.

In a recent study using voxel-based morphometry (VBM) Lebreton *et al* (2009), showed evidence of a structural disposition towards social cognition (Reward Dependence (RD)). Higher social RD in men was related to increased GM density in the orbitofrontal cortex, basal ganglia and temporal poles. An Imposing Memory Task (IMT) was used in this study to assess intentionality competence (see Appendix 1): a social cognitive competence. The task involves complex metalizing about a character's perspective on a social situation (see Section 4.2.3) and is therefore a measure of social cognition. It does not involve past education and knowledge; instead it involves on-the-spot processing and in this respect can be seen as a measure of social fluid intelligence. This particular function is considered important in terms of evolutionary development being thought of as one function responsible for the increase in human brain size. Additionally it is hypothesised here that a close relationship would exist between intentionality and PFC volume as the PFC is the last region to develop in evolution as well as ontogeny. Furthermore the fact that intentionality, as measured here, closely parallels fluid intelligence rather than crystallised intelligence suggests a strong relationship between PFC volume and intentionality is likely: fluid intelligence is typically associated with the frontal lobe (Duncan *et al*., 1995; Roca *et al*., 2010).

The effect of handedness on the association between intentionality and PFC volume is explored. Handedness is a strongly lateralized human behaviour that is observed throughout history and across populations distributed in different geographical locations, suggesting the involvement of some evolutionary mechanisms. However, for selection of this trait to take place, hand laterality should also be heritable (Llaurens *et al.*, 2009). Social cognition itself is considered to involve some evolutionary mechanisms. This thesis considers the interaction between these two functions i.e. handedness and intentionality and the effect of this association on PFC volume.

Little consideration has been given to the neuroanatomical correlates of intelligence of different populations/groups of individuals, with the notable exception of sex (Haier *et al*., 2005; Narr *et al*., 2007). Haier *et al* (2005) suggested that there is no single underlying neuroanatomical structure to *g* and that different types of brain design may manifest equivalent intellectual performance. Identical intelligence test scores in two healthy individuals may be evident, however, such scores may be achieved through different neuronal mechanisms as a result of differences in brain structure and organisation, expertise and training or the cognitive strategies used (Deary *et al*., 2010; Haier *et al*., 2005; Johnson and Bouchard, 2007; Johnson *et al*., 2008a,b). Differences in the neuroanatomical correlates of intelligence in different groups of individuals need to be addressed in order to clarify the normal variation in brain organisation. This principle might apply to other groups known to differ in brain structure and organisation such as left- and right-handers. This thesis investigates the association between regional brain volume estimates (including GM across the whole brain and PFC) and cognitive ability, including verbal comprehension, perceptual organisation, working memory and intentionality in left- and right-handers. The psychometric tests used in this study include subtests from the WAIS-III and an IMT.

2.6 RESEARCH AIMS AND HYPOTHESES

Collectively the literature shows that structural, functional and diffusion data obtained using MRI techniques can contribute to our understanding of the association between handedness, brain laterality and neuroanatomical asymmetry. The reviewed literature highlights a need for further research in a number of important areas outlined below which fall within two main areas. Subsequently this thesis has two main aims. The first is to establish differences in brain structure and function between left- and right-handers and is subdivided into three studies (referred to below as studies I, II and III presented in Chapters 5, 6, and 7 respectively). The second main aim of the thesis is to explore the effect of handedness on the neuroanatomical correlates of cognitive ability, including intentionality (social cognition) and verbal comprehension, perceptual organisation nad working memory (metacognitive EFs). This aim is subdivided into three investigations (referred to below as studies IV, V and VI and are presented in Chapters 7, 8 and 9 respectively).

Study I (Chapter 5**) -** *Sex, handedness and the structural asymmetry of Broca's area*. This study was divided into two parts.

Part one: The aim of part one was to: (i) explore the effect of handedness and sex on the sulcal contours defining PO and PTR, specifically the inferior frontal sulcus (IFS) and diagonal sulcus (DS) and; (ii) investigate the effect of handedness and sex on PO and PTR volume and volume asymmetry.

Volume estimates of the PO and PTR were obtained from T_1-weighted using the Cavalieri method of stereology in combination with point counting. Sulcal contours were assessed using a well defined classification scheme. Linear mixed-effects models were used to test the effect of sex and handedness on PO and PTR volume. The effect of sex and handedness on sulcal contours was tested for using logistic mixed-effects regression analysis.

Part two: The aim of part two was to investigate: (i) the heritability of handedness by exploring the relationship between participant and parental handedness, and (ii) the association between handedness and other lateralized behaviours, specifically foot preference for kicking and eye preference.

The relationship between participants' handedness, eye and foot preference is explored using Chi-Square tests. The effect of parental handedness on participant handedness is explored using a logistic regression model.

Study II (Chapter 6**) -** *Handedness and white matter anisotropy*: This study investigated the effect of handedness on WM anisotropy and WM anisotropy asymmetry across the whole brain. Voxel-wise statistical analysis was performed on fractional anisotropy (FA) maps to compare the underlying WM anisotropy and WM anisotropy asymmetry between left- and right-handed individuals while controlling for other variables.

Study III (Chapter 7**) -** *Handedness, language laterality, spatial laterality and executive function*. This study assessed the effect of handedness on language and spatial processing including both activation and laterality. A word generation task was used to assess language production, and a landmark task was used to assess spatial processing. Laterality indices (LI's) were calculated to assess hemispheric dominance for language and spatial processing in pre-defined ROIs. Activation in response to the word generation task was also calculated in left and right hemisphere IFG for each participant to determine differences in activation between left- and right-handers.

Study IV (Chapter 7**):** Using language and spatial LI's obtained from Study III, a multivariate model was performed to detect the predictive value of a set of variables (handedness direction, sex, language laterality and spatial laterality) on working memory, verbal comprehension and perceptual organisation score.

Study V (Chapter 8**) -** *Handedness, grey matter volume, fluid and crystallised intelligence*: This study investigated the GM correlates of crystallised intelligence (verbal comprehension), and fluid intelligence (the sum of perceptual organisation, working memory and intentionality). Using VBM smoothed normalised GM images obtained from T_1-weighted MR images were entered in a full-factorial design matrix with the predictor variables: handedness degree, age, sex, ICV, verbal comprehension, working memory, perceptual organisation and intentionality. Handedness direction was also entered into the model as a factor with two levels.

Study VI (Chapter 9**) -** *Handedness, prefrontal volume and intentionality*: This study aimed to: (i) investigate the effect that hand direction has on intentionality and its relationship with PFC volume estimates; (ii) explore the relationship between PFC volume and intentionality in left-handers; and (iii) confirm previous findings of a relationship between intentionality and orbital PFC in right-handers (Powell *et al.*, 2010) using a different cohort of right-handed subjects. While intentionality is included as a predictor variable in the model presented in Study V (Chapter 8), it should be noted that in that study it is used as a measure of fluid intelligence along with other scores from the WAIS-III. The study presented in Chapter 9 explores the relationship between PFC volume (from both grey and white matter from stereological analysis) and intentionality score. Results therefore do not offer direct support to those presented in Chapter 8.

CHAPTER 3:

PRINCIPLES OF MR IMAGE ACQUISITION

3.1 STRUCTURAL MR IMAGING

Magnetic Resonance Imaging (MRI) is based on the natural magnetisation that is induced in the human body when it is placed in the scanner. Specifically it is the signal obtained from the magnetic moment of hydrogen nuclei that forms the basis of MRI. Conventional MRI produces spatial maps of mobile hydrogen protons that are contained mainly in water molecules, providing anatomic details with exquisite resolution (on the order of 1 mm or better) (Gore, 2003).

All MR images used in this thesis were acquired using a 3 Tesla MRI scanner (for further details see Section 4.3). An MRI sequence contains radiofrequency (RF) pulses and gradient pulses which have carefully controlled durations and timings. The gradient fields are produced by three sets of gradient coils, one for each direction (x, y, z), through which large electrical pulses are applied repeatedly in a carefully controlled pulse sequence. Further information on the acquisition of MR images can be obtained elsewhere (e.g. Buxton 2002; Hashemi *et al.*, 2004; Horowitz, 1995; Jezzard *et al.*, 2001; Schild, 1990; Westbrook and Roth, 2005).

MRI pulse sequences

Three characteristics of the tissue being measured which influence the signal intensity of MR images are the T_1 relaxation time, T_2 relaxation time and proton density (PD). There are many different types of pulse sequence, but they all have timing values called TR (repetition time) and TE (echo time) which can be modified. The TR is the time between RF pulses and, for a given T_1, determines the amount of longitudinal relaxation. The TE is the time between application of an RF pulse and measurement of the MR signal and, for a given T_2 determines the amount of transversal relaxation.

Contrast in a T_1-weighted image results from differences in longitudinal relaxation times between tissues and structures. A pulse sequence with a short TR (e.g. 300-800 milliseconds) and a short TE (e.g. ~20 milliseconds) will accentuate the effects of longitudinal relaxation and reduce the loss of magnetization that occurs from T_2 dephasing. For T_2-weighted images a pulse sequence with a long TR (e.g. ≥1 second) and a longer TE (e.g. 100-500 milliseconds) are used. This will ensure no T_1-weighting is present in the signal of interest and will exploit differences in T_2 relaxation times of the tissues.

Spin echo pulse sequence

Two factors influence transversal relaxation over time: loss of phase, and inhomogenieties in the magnetic field. The loss of signal can be reduced by applying a 180º refocusing RF pulse a short time TE/2 after the 90º RF pulse. This in effect, causes the precessing protons to turn around resulting in phase coherence and a stronger transversal magnetization. Many 180º RF pulses can be applied to 'neutralise' effects that influence the protons in a constant manner.

Gradient Echo Pulse Sequence

The gradient echo (GRE) pulse sequence is used to reduce scan time. Instead of using a 180º refocusing pulse the GRE pulse sequence uses a magnetic field gradient to refocus the FID signal at the end of each TR, by reversing the polarity of the frequency-encoding gradient. The TR is generally the most time consuming parameter in a pulse sequence. The GRE sequence reduces this time by using a smaller flip angle of less than 90º to convert only a fraction of the longitudinal magnetisation into the transverse plane, meaning that a portion of the longitudinal magnetization will remain for the subsequent RF pulse to excite (McRobbie *et al*., 2003). By applying RF pulses at short TRs, the time it takes for longitudinal magnetization to recover is decreased and an ideal T_1-weighted contrast can be achieved in a relatively short amount of time. However, the omission of the refocusing 180º RF pulse means that the dephasing of spins resulting from magnetic field inhomogenieties are not rephased and thus GRE sequences are more susceptible to artefacts. Quite often the standard GRE sequence is modified to obtain T_1–weighted MR images. All T_1-weighted MR images analysed in this thesis were obtained using a GRE pulse sequence.

3.2 FUNCTIONAL MR IMAGING

The BOLD Signal

fMRI detects the blood-oxygenated-level-dependent (BOLD) changes in the MRI signal which result from an increase in neuronal activity in a region of cortex following a change in brain state, which may be produced by a stimulus or task. The BOLD technique is based on the fact that neural activity and haemodynamics (regulation of blood flow and oxygenation) are linked in the brain (Heeger and Ress, 2002; Ogawa *et al*., 1992). BOLD fMRI reveals which parts of the brain are active in certain tasks with a spatial resolution of 2-5 millimetres.

An increase in neural activity stimulates an increase in the local blood flow in order to meet the larger demand for oxygen and other substrates. The BOLD fMRI technique measures changes in the inhomogeneity of the magnetic field, which are the result of changes in the level of oxygen present in the blood (blood oxygen) (Aguire *et al*., 2002; Detre and Wang, 2002; Heeger *et al*., 2002; Ogawa *et al*., 1990, 1992). While blood that contains oxyhaemoglobin is not very different in terms of susceptibility from other tissues or water, deoxyhaemoglobin is significantly paramagnetic (like the agents used for MRI contrast materials such as gadolinium) and thus deoxygenated blood differs substantially in its magnetic properties from surrounding tissues. Therefore, a high level of deoxyhaemoglobin in the blood will result in a greater field inhomogeneity and therefore a decrease in the fMRI signal (Ogawa *et al*., 1990).

The haemodynamic response function (HRF)

The function of the BOLD fMRI signal against time in response to a temporary increase in neuronal activity is known as the haemodynamic response function (HRF) (Heeger *et al*., 2002). After an increase in neuronal activity there is an increase in the relative level of deoxyhaemoglobin in the blood as active neurons use oxygen, resulting in a decrease of the signal (Heeger *et al*., 2002; Vanzetta and Grinvald, 1999). The decrease however, is tiny and is not always found (Detre and Wang, 2002; Ugurbil *et al*., 2003). Following this initial decrease, there is a large increase in the BOLD fMRI signal which reaches its maximum after approximately 6 seconds, due to a massive oversupply of oxygen rich blood (Fox *et al*., 1988; Heeger *et al*., 2002). The result of this oversupply of oxygen is a large decrease in the relative level of deoxyhaemoglobin, which in turn causes the increase in the BOLD fMRI signal. Finally, the level of deoxyhaemoglobin slowly returns to normal and the BOLD fMRI signal decays until it has reached its original baseline after an initial undershoot after approximately 24 seconds (Heeger *et al.*, 2002). Further information on the signal obtained in fMRI can be found elsewhere (Gore, 2003).

fMRI signal of interest

Block design (Aguirre and D'Esposito, 2000; Donaldson and Buckner, 2001) is the most commonly used experimental design in neuroimaging, and is the design used for all fMRI tasks in this thesis. Two or more conditions are alternated in blocks. The so-called subtraction paradigm involves making the conditions in each block differ in only the cognitive process of interest (Aguirre and D'Esposito, 2000; Donaldson and Buckner, 2001). The fMRI signal that differentiates the conditions should represent the cognitive process of interest. The main advantage of block design is that the increase in fMRI signal in response to a stimulus is additive, meaning that the amplitude of the HRF increases when multiple stimuli are presented in rapid succession. When each block is alternated with a rest condition in which the HRF has enough time to return to baseline and a maximum amount of variability is introduced in the signal. Therefore, block designs offer considerable statistical power.

3.3 DIFFUSION TENSOR MR IMAGING

Diffusion tensor imaging (DTI) is used to infer the axonal organisation of the brain by measuring the translational displacement of water molecules (LeBihan, 1995). The motion or diffusion of water molecules is much faster along the WM fibres than perpendicular to them (Basser, 1995; Basser *et al.*, 1994; Basser and Pierpaoli, 1996, 1998) because there are fewer obstacles to prevent movement along the fibres (Stejskal, 1965). DTI takes diffusion measurements in multiple directions and using tensor decomposition, extracts the diffusivities parallel and perpendicular to the fibres (also termed principle diffusivities) (Basser, 1995; Basser *et al.*, 1994; Basser and Jones, 2002; Basser and Pierpaoli, 1996, 1998; Pierpaoli *et al.*, 1996). The difference between these two motions (parallel and perpendicular to the fibres), is referred to as diffusion anisotropy and forms the basis of DTI. Details on the MR technique used to acquire DT-MR images are given elsewhere (see Mori and Zhang, 2003).

DT-MRI measurements

Inside cells where water is constrained, the mean diffusion (ADC) is slow. The intensity of each pixel in the ADC map is proportional to the extent of diffusion; water molecules in bright regions diffuse faster than those in dark regions (Figure 3.1, left image). Fractional anisotropy (FA) is the most widely used DTI-based index in brain research for representing the motional anisotropy of water molecules, being sensitive to the presence and integrity of WM fibres (Figure 3.1, centre image). Water motion in CSF is isotropic, meaning that the diffusion is roughly equivalent in all directions (i.e. water diffuses freely). In WM diffusion is anisotropic (highly directional), as axonal membranes and myelin sheaths present barriers to the motion of water molecules in directions not parallel to their own orientation (Jellison *et al*., 2004).

FA images (also referred to as FA maps) are grey scale, 2D maps representing diffusion anisotropy on a voxel-by-voxel basis with intensity limits between zero and one (Figure 3.1, centre image). FA maps exhibit a high signal (where intensity limits approach 1) in areas of significant anisotropic motion. In contrast, a low signal (where intensity limits would be around 0) is shown in areas of isotropic motion (Pierpaoli *et al*., 1996). High levels of diffusion in WM (represented by the ADC map) are indicative of poorly developed, immature or structurally compromised WM. High levels of anisotropy (represented in the FA map) are considered a reflection of coherently bundled, myelinated fibres oriented along the axis of the greatest diffusion.

Local values for diffusion or anisotropy can be computed within a small ROI and compared by contrasting values in two or more ROIs. In population studies, differences between two groups of subjects can be calculated by coregistering the images into the same coordinate system and performing individual t-tests at each voxel, producing a map that displays all voxels which the groups differ significantly in anisotropy or diffusion. This latter approach was performed in this thesis, to compare diffusion anisotropy between left- and right-handed groups (see Chapter 6).

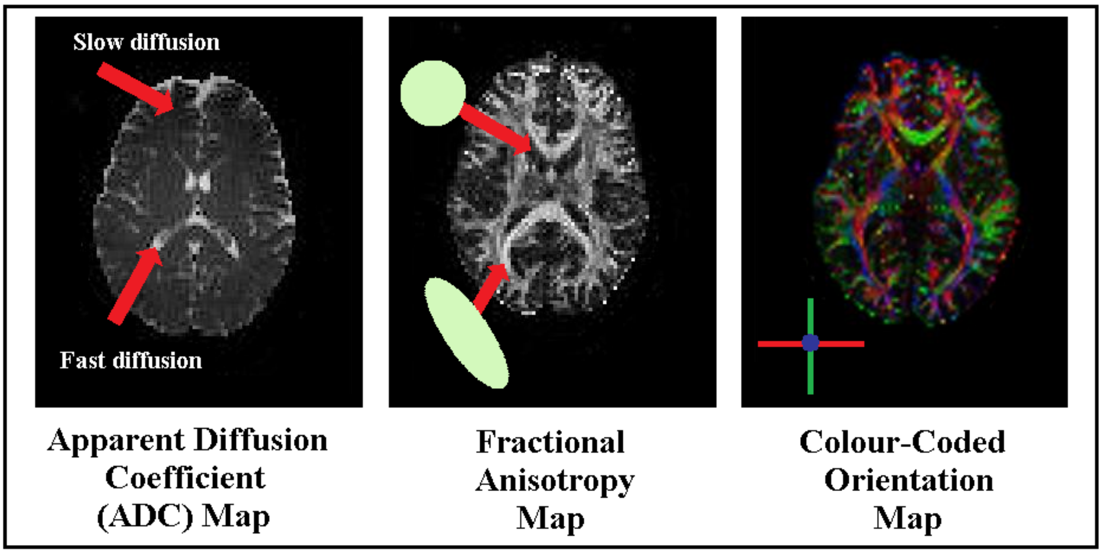


Figure 3.1. Images representing the ADC (left), fractional anisotropy (centre), and colour-coded orientation (right) maps from the diffusion data of a single subject. (Image inspired by Mori and Zhang, 2006).

Pajevic and Pierpaoli (1999) suggested colour-coded schemes to visualise the 3D information in FA maps, in two dimensions (see Figure 3.1, right image). The direction of maximum diffusivity may be mapped using red, green and blue (RGB) colour channels with colour brightness modulated by FA, resulting in a convenient summary map from which the degree of anisotropy and the local fiber direction can be determined. The most basic RGB colour-coded scheme distributes a colour for each orientation of the fibres: fibres crossing left-to-right are visualised in red, fibres crossing anteriorly-posteriorly are visualised in green, and fibres crossing inferiorly-superiorly are visualised in blue. Following voxel-wise comparison of the handedness groups, regions of significant difference are mapped onto the colour-coded orientation maps to determine direction of WM.

Measuring the diffusion tensor

Fibre orientations are estimated from three independent diffusion measurements along the x, y and z axes (Figure 3.2). However these measurements are not enough because fibre orientation is not always along one of these axes. To accurately find the orientation with the largest ADC, diffusion would need to be measured along thousands of axes, which is not practical. To simplify this issue, the concept of diffusion tensor was introduced in the early 1990's (Basser *et al.*, 1994).

The tensor matrix of diffusion consists of a 3x3 matrix, which is diagonally symmetric (Dij = Dji). The tensor matrix may be visualised as an ellipsoid (Figure 3.2) whose diameter in any direction estimates the diffusivity in that direction and whose major principle axis is oriented in the direction of maximum diffusivity (note: the ellipsoid represents average diffusion distance in each direction, not ADC) (Basser *et al.*, 1994). The tensor matrix is subjected to a linear algebraic procedure known as diagonalization, resulting in a set of three orientations (V1, V2, and V3) representing the major, medium and minor principle axes of the ellipsoid and the corresponding three eigenvalues (λ_1, λ_2, λ_3) representing the length of the longest, middle and shortest axes (Jellison *et al.*, 2004). The properties of the 3D ellipsoid (used for ADC measurement) can therefore be defined by six parameters.

Using more than six encoding directions will improve the accuracy of the tensor measurement for any arbitrary orientation (Jones *et al.*, 1999; Papadakis *et al.*, 1999). This procedure may be thought of as a rotation of the x, y, and z coordinate system in which the data were acquired (dictated by scanner geometry) to a new coordinate system whose axes are dictated by the directional diffusivity information (Jellison *et al.*, 2004).

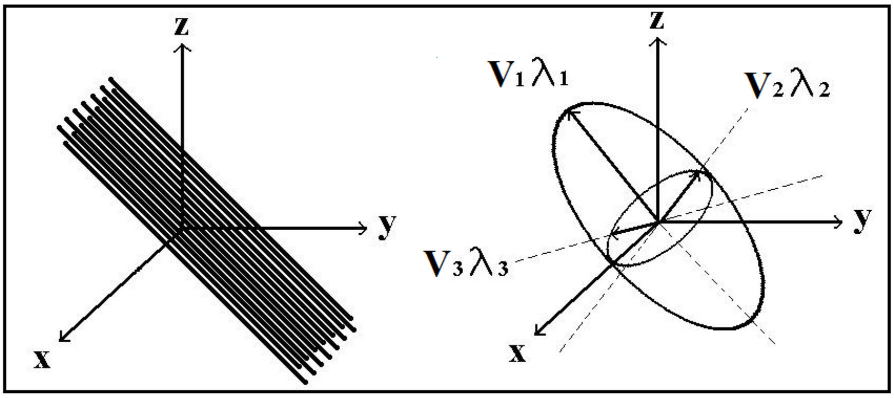


Figure 3.2. Fibre orientations are estimated from three independent diffusion measurements along the x, y, and z axis. Fibre orientation is represented by a tensor ellipsoid. The properties of the 3D ellipsoid can be defined by six parameters namely, the length of the longest, middle and shortest axes (eigenvalues $\lambda 1$, $\lambda 2$, and $\lambda 3$) and their respective orientations (eigenvectors V1. V2, and V3).

Measuring diffusion anisotropy

Diffusion anisotropy is easily understood as the extent to which the shape of the tensor ellipsoid deviates from that of a sphere; mathematically, this translates as the degree to which the three tensor eigenvalues differ from one another. Any of several anisotropy metrics may be used, one of the commonest being fractional anisotropy (FA) which derives from the standard deviation of the three eigenvalues and ranges from 0 (isotropy) to 1 (maximum anisotropy). For example, the degree of diffusion anisotropy can be measured by using a measurement of difference among the three eigenvalues shown in Equation (3.1):

$$FA = \sqrt{\frac{1}{2}}\;\sqrt{\frac{((\lambda 1 - \lambda 2)^2 + (\lambda 2 - \lambda 3)^2 + (\lambda 3 - \lambda 1)^2}{\sqrt{\lambda 1^2 + \lambda 2^2 + \lambda 3^2}}} \tag{3.1}$$

where λ1, λ2 and λ3 represent the length of the longest, middle and shortest apparent diffusivities respectively. If diffusion is isotropic, (λ1 = λ2 = λ3) this measure becomes 0. Large numbers indicate high diffusion anisotropy. After a diffusion ellipsoid is determined, the information can be reduced to a vector of the longest axis (eigenvector V1) which is assumed to represent the fibre orientation. Because it is very difficult to visualise 3D vectors, this information is generally converted to a colour coded orientation map. By estimating the diffusion tensor in each voxel and subsequently its orientation, it is possible to estimate and display the principal orientation of anisotropic structures in vivo, and several methods have been developed for achieving this (Coremans *et al*., 1994; Jones *et al*., 1997; Nakada and Matsuwaza, 1995; Pajevic and Pierpaoli, 1999). One method, called tractography, usually requires seeds from which streamlines are propagated based on V1 orientation (Basser *et al*., 2000; Conturo *et al*., 1999; Jones *et al*., 1999; Mori *et al*., 1999; Parker *et al*., 2002; Poupon *et al*., 2000). The streamlines are terminated when they reach a low anisotropy region where there is no coherent fibre organisation (see Figure 3.3). An example of the streamlines representing perisylvian language fibre tracts can be seen in Figure 3.4.

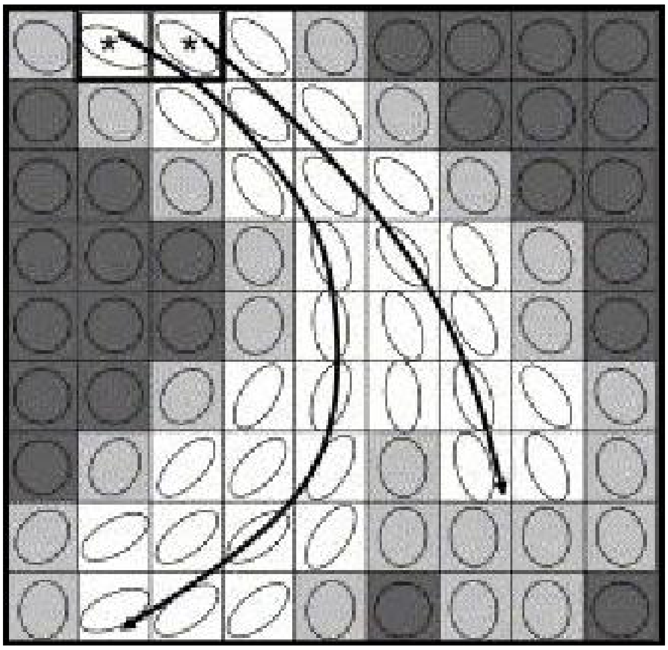


Figure 3.3. Three-dimensional tractography streamlines through user defined ROIs (or seedpoints), shown here as two stars. These are virtual representations of WM fibres, and follow a continuous path of greatest diffusivity (i.e. least hindrance to diffusion). (Image taken from Mori and Zhang, 2006).

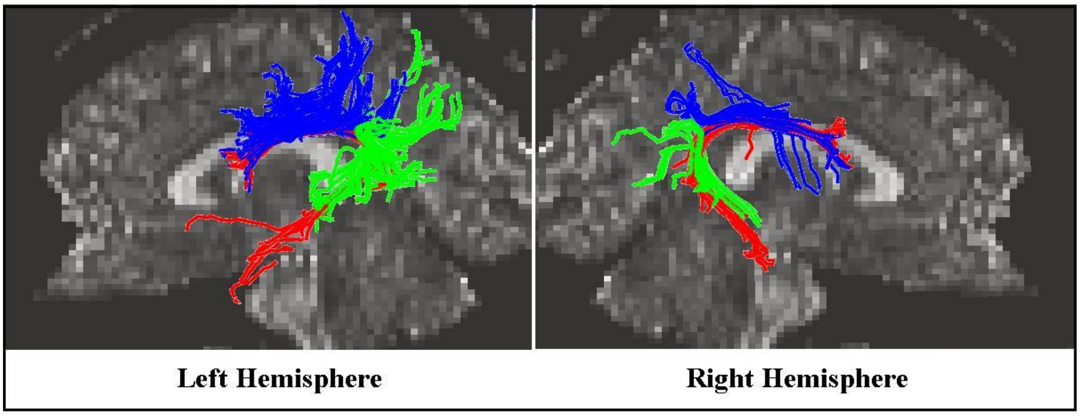


Figure 3.4. Streamlines representing the three language fibres tracts in the left and right hemisphere of one subject used in this thesis. Red streamlines represent the arcuate fasciculus, blue and green streamlines represent the anterior and posterior indirect language pathways respectively (for further information on these tracts see Catani *et al.*, 2005, 2007). Tracts were created using DTIStudio (http://www.mristudio.org/).

CHAPTER 4:

PARTICIPANTS, MATERIALS AND METHODOLOGY

4.1 PARTICIPANTS

For this thesis participants were recruited from the University of Liverpool, all being either students or staff of the university. Two approaches were used for recruitment: (i) advertisements posted around the university or on the announcement page of the universities intranet, and (ii) word of mouth.

Participants were 42 right-handers (16 males) and 40 left-handers (16 males), aged 18-31 years (mean age=21.4±3.0 years). Mean age was similar for right-handers (21.8±3.1 years) and left-handers (21.0±2.8 years), and between males (21.1±2.3 years) and females (21.6±3.3 years). All participants completed the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971), which was used to assess both the direction and degree of handedness. Details of the EHI, including how scores are calculated, are shown in Section 4.2.1. Descriptive statistics and handedness scores for the total sample of participants separated by sex and handedness are shown in Table 4.2. All participants were neurologically and psychologically healthy, gave signed informed consent and the study had local research ethics committee approval.

4.2 NEUROPSYCHOLOGICAL PROTOCOL

Each neuropsychological test administered to each participant is outlined below, along with the cognitive domain or behavioural measure it assesses. A summary of each of these tests is given in Table 4.1. The neuropsychological protocol comprised: the Edinburgh Handedness Inventory (EHI) to assess hand degree and handedness classification; sub-tests from the WAIS-III designed to assess working memory, verbal comprehension and perceptual organisation; and an Imposing Memory Task (IMT) designed to assess Intentionality (see Appendix 1).

4.2.1 Edinburgh Handedness Inventory (EHI)

The EHI is made up of ten different questions about hand preference (writing, drawing, throwing a ball, cutting with scissors, holding a toothbrush, holding a knife (without fork), holding a spoon, holding a broom (top hand), lighting a match, and opening a lid). Participants are asked to assign a number of crosses to each task depending on how often they use each hand for each task. They assign one cross to either the left- or right-hand to indicate which hand they habitually use for each of these activities. Where the preference for that hand is so strong that they would never use the other hand unless absolutely forced to, they would assign two crosses to that hand. When they are indifferent one cross is assigned to each hand. Handedness quotients were calculated using the formula:

Handedness = [(R-L)/(R+L)]*100, where R and L are the number of crosses allocated to the right and left hands, respectively. Results on the EHI range from -100 for strong left-handers and +100 for strong right-handers, enabling individuals to be grouped for handedness e.g. left- or right-handed or assigned a degree of handedness. For instance, if mixed-handedness was pre-defined as any score falling within the extent of -20 to +20 and an individual obtained a score of -13 that individual would be categorised as being mixed-handed.

In this thesis participants were assigned a handedness category based on their responses to the EHI. In all participants except two, handedness classification corresponded with their writing hand preference. The two participants who were discordant for hand degree and writing hand were left-handed for writing however their EHI score showed that their degree of handedness was right-handed. These two individuals were classified as left-handed owing to the fact that their writing hand was left-handed and their degree of handedness whilst being overall rightward remained low i.e. +20 and +33.3. All other left-handed participants reported a score of -6.66 or less with a mean handedness degree of -57.5 (SD=34). For right-handers mean handedness score was 74.8 (SD=26), only one participant had a hand degree score of +30 and all other right-handers reported a score above 33.3. Overall left-handers showed greater variance in their handedness degree and less lateralized handedness scores. This supports previous literature which has shown that left-handers have less pronounced lateralities in hand skill than right-handers (Curt *et al*., 1992; Judge and Stirling, 2003; Peters and Servos, 1989) and greater inter-manual coordination than right-handers (Gorynia and Egenter, 2000; Judge and Stirling, 2003).

Writing is the only task that most people cannot learn to perform equally well with either hand even after considerable training. Most individuals will categorise their handedness based on their writing hand (Perelle and Ehrman, 2005). When assessing handedness characteristics which are less influenced by external forces, the hand with which the individual writes with is often considered a good indicator of handedness. A greater degree of variance in hand preference and weaker hand dominance is expected in left-handers. This is owing to the fact that at least in western societies we live in a predominantly right-handed world with instruments and tools that are designed for right-handers: scissors are a good example of this.

Hand degree scores separated by hand category and sex can be seen in Table 4.2. A two-way ANOVA was performed to compare handedness degree between left- and right-handers and between males and females. This statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software. An alpha level of $P<0.05$ was used for all tests of statistical significance. Results from the two-way ANOVA showed a significant difference in handedness score between left- and right-handers ($F_{(1,79)}=6.65$, $P=0.01$) with right-handers showing a greater degree of right-handedness when compared to the degree of left-handedness in left-handers. No significant difference in hand degree was found between males and females ($F_{(1,79)}=2.76$, $P=0.1$).

In addition to hand preference, the EHI also asks two questions concerning eye and foot preference: “Which foot do you prefer to kick with?” and “Which eye do you use when using only one?” As with the questions related to handedness, the participant is asked to assign a cross to either the left or the right to indicate their foot or eye preference. A cross is given under both right and left headings when there is no preference. Scores for these two categories are used in Chapter 5 (Part two) and descriptive statistics for these categories can be found in Table 5.5.

4.2.2 Wechsler Adult Intelligence Scale (WAIS-III)

All participants were assessed on thirteen sub-tests from the Wechsler Adult Intelligence Scale–version III (WAIS-III; Wechsler, 1997a, 1997b). The sub-tests measure a wide array of cognitive abilities. In his encyclopaedic review of the literature, Carroll (1993) indicates that the available studies consistently show three main factors underlying the WAIS: a verbal or language factor; a non-verbal factor derived from the performance sub-tests (block design, picture completion etc); and a short-term or working memory factor. Seven sub-tests were selected for inclusion in the current study, which best represent the three executive functioning abilities of interest i.e. verbal comprehension, working memory, and perceptual organisation. These 7 sub-tests are described in Table 4.1. Scores for each of these sub-tests are summarised in Table 4.2.

Verbal comprehension

Verbal comprehension is a measure of verbal reasoning and concept formation. In this thesis verbal comprehension testing comprises the sub-tests Vocabulary and Comprehension.

- Vocabulary involves presenting participants with a list of words which vary in degree of their everyday use (e.g. sanctuary, ponder, reluctant, encumber), who are then asked to describe the meaning of the word. Scores are marked based on the degree to which the participant has understood the concept of the word. For example, when asked what the word encumber means, a response of “to burden; overload” or “to weigh down” would achieve a mark of 2 as they have understood the concept of the word. A response “to take on” or “inhibit” would receive a mark of 1 as the concept of the word has not been fully understood and a response of “encircle” or “include” would receive no mark as the concept of the word has clearly not been understood.
- Comprehension involves asking a series of questions such as “Why should people pay taxes?” and “Why is a free press important in a democracy?” This sub-test requires the individual to verbalise meaningful concepts and retrieve meanings of words from long-term memory. Scores are marked based on the degree to which the participant has understood the concept or meaning of the question. For example, when asked “Why should people pay taxes?” an understanding that taxes are used for public services for instance, would achieve a mark of 2 as they have understood the concept of the question. The marking criterion, included in the WAIS-III administration and scoring manual, provides details of answers corresponding to a mark of 0, 1 or 2 for each question for both the Vocabulary and Comprehension sub-tests. Both tasks are taken as a measure of verbal comprehension as they assess the degree to which one has learned,

been able to comprehend and verbally express vocabulary such as knowledge of the meanings of words.

Working Memory

Working memory is a measure of auditory short-term memory and is measured using the sub-tests digit-span and letter-number sequencing.

- <u>Digit-span</u> involves remembering strings of digits in forward and reverse order. The participant is verbally given a sequence of digits (e.g. 2,5,4,9) and asked to recall the sequence in the reverse order (i.e. 9,4,5,2).
- <u>Letter-Number Sequencing</u> involves mentally unscrambling a mixture of numbers and letters. The participant is presented a list of numbers and letters (e.g. Q1B3J2) and asked to place the numbers in numerical order followed by the letters in alphabetical order (i.e. 123BJQ). Both of these tasks require a high degree of attention/concentration. For both tasks the list of letters and numbers becomes increasingly longer, making the tasks increasingly more difficult. Each list carries a score of 1.

Perceptual Organisation

Perceptual organisation is a measure of visual reasoning skills and includes the sub-tests Picture Completion, Block Design and Matrix Reasoning (shown in Figure 4.1).

- <u>Picture Completion</u> involves the ability to quickly perceive visual details. Participants are presented with pictures and asked to spot the missing details e.g. a missing shadow, or tooth from a comb (example shown in Figure 4.1A). A maximum score of 1 for each picture is given for this sub-test and the participant has only 20 seconds to respond to each item.
- <u>Block Design</u> involves spatial perception, visual abstract processing and problem solving abilities. In this task participants are presented with a series of patterns which they are required to replicate using a selection of blocks (example presented in Figure 4.1B). Participants may receive a mark of 0, 1 or 2 depending on the speed with which they complete each design.
- <u>Matrix Reasoning</u> involves non-verbal abstract problem solving, inductive reasoning and spatial reasoning skills. In this task the participant is presented with complex visual patterns and asked to logically complete the pattern

(example shown in Figure 4.1C). A maximum score of 1 for each pattern is given for this sub-test.

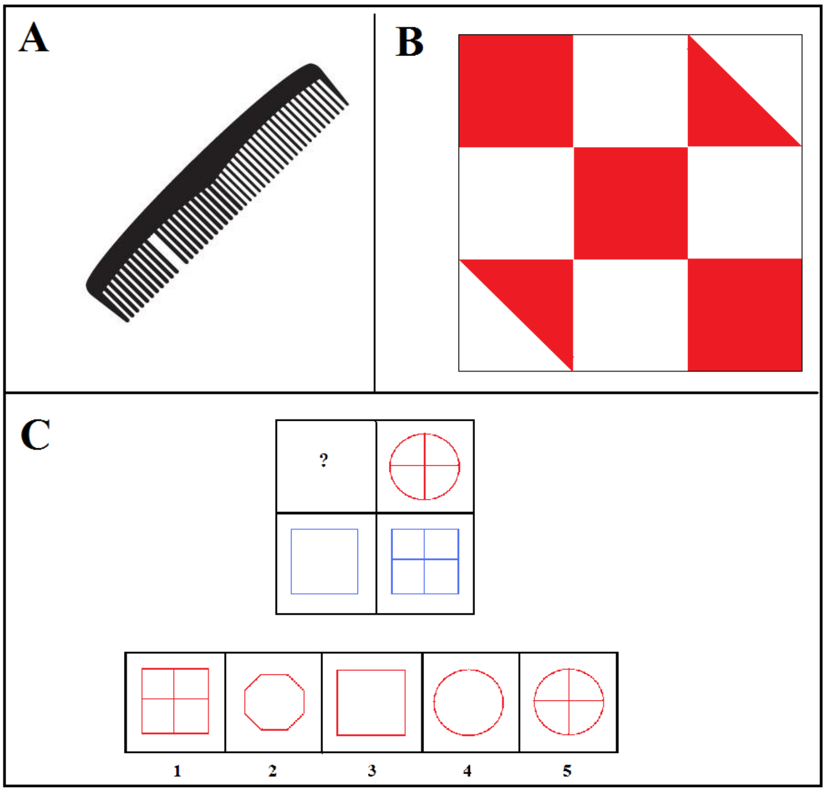


Figure 4.1. Examples taken from the WAIS-III perceptual organisation sub-tests: A = Picture Completion task, B = Block Design and C = Matrix Reasoning task.

Scoring the WAIS-III

Cognitive ability scores (obtained by using the WAIS-III) in the general population approximately follow a normal distribution, with the exception of a slight excess at the lower end of the distribution caused by severe disorders that involve disrupted cognitive abilities. Males have a slight but consistently wider distribution than females at both ends of the range (Johnson *et al*., 2008a). Most tests of general intelligence such as the WAIS-III are centred at 100 with a standard deviation of 15. In a normal distribution this intelligence quotient (IQ) range (mean ± 1 SD) is where approximately 68% of adults would fall, indicating that approximately 68% of adults score between 85 and 115. The full-scale intelligence quotient (FSIQ) comprises the sum of all the sub-tests from the WAIS-III. WAIS-III scores are usually converted to a standardised score based on the age population to which the individual belongs. In the current study (where the age range is particularly narrow), however, raw scores were converted into percentages for the purposes of interpretation. The WAIS-III administration and scoring manual provides details of the scoring system used and the answers to each of the sub-tests. The manual also provides extensive details on how to administer each of the sub-tests to increase consistency and standardisation of administration across participants.

4.2.3 Imposing Memory Task (IMT)

While the WAIS-III is used as a measure of metacognitive executive functioning (EF) the IMT, which constitutes a written questionnaire is used to assess intentionality, which is just one measure of social cognitive competence (for IMT see Appendix 1). The IMT consists of a series of five short stories which has been used in a previous study (i.e. Powell *et al.,* 2010). IMT stories are revised versions of those used by Stiller and Dunbar (2007). Each story is approximately 200 words in length and describes a social interaction involving several individuals.

Participants were asked to read the stories themselves twice and then proceed to the 20 questions that immediately followed each story. They were instructed not return to the story for assistance in answering the questions once they had finished the second reading. Questions are composed of 10 intentionality questions varying from 1st to 6th order intentionality and 10 factual (memory) questions varying from 1 to 6 facts. An equal number of verbal memory questions and intentionality questions are used to distinguish between the participants' mind-reading (intentionalizing) ability and their ability to remember the factual contents of the story (i.e. short-term memory).

Intentionality questions require complex metalizing about a character's perspective on a social situation. The participant's own mind state was defined as first order intentionality, and the mind state of each protagonist from the story included in a question added successive levels of intentionality. A 6th order intentionality question thus involved tracking the mind states of five individuals in the story, as well as the reader's own mind state. Memory questions here can therefore be considered as a measure of short-term memory which is typically associated with the capacity to remember 7±2 elements. This is separate from the concept working memory which refers to different processes used for the storage and manipulation of information. As such there will always be some component of short-term memory when we refer to working memory. One can see the difference if the working memory component of the WAIS-III is considered. Working memory in this case is assessed using tasks that require individuals to manipulate the material presented to them and automatically retrieve it. Additionally the way in which material is presented has an effect on short-term memory. In the IMT information is embedded in a story which is presented to subjects in written format whereas the two sub-tasks used to assess working memory in the WAIS-III are verbally presented to subjects.

Scoring the IMT

Performance was assessed in an identical manner for both intentionality and memory. Following Stiller and Dunbar (2007) the mean 'fail point' was calculate using a re-scaled weighted mean of performance at 5 levels of complexity (levels 2-6) for both intentionality and short-term memory. The equation for the weighted mean (Szulc, 1965) is given as follows:

$$weighted\ mean = \frac{v\ \sum_{i=1}^{i=n}(w_i x_i)}{\sum_{i=1}^{i=n} w_i} = \frac{v(w_1 x_1 + \ w_2 x_2 + \cdots + w_n x_n)}{(w_1 + \ w_2 + \cdots + w_n)} \tag{4.1}$$

where w_i is the intentionality level, x_i is the score that the individual obtained for the corresponding intentionality level, and n is the number of intentionality levels considered in the calculation (in this case n = 5). Each story in the IMT had 6 levels of intentionality competence. Note that only the levels 2 to 6 were examined, the participant's own perspective, which constitutes level 1 is excluded. The sum of the weights (i.e. $\sum_{i=1}^{i=n} w_i = 2 + 3 + 4 + 5 + 6)$ is 20. The quantity v is the scaling value, and can be calculated using Equation (4.2).

$$v = \frac{\sum_{i=1}^{i=n}(w_i\ )w_n}{\sum_{i=1}^{i=n}(\ w_i\ x_{i,max})} = \frac{(2+3+4+5+6)\cdot 6}{(2\cdot 10)+(3\cdot 10)+(4\cdot 9)+(5\cdot 8)+(6\cdot 2)} = 0.87 \tag{4.2}$$

when w_n is 6, $v = 0.87$. The sum of $w_i x_{i,max}$ is equal to 138 when the maximum score is obtained on the IMT used in this thesis. Therefore $x_{i,max}$ is the maximum score that can be obtained for the corresponding intentionality level. By multiplying the sum of $w_i x_i$ by a scaling value $v = 0.87$, we can obtain a number that when divided by the sum of the weights (see Equation (4.1)) yields an answer that represents the level of intentionality at which the participant fails on a scale of 0-6. This method provides an appropriate level of intentionality and/or short-term memory, at which each participant typically fails. The benefit of this method is that it takes into account that a participant might fail a low order question and yet, by chance alone, succeed at a higher level.

An individual who obtained an intentionality (or short-term memory) score of 130 on the IMT would therefore be:

$$weighted\,mean = \frac{130 \cdot 0.87}{20} = 5.66 \tag{4.3}$$

giving the participant a weighted intentionality score of 5.66. Tests of cognitive ability are usually designed to assess the point at which an individual begins to “fail” i.e. the individual reaches a point of difficulty in which they can no longer successfully perform on that particular task. This marking procedure allowed the investigation of the individuals’ intentionality and short-term memory fail point or score. Scores for the IMT including, intentionality and short-term memory are shown in Table 4.2, separated by sex and handedness.

Table 4.1. Summary of the neuropsychological tests administered including sub-tests and the cognitive ability it assesses. A description of each of the cognitive abilities measured is also given.

	Cognitive test	**Sub-test**	**Cognitive ability**	**Description of ability**
Handedness and other behavioural lateralities	EHI		Handedness direction	Left- or right-handedness is classified based on the handedness score (positive/negative).
			Handedness degree	The degree to which the left- or right-hand is used for a variety of different tasks.
			Foot preference for kicking	The foot that the individual uses to kick with
			Eye preference	The eye that the individual uses when using only the one eye
Executive functioning	WAIS-III	Vocabulary	Verbal comprehension	Verbal reasoning and concept formation. Verbalise meaningful concepts and retrieve meanings of words from long term memory.
		Comprehension		
		Digit Span	Working Memory	Auditory short-term memory. Requires attention, concentration and a degree of mental control.
		Letter-Number Sequencing		
		Picture Completion	Perceptual organisation	Visual reasoning skills. Assesses non-verbal concept formation, visual perception and organisation, and visual-motor coordination
		Block Design		
		Matrix Reasoning		
Social cognition	IMT	Intentionality questions	Intentionality	Levels of mind states. Ability to explain and predict behaviour of others by attributing to them mental states, beliefs or intentions.
		Memory questions	Short-term memory	Ability to remember written verbal factual information.

Table 4.2. Descriptive statistics for neuropsychological variables separated by sex and handedness. These include the number of participants (percentage of the total sample) and number of males. Mean values (standard deviations) are given for age, handedness degree and cognitive ability scores assessed by the WAIS-III and IMT.

	Total	**Males**	**Females**	**Right-handers**	**Left-handers**	**Right-handed males**	**Right-handed females**	**Left-handed males**	**Left-handed females**
No of Participants	82 (100%)	32 (39%)	50 (61%)	42 (51%)	40 (49%)	16 (20%)	26 (32%)	16 (20%)	24 (28%)
Sex	36 males	-	-	16 males	16 males	-	-	-	-
Age	21.4 (3.0)	21.1 (2.3)	21.6 (3.3)	21.8 (3.1)	21.0 (2.8)	20.8 (1.8)	22.4 (3.5)	21.4 (2.9)	20.6 (2.8)
Handedness degree	10.0 (73)	11.4 (69)	9.1 (76)	74.8 (26)	-57.5 (34)	70.5 (31.2)	77.4 (23.2)	-47.7 (39.4)	-64.9 (27.4)
Working Memory	70.6 (12.2)	72.9 (13.4)	69.2 (11.4)	74.8 (11.1)	66.2 (12.0)	77.4 (11.7)	73.2 (10.6)	68.4 (13.7)	64.8 (10.8)
Verbal Comprehension	72.9 (11.5)	71.0 (12.2)	74.2 (11.1)	74.8 (10.5)	71.0 (12.4)	72.3 (12.9)	76.3 (8.6)	69.6 (11.7)	71.9 (13.0)
Perceptual Organisation	81.9 (8.0)	84.1 (6.7)	80.5 (8.6)	82.1 (8.3)	81.7 (7.8)	84.7 (6.3)	80.5 (9.1)	83.5 (7.2)	80.5 (8.1)
Intentionality	4.6 (0.6)	4.5 (0.5)	4.6 (0.6)	4.7 (0.5)	4.5 (0.6)	4.7 (0.5)	4.6 (0.5)	4.3 (0.5)	4.6 (0.7)
Short-term Memory	5.5 (0.6)	5.4 (0.5)	5.5 (0.7)	5.5 (0.6)	5.6 (0.7)	5.4 (0.4)	5.5 (0.6)	5.5 (0.5)	5.6 (0.7)

4.3 MR IMAGE ACQUISITION

All MR images presented in this thesis were acquired using a Siemens Trio 3 Tesla (Siemens, Erlangen, Germany), whole body MRI system, with an eight channel head coil. Foam padding and head restraints were used to control head movement during all imaging protocols. The image acquisition parameters were as follows:

- T_1-weighted MR images were acquired sagitally with the following parameters: TE 5.57ms, TR 2040 ms, flip angle 8º, FOV= 256×256 mm^2, 176 slices, voxel size 1×1×1 mm^3.

- Diffusion-weighted images were acquired with a diffusion-weighted spin echo sequence implemented with 60 isotropic gradient directions (TR=8000ms, TE=111ms, FOV=320mm, voxel size=2.5×2.5×2.5 mm^3, b-factor=1000s/mm^2), and 5 images with no diffusion weighting (b=0s/mm^2).

- Functional images were obtained using a T_2-weighted gradient echo EPI sequence (TE=35ms; TR=3000ms; flip angle 90 , slice thickness 3mm, 0.3 mm gap, matrix 64×64, FOV=192×192 mm^2; in-plane resolution 3×3 mm, 43 slices). Forty-three axial slices oriented parallel to the AC-PC line were taken, covering the whole brain.

Measurements obtained from the different MR imaging modalities and the statistical analysis performed on the obtained measurements can be seen in Table 4.3.

Table 4.3. Measurements obtained from structural, diffusion and functional MR imaging modalities including the output from pre-processing and outcome variables. The effects of interest in each chapter are given along with the imaging technique used in each study and the statistical analysis performed. T1w MRI=T_1 weighted MR images; DT MRI=diffusion tensor MR images; DS=diagonal sulcus; L=left; R=right; ICV=intra-cranial volume; GM=grey matter; IFS=inferior frontal sulcus; IFG=inferior frontal gyrus; LI=laterality index; MD=mean diffusivity.

Chap	**Effects studied**	**Imaging technique**	**ROI**	**Output from pre-processing**	**Statistical analysis**	**Explanatory variables**	**Outcome variables**
5	Sex and handedness on: sulcal contours	T1w MRI	Broca's area	AC-PC corrected images	Logistic mixed-effects regression	Handedness (R/L) Sex (M/F) Hemisphere (R/L) Hemisphere volume Tissue (GM/WM)	Continuous IFS (Yes/No) Present DS (Yes/No)
	volume of Broca's area				Linear mixed-effects models		volume of PO and PTR for WM & GM
6	Handedness on: WM anisotropy	DT MRI	Whole brain FA maps	FA maps	t-tests using general linear model	Handedness (R/L), Sex, Age	FA differences
	FA asymmetry			Asymmetric FA maps			FA asymmetry
7	Handedness on: language laterality	fMRI	IFG (language)	SPMs of significant BOLD changes	Multivariate analysis of variance	Handedness (R/L) Language LI, Spatial LI Language*Spatial	Language laterality
	spatial laterality		Parietal lobe (spatial)				Spatial laterality
7	Language & spatial laterality on intelligence		IFG, Parietal lobe				Verbal comprehension Working memory Perceptual organisation
8	Handedness on GM correlates of intelligence	T1w MRI	Whole brain GM segment	Segmented GM, WM & CSF images	t-tests using general linear model	Handedness (R/L), Sex, Age, ICV, WAIS-III scores, Intentionality	GM volume
9	Handedness on the association between intentionality & PFC volume	T1w MRI	PFC	AC-PC corrected images	Linear mixed-effects model	Handedness (R/L), Hemisphere (R/L), Hemisphere vol, Intentionality, memory	PFC volume

4.4 STRUCTURAL QUANTIFICATION OF MR IMAGES

Stereological volume estimates from T_1-weighted MR images were obtained to investigate: (i) the effect of handedness and sex on PO and PTR volume and volume asymmetry (for study see Chapter 5) and (ii) the effect of handedness on the association between intentionality and PFC volume (for study see Chapter 9).

4.4.1 Stereological measurements

Stereology is a collection of methods designed for quantifying the geometrical features of material objects and biological structures. Design-based methods are assumption-free and rigorously mathematically derived. The strength of design-based stereological methods is that, under a well-defined sampling design, they are unbiased regardless of the geometry of the object under study.

An estimator of GM volume is said to be unbiased when the average of all the possible estimates of GM volume that can be obtained is equal to the true value of GM volume. Unbiasedness itself however, cannot be proven from the data alone as it is an inherent feature of the methodological design (Dorph-Petersen and Lewis, 2010). The precision of an estimator measures the variability (variance) of the estimates, or how close/far the estimates are to one another and can be observed directly from the scatter of the final data. Increasing the sample size cannot eliminate or decrease an existing bias but it can increase the precision of the assessment, thus it could make the group mean more precisely inaccurate.

Design-based stereological methods have been widely applied to measure regional brain volumes on MR images in both healthy (García-Fiñana *et al.*, 2003; Howard *et al.*, 2003; Keller *et al.*, 2007, 2009b; Mackay *et al.*, 1998; Powell *et al.*, 2010; Roberts *et al.*, 2000; Sheline *et al.*, 1996) and clinical populations (Dorph-Peterson and Lewis, 2010; García-Fiñana *et al.*, 2006, 2009; Keller *et al.*, 2002; MacKay *et al.*, 2000; Salmenpera *et al.*, 2005). Point-counting in combination with the Cavalieri method has been shown to have excellent inter- and intra-rater reliability (Cowell *et al.*, 2007; Doherty *et al.*, 2000; Howard *et al.*, 2003; Mackay *et al.*, 1998, 2000; Keller *et al.*, 2002, 2007). Keller *et al* (2007) for instance, demonstrated reliability in the repeatability of measurements of the PO and PTR using stereological methods.

The Cavalieri Method

The Cavalieri method is one sampling design-based stereological technique for obtaining an unbiased estimator of a reference volume. The Cavalieri method in conjunction with the well-established point counting technique is particularly useful in instances where the volume of a structure cannot be easily confined to a well-defined regular region such as that of cortical regions (Howard and Reed, 2005). The Cavalieri method can be used to obtain an unbiased estimator of the volume of a structure of arbitrary shape and size from high resolution 3D MR images. The Cavalieri method involves sectioning the structure of interest end-to-end with a series of parallel planes (or sections) with a uniform random position and a fixed distance apart, *T* (Figure 4.2).

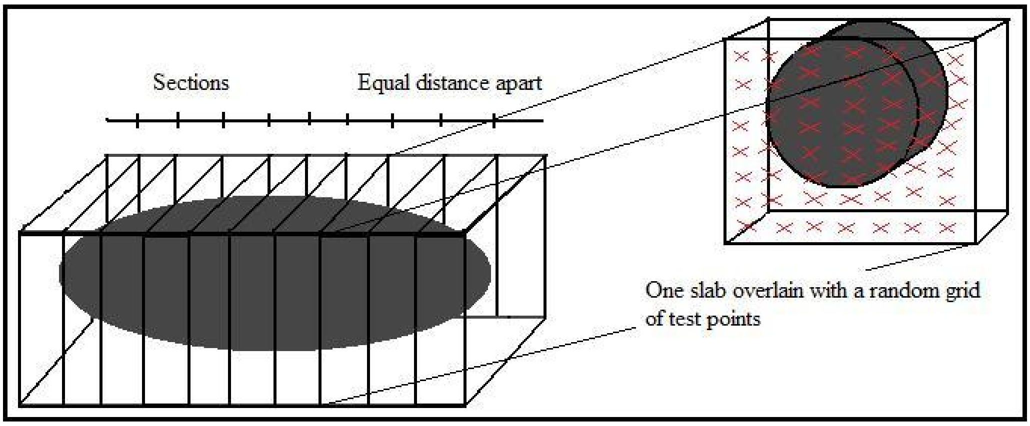


Figure 4.2. The basis of the Cavalieri sections method of volume estimation in combination with point counting. A structure of interest is sectioned into a series of slices or sections. Each section is the same thickness or distance apart. Each section is overlain with a random grid of test points. Points falling within the structure of interest are counted.

When point counting is applied in combination with the Cavalieri method, each MR section is superimposed with a regular array of test points with uniform random position and points falling within the anatomical boundary of the subfield of interest are counted. The section area is estimated by counting the number of test points falling within the boundary of the ROI (see Equation (4.5)). The volume of the structure is estimated as the sum of the areas of the sections multiplied by the sampling distance (Gundersen and Jensen, 1987). The unbiased volume estimator ($\tilde{V}$) can be expressed as:

$$\tilde{V} = T \cdot \mathrm{a_p} \cdot (P_1 + P_2 + P_3 + \ldots + P_n) \tag{4.4}$$

where T is the distance between sections, $P_1 + P_2 + P_3 + \ldots + P_n$ represents point counts within image sections 1 to n, respectively, and $\mathrm{a_p}$ represents the unit area per test point. The unbiased volume estimator as expressed in Equation (4.4) is based on two sampling stages, namely Cavalieri sampling and point counting. In order for the Cavalieri estimator to be unbiased, there should be no preferred starting position for slicing and sectioning should begin at a random position. The derivation of Equation (4.4) is based on the fact that an unbiased estimator of each section area, $\hat{A}_i$ can be expressed as:

$$\hat{A}_i = \mathrm{a_p} \cdot P_i \tag{4.5}$$

where P_i is the number of points hitting the object on the *i*th section and $\mathrm{a_p}$ is the unit area per test point. A benefit of the Cavalieri method in combination with point counting is that it is an efficient method for estimating the volume of a defined ROI, in comparison with traditional planimetry approaches. The efficiency is dependent upon the choice of sampling parameters i.e. the number of Cavalieri sections and the density of the point grid.

Prediction of Coefficient of Error

The technique used to calculate the volume of ROIs in this thesis, provides a mathematically unbiased volume estimator whose precision can be computed by applying an error-prediction formula (see e.g. Cruz-Orive, 1989; García-Fiñana and Cruz-Orive, 2004; Gundersen and Jensen, 1987; Kiêu *et al*., 1999) called the coefficient of error (CE). The CE is defined as the square root of its variance divided by its mean. The conventional formula used to estimate the variance of a volume estimator $(\hat{V})$ when the observations (i.e., section area estimates) are independent is given in Equation (4.6).

$$CE\,(\hat{V}) = \frac{SD(\hat{V})}{\sqrt{n}} \tag{4.6}$$

where $SD(\hat{V})$ is the standard deviation of the volume estimator from one observation, and n is the total number of observations. This equation cannot be used when the observations are equally spaced since they cannot be regarded as independent. It is known that the variance of the Cavalieri volume estimator depends on the geometrical features of the structure under analysis (e.g., Cruz-Orive, 1999; García-Fiñana and Cruz-Orive, 2000; Gundersen *et al.*, 1999; Kiêu *et al.*, 1999; Matheron, 1965, 1971). Several expressions have been derived to take into account the connection of the precision of the Cavalieri estimator with the geometry of the structure. An estimator of the variance has been proposed in García-Fiñana and Cruz-Orive (2004, see also application in 2003) and this is the approach used in this thesis to calculate the CE.

The section areas of MRI slices are not independent and therefore the variance of the volume estimator in Equation (4.5) is affected by 2 different types of stereological error. The first is due to the variability among sections (Cavalieri sampling) and the second is due to the variability within sections (point counting). In terms of coefficient of error this can be expressed as:

$$CE^2(\tilde{V}) = \mathrm{CE}^2_{sec}(\tilde{V}) + \mathrm{CE}^2_{PC}(\tilde{V}) \tag{4.7}$$

where $\mathrm{CE}^2_{sec}(\widetilde{V})$ represents the contribution of the variability due to sectioning and $\mathrm{CE}^2_{PC}(\widehat{\widetilde{V}})$ represents the variability due to point counting within sections. Equations for calculating the contribution of the variability due to sectioning and point counting are given elsewhere (see García-Fiñana and Cruz-Orive (2004) and García-Fiñana *et al* (2003).

In this thesis, EasyMeasure software (Roberts *et al.*, 2000) was used to estimate regional brain volumes. A coefficient of error for each regional brain structure was automatically calculated within the software using the above formula. Stereological parameters were entered into the software manually.

4.4.2 Repeatability and Reproducibility

It is necessary to establish the repeatability and reproducibility of volumetric estimation techniques, prior to their application to a large-scale sample. The repeatability is the capacity of a same rater to obtain “similar” repeated measures of a given object (intra-rater) using an identical method, whereas reproducibility is the capacity of different raters (inter-rater) to obtain “similar” measures of a given object using an identical method. In this thesis, blind inter-rater and intra-rater studies were undertaken on PO, PTR and PFC subfields using the Cavalieri and point counting methods. Studies of inter-rater reliability were undertaken based on the analysis of a number of randomly selected T_1-weighted MR images following a period of training for each region by a second observer. Specifically the following intra- and inter-rater studies were performed.

Intra- and inter-rater studies

Inter-rater study: The volume of PFC, PO and PTR subfields of 10 brains were measured independently by two raters. Specifically, raters JP and SL measured PFC subfields and raters JP and CC measured PO and PTR subfields. Measurements were performed using the same demarcation, same Cavalieri sections and random grid positions. Raters SL and CC measured each ROI subfield once. Rater JP measured each ROI twice and the average of these measurements was taken when performing the inter-rater study. This study allows the estimation of the contribution to the variance of the volume estimator that is due to point counting and differences between observers.

Intra-rater study 1: The volume of PFC, PO and PTR subfields of 10 brains were measured by the same rater (JP) twice with several weeks between the first and second measurement sessions using different demarcations, different Cavalieri sections and random grid positions. This study was performed to investigate the variance of the volume estimator that is due to demarcation, Cavalieri sectioning, point counting and differences within observer.

Intra-rater study 2: Volumes of PFC, PO and PTR subfields were measured 10 times on one brain on 10 consecutive days by the same rater (JP). Measurements were performed using the same demarcation, same Cavalieri sections and same grid positions to investigate the variability of measurements within observer.

Intra-rater study 3: The volume of PFC, PO and PTR subfields were measured on 2 brains and each brain was measured 10 times by the same rater (JP). Measurements were performed using the same demarcations, Cavalieri sections and random grid positions to investigate the variability due to differences within observer and point counting.

Statistical Analysis of inter- and intra-rater studies

Agreement between two measurements of a ROI can be quantified using the differences between measurements obtained on two different occasions on the same ROI by the same rater and different raters. Some lack of agreement between different measurements is inevitable (Bland and Altman, 1999). The 95% limits of agreement, estimated by the mean difference ± 1.96 standard deviation of the differences, provide an interval within which 95% of differences between measurements by the two raters (or based on two different occasions by the same rater) are expected to lie. The mean difference between raters (or occasions for the intra-rater studies) and the standard deviation of the differences between measurements is calculated. The 95% limits of agreement were estimated for the sum of the four PFC subfields within the left hemisphere (i.e. DM, DL, OM, and OL subfields) and then the right hemisphere for each rater. Similarly the 95% limits of agreement were estimated for the sum of the four PO and PTR regions (Broca's area) in the left hemisphere (i.e. grey/white matter PO and PTR) and then the right hemisphere.

Results of inter- and intra-rater studies

Results for the inter- and intra-rater studies are shown in Table 4.4. Table 4.4 shows that for the inter-rater study the mean value of the right PFC is slightly larger than the mean value of the left PFC (i.e. 94.8 vs. 91.17cm^3 respectively). In intra-rater study 1 the right PFC is also larger than the left PFC (i.e. 90.85 vs. 89.45cm^3 respectively). This could be explained by the "Yakovlevian torque" which is a clockwise twist in brain morphology resulting in larger right hemisphere frontal lobe than left hemisphere frontal lobe (Kertesz *et al.*, 1986; LeMay and Kido, 1978). Mean values for the left and right Broca's area for the inter-rater study are 16.14 and 13.33cm^3, and for intra-rater study are 16.43 and 13.62cm^3 respectively which are very similar.

Inter-rater study: The 95% limits of agreement included zero indicating that one rater did not systematically overestimate or underestimate the volume when compared to the other rater. The CE is less than 6% in all cases, which shows good inter-rater reliability.

Intra-rater study 1: Table 4.4 shows that the mean difference and the standard deviation of the difference in measurements within observer was small (i.e. less than 1cm^3) for all regions. Also, the 95% limits of agreement included zero indicating that rater JP did not systematically overestimate or underestimate volume for ROIs on different occasions. The CE is less than 8% for all the subfields. The CE is expected to be higher for this intra-rater study than for the other two intra-rater studies as this takes into account the error that appears in the measurement due to Cavalieri sectioning, point counting and within observer variability.

Intra-rater study 2: Results indicate an average CE$_{ow}$ (within observer) of less than 3% for each ROI. A CE of less than 5% is considered necessary. This study indicates that only a small percentage of the error comes from variability within observer. This is particularly important as rater JP performed all volume estimates in this thesis.

Intra-rater study 3: The CE for all subregions in this intra-rater study is less than 4% and this value takes into account both the contribution to point counting and within observer variability.

Table 4.4. Results for the 95% limits of agreement for volume estimates for inter- and intra-rater studies. The lower and upper 95% limits of agreement define the range within which 95% differences between measurements by the two raters (or based on two occasions by the same rater) lie. Values are given in cm^3. LH=left hemisphere, RH=right hemisphere.

<table>
<tr><th rowspan="2"></th><th rowspan="2">Mean average</th><th rowspan="2">Mean difference</th><th rowspan="2">Standard deviation of the difference</th><th colspan="2">Limits of agreement</th><th rowspan="2">CE (%)</th></tr>
<tr><th>Lower 95%</th><th>Upper 95%</th></tr>
<tr><td colspan="7">Inter-rater study:</td></tr>
<tr><td>LH PFC</td><td>91.17</td><td>3.42</td><td>2.13</td><td>-0.76</td><td>7.60</td><td>2.7%</td></tr>
<tr><td>RH PFC</td><td>94.80</td><td>7.88</td><td>9.91</td><td>-11.53</td><td>27.30</td><td>5.9%</td></tr>
<tr><td>LH Broca</td><td>16.14</td><td>-0.61</td><td>0.64</td><td>-1.88</td><td>0.65</td><td>2.8%</td></tr>
<tr><td>RH Broca</td><td>13.33</td><td>-0.05</td><td>2.00</td><td>-3.96</td><td>3.87</td><td>4.0%</td></tr>
<tr><td colspan="7">Intra-rater study 1:</td></tr>
<tr><td>LH PFC</td><td>89.45</td><td>-0.73</td><td>1.46</td><td>-3.60</td><td>2.13</td><td>1.1%</td></tr>
<tr><td>RH PFC</td><td>90.85</td><td>-0.59</td><td>1.87</td><td>-4.27</td><td>3.08</td><td>1.3%</td></tr>
<tr><td>LH Broca</td><td>16.43</td><td>0.51</td><td>0.90</td><td>-1.26</td><td>2.27</td><td>2.4%</td></tr>
<tr><td>RH Broca</td><td>13.62</td><td>0.69</td><td>1.71</td><td>-2.66</td><td>4.05</td><td>7.7%</td></tr>
<tr><td colspan="7">Intra-rater study 2:</td></tr>
<tr><td></td><td colspan="2">LH PFC</td><td>RH PFC</td><td colspan="2">LH Broca</td><td>RH Broca</td></tr>
<tr><td>CE_{ow}(%)</td><td colspan="2">2.8%</td><td>1.7%</td><td colspan="2">1.7%</td><td>1.7%</td></tr>
<tr><td colspan="7">Intra-rater study 3:</td></tr>
<tr><td></td><td colspan="2">LH PFC</td><td>RH PFC</td><td colspan="2">LH Broca</td><td>RH Broca</td></tr>
<tr><td>CE_{PC}(%)</td><td colspan="2">1.2%</td><td>0.9%</td><td colspan="2">1.8%</td><td>3.1%</td></tr>
</table>

Biological Variability

Biological variability of a geometrical parameter of a biological structure, such as brain volume, refers to the true variability in volume across individuals' studied, assuming volume has been obtained without measurement error. Inter-individual variability includes the contributions from both the biological variation among a given sample, and the variability due to sampling error on the obtained estimates (i.e. volume). This sampling error is contained in the CE. The coefficient of variation (CV) represents the ratio of the standard deviation to the mean and can be represented as a percentage when multiplied by 100 (CV = SD/mean x 100). In this case the CV represents the degree of variation in volume for each structure among individuals. The contribution of biological variability to the overall variance can be determined by calculating the predicted CE from the obtained estimates (which comes from the variance due to Cavalieri sectioning, demarcation, point counting and differences within and between observers) and subtracting this from the total CV. This can be expressed using Equation (4.8).

$$CV_B^2 = CV_T^2 - CE^2 \tag{4.8}$$

In this equation CV_B^2 represents the coefficient of variation attributable to biological variation, CE^2 is the mean coefficient of error calculated as the mean of the coefficient of errors of the volume estimator for the different levels of sampling involved, and CV_T^2 represents the total coefficient of variation based on the sample. The results of the average CE for each region in each inter- and intra-rater study performed on sample data are given in Table 4.4.

Equation (4.8) does not however, take into account biasedness in the volume estimates. Bias is systematic error in the measurement and there is no way of being able to measure this from the data. In this thesis all volume estimates were obtained by rater JP. Assuming there is any bias this is expected to be consistent across all measurements obtained and therefore will not affect the findings reported which show significant differences between left- and right-handers (e.g. Broca volume the results of which are shown in Chapter 5).

4.4.3 Anatomical Regions of interest

Image pre-processing

Prior to demarcation the newly acquired MR datasets were first imported into BrainVoyager software (www.Brainvoyager.com, Brain Innovation, Maastricht, The Netherlands) for pre-processing. Pre-processing required re-orienting images to a standardised sagittal plane, orthogonal to the bi-commissural plane, following the approach used by others (Cowell *et al*., 2007; Howard *et al*., 2003; Keller *et al*., 2007; Powell *et al*., 2010).

Re-alignment of the structural images was carried out using the 3D volumes tool in the Analysis menu of BrainVoyager software, which allows the operator to view images in sagittal, coronal and axial planes (see Figure 4.3). On a sagittal section closest to midline, a line was drawn (AC-PC line) connecting the anterior commissure (AC) and posterior commissure (PC) so that both structures could be viewed in the same axial slice. This can be seen in Figure 4.3D.

The bi-commissural plane (containing the AC-PC line) was taken on the axial slice to correct for anterior-to-posterior tilt (Figure 4.3A and D). Side-to-side tilt (i.e. left-to-right tilt) was corrected for by aligning the superior-most aspect of the orbital cavities at their maximum cross-sectional area in the coronal plane (Figure 4.3B and E). The orbital cavities are extrabrain landmarks, however, since the frontal lobe is larger in the right hemisphere, a system was chosen that would be reproducible across raters and would not add systematic error (bias).

To correct for deviations from sagittal midline, a plane taken through the longitudinal fissure of the corrected transaxial plane resulted in the standardised sagittal plane (Figure 4.3C and 4.3F). This corrects for a twist in head positioning. The standardised sagittal image was then rotated so that the bi-commissural axis (i.e. the superior view of the AC-PC corrected image) was positioned at zero degrees. This correction in positioning ensured that vertical and horizontal lines used in the parcellation process would transect similar anatomical landmarks across all participants. These pre-processed, AC-PC corrected images were then used for PFC subfield and Broca area subfield demarcations.

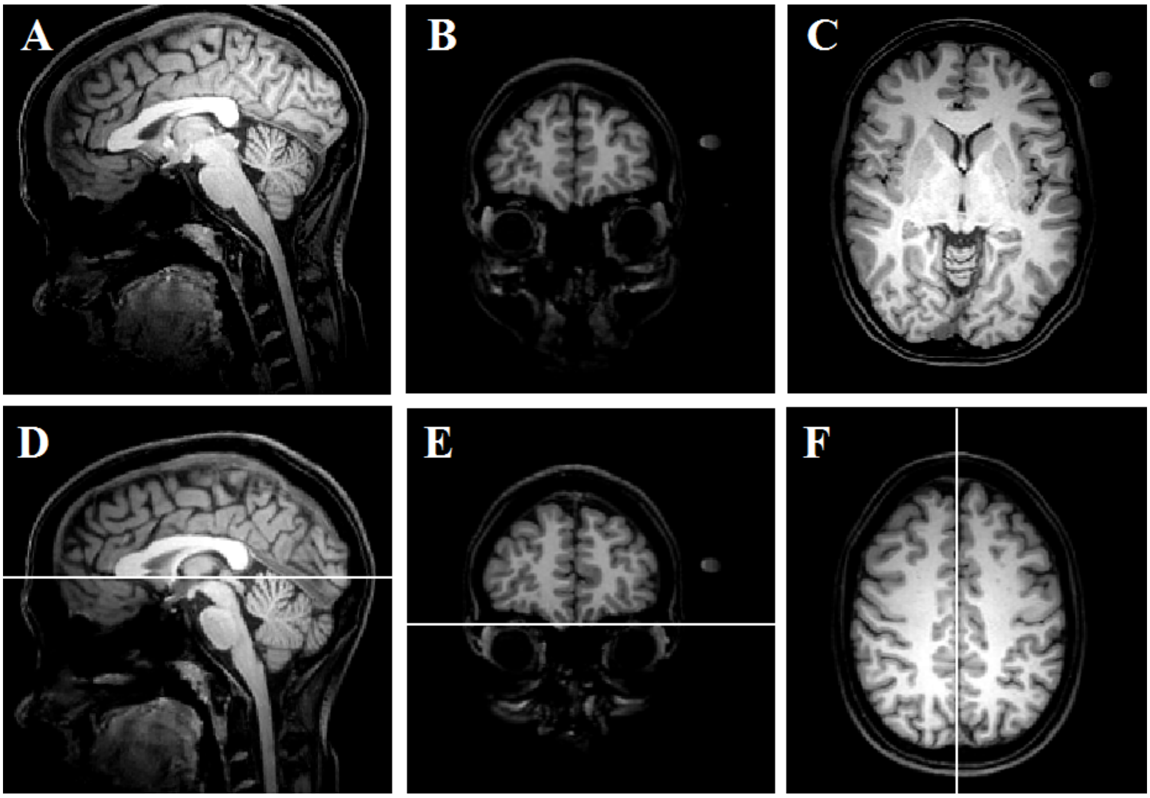


Figure 4.3. Sagittal, coronal and axial planes from a T_1-weighted MR image prior to standardised sagittal orientation (A-C). A plane is taken through the AC-PC line to correct for anterior-to-posterior tilt (D). A plane was taken at the superior most point of the orbital cavities where the cavities were at their maximum to correct for side-to-side tilt (E). A sagittal plane was taken along the longitudinal fissure from a more superior view (F) to that shown in C to correct for the twist in head positioning.

Prefrontal cortex measurements

The protocol employed to estimate volumes of anatomically defined subfields of the PFC is based on the previously established methodology developed by Howard *et al* (2003). The protocol divides the right and left PFC into dorsolateral (DL), dorsomedial (DM), orbitolateral (OL) and orbitomedial (OM) regions, yielding 8 subfields which can be seen in Figure 4.4. Volume estimates for the 8 PFC subfields are given in Table 4.6, separated by sex and handedness groups.

Parcellation of the 3D dataset was made according to macroanatomical landmarks. These landmarks were either fixed boundaries (such as the division between medial and lateral regions and the division between dorsal and orbital regions represented by the blue and green lines in Figure 4.4, respectively) or were visualised by the rater from one slice to the next (such as the posterior region of the orbital area, see green area in Figure 4.4) when anatomical landmarks provided natural boundaries to the region of interest. Points falling within the boundary of the region were selected by the rater during the point counting process and can be seen in Figure 4.5.

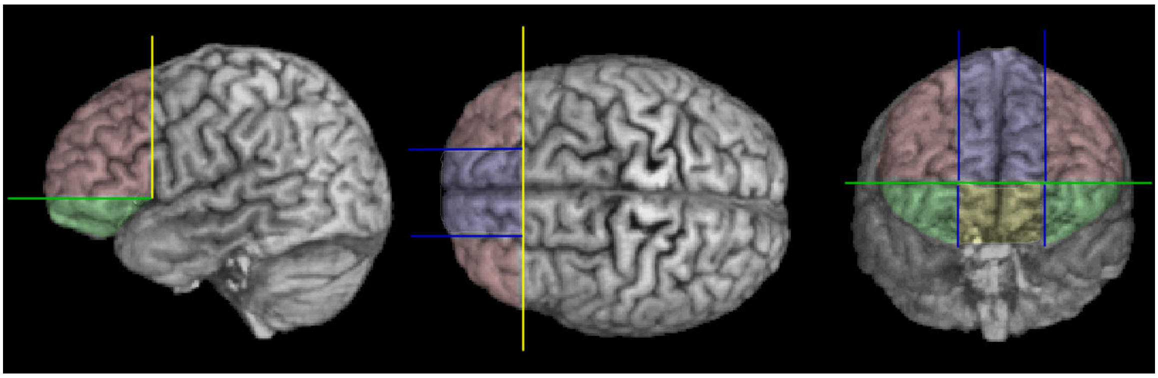


Figure 4.4. The 8 PFC subfields. In all frames the yellow lines indicate the prefrontal demarcation from the remaining brain, green lines indicate the demarcation boundary between dorsal and orbital regions, and blue lines indicate the demarcation between medial and lateral regions. Pink and blue areas represent DL and DM subfields respectively. Green and yellow areas represent OL and OM subfields respectively.

The division between orbital and dorsal regions was delineated by the bi-commissural plane. Demarcation of the medial from lateral regions used the first axial slice superior to the olfactory sulcus, and in particular, the medial-most aspect of GM of the arcuate (Duvernoy, 1991, p.26) or transverse orbital sulcus (Damasio, 1995, p.114) (this is shown in Howard *et al.*, 2003 in Figure 2). The medial/lateral demarcation allowed cingulate regions to be separated from other cortical structures in both dorsal and orbital regions. The anterior tip of the corpus callosum, viewed at sagittal midline, formed the posterior boundary of the DL and DM regions. This is represented by the yellow line in Figure 4.5A and B.

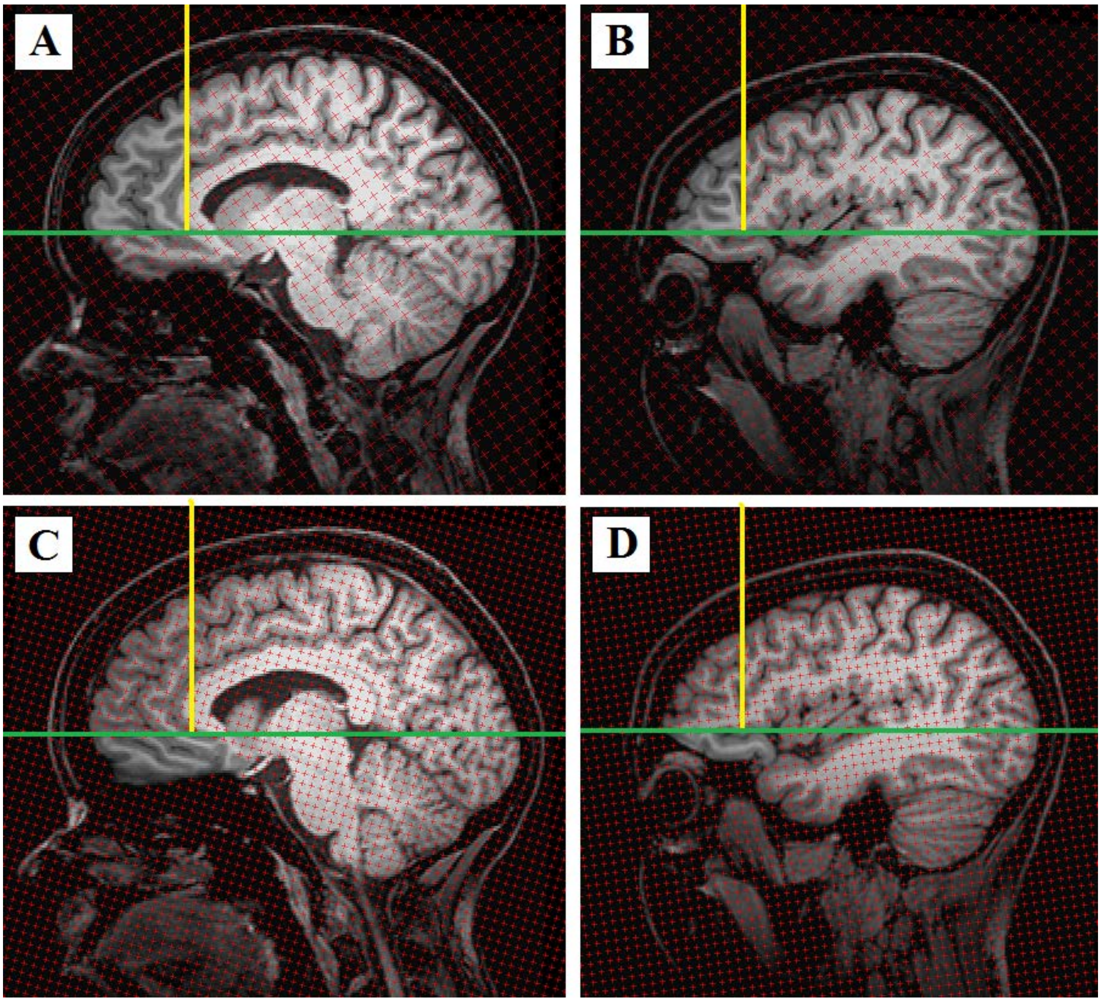


Figure 4.5. Images A-D represent point counting during stereological analysis of DM (A), DL (B), OL (C) and OM (D) prefrontal subfields. Stereological grids appear as red crosses, with counted points removed in sample sections. In all frames yellow lines indicate the prefrontal demarcation from the remaining brain, and green lines indicate the demarcation boundary between dorsal and orbital regions.

Natural anatomical borders were easily identifiable and used to demarcate posterior boundaries of the orbital regions (Figure 4.5C and D). At the midline, in most cases, a boundary between medial prefrontal brain tissue and CSF was clearly visible. In cases where the cortical border with the CSF was not visible in the midline slices of the MR image, the anteroventral tip of the corpus callosum guided the posterior cortical boundary. Laterally, the boundary followed the anterior-most portion of the caudate nucleus. More laterally, the boundary was demarcated by the anterior branch of the

Sylvian fissure. These anatomical features were visualised by the rater during point counting. This methodology enabled inclusion of orbital prefrontal regions in their entirety (e.g. full posterior extent of BA47 and BA11, laterally, and BA12 and BA25, medially).

Following parcellation of PFC subfields, images were imported into EasyMeasure software (Roberts *et al.*, 2000) for point counting and Cavalieri volume estimation. Details of the sampling parameters used for each of the PFC subfields are shown in Table 4.5. A grid of 6x6 pixels (=36mm^2) were used for DL and DM subfields and 4x4 pixels (=16mm^2) were used for OL and OM regions. Points were counted on randomly superimposed point grids, on every second slice. The density of grid points was appropriate to maintain a coefficient of error below 5%. The shape coefficients calculated in Howard *et al* (2003) (5.65, 5.99, 5.48 and 5.19 for DL, DM, OL, and OM respectively) were used here to estimate the contribution from point counting to the coefficient of error of the volume estimator. The shape coefficient, measures how irregular the geometry of the PFC structure is based on the observation of the sagittal sections.

Table 4.5. Sampling parameters used during stereological volume estimation for PFC, PO and PTR subfields. The shape coefficient and smoothness constant estimated for subject RM34 are also given. 1mm is equal to 1 pixel.

Region of interest	**Distance between slices (mm)**	**Area per point (mm^2)**	**Grid size (mm)**	**Shape coefficient**	**Smoothness constant *q***
Dorsolateral	2	36	6 x 6	5.65	0.03
Dorsomedial	2	36	6 x 6	5.99	0.18
Orbitolateral	2	16	4 x 4	5.48	0.06
Orbitomedial	2	16	4 x 4	5.19	0.22
PO grey matter	1	9	3 x 3	7.7	0.13
PO white matter	1	9	3 x 3	7.7	0.37
PTR grey matter	1	9	3 x 3	7.7	0.11
PTR white matter	1	9	3 x 3	7.7	0.23

Broca's area measurements

Delineation of the PO and PTR was based on the protocol outlined by Keller *et al* (2007) who followed the anatomical definitions described by others (Duvernoy, 1991; Petrides, 2006; Petrides and Pandya, 2004; Tomaiuolo *et al*., 1999). Grey and white matter volume of the PO and PTR were measured separately on coronal images, yielding four volume measurements per hemisphere. Volume estimates for PO and PTR regions are given in Table 4.6. The sulcal contours defining these regions were clearly visible on high resolution T_1-weighted MR images (Figure 4.8) and were marked first in the realigned standardised sagittal image on coronal, sagittal and axial sections using BrainVoyager software. The sulcal contours of the PO and PTR were documented prior to performing the PO and PTR volume estimates as sulcal assessment was a prerequisite to performing PO and PTR stereological volume estimates.

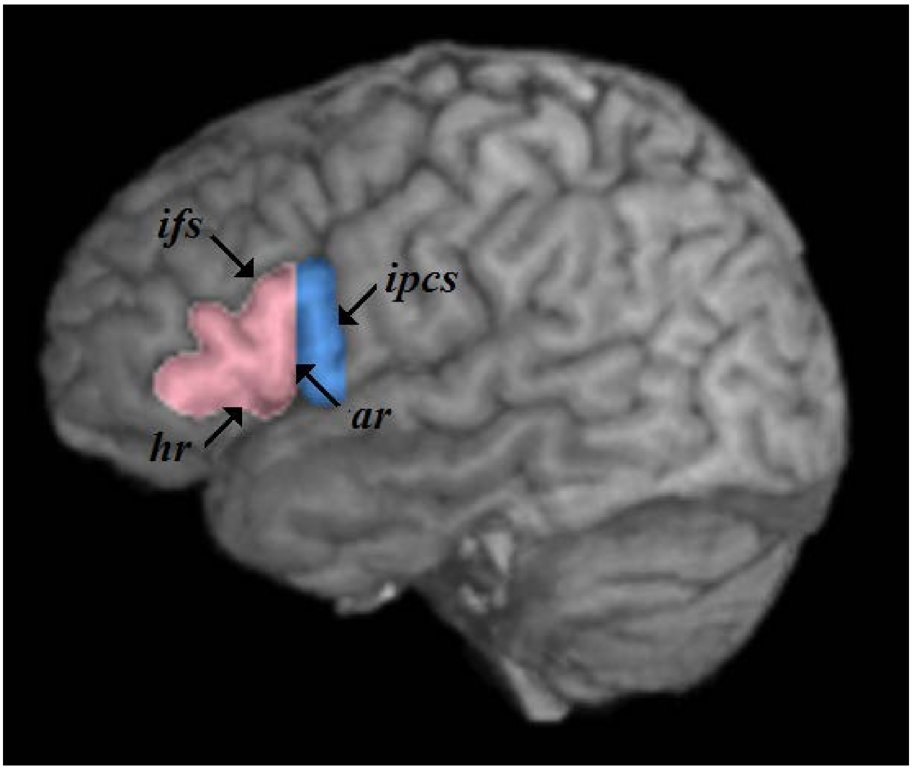


Figure 4.6. The major sulcal contours defining the PO (blue) and PTR (pink). The PO is a region of cortex located anterior to the inferior precentral sulcus (IPCS), ventral to the inferior frontal sulcus (IFS) and posterior to the anterior ascending ramus (AR) of the Sylvian fissure. The PTR is located ventral to the IFS, the AR forms the posterior boundary, and anterior horizontal ramus (HR) of the Sylvian fissure forms the anterior-inferior border.

PO demarcation: The IPCS marks the posterior boundary, separating the PO from precentral gyrus. The IFS marks the superior boundary of the PO, separating PO from middle frontal gyrus. The AR of the Sylvian fissure is used to separate PO and PTR regions.

PTR demarcation: The AR of the Sylvian fissure forms the posterior boundary of the PTR. The IFS forms the superior boundary, separating PTR from middle frontal gyrus. The HR of the Sylvian fissure forms the anterior-inferior border of the PTR.

The demarcated MR images were imported into EasyMeasure software to estimate volume of the 8 Broca subfields. A grid of 3x3 pixels (=9mm^2) was used for all PO and PTR regions (Figure 4.7) and points were counted on randomly superimposed point grids, on every slice (distance between MR images = 1mm). Again grid point density was appropriate to maintain CE<5%. The shape coefficient of a given object can, according to Uylings *et al* (2005), be estimated from a few sections of ‘eye-balled’ from the nomogram of Gundersen and Jensen (1987, see their Figure 18). Uylings *et al* (2005) estimate the shape coefficient of Broca’s area to be about 7 and this is the value that they use to estimate volume of BA44 and BA45, which correspond to PO and PTR respectively (although see Section 10.3 for a discussion on this). A shape coefficient of 7.7 was chosen in this thesis for the prediction of the coefficient of error of the volume estimation. Details of the sampling parameters used to estimate PO and PTR grey and white matter volume can be found in Table 4.5. Stereological volume estimates for the PO and PTR were used to explore the effect of sex and handedness on the structure and asymmetry of Broca’s area. This study is presented in Chapter 5.

Hemisphere volume

All grey and white matter within each cerebral hemisphere excluding the brain stem and cerebellum was included in each hemisphere measurement. A grid with a large unit area (8x8 pixels) was chosen to accommodate the larger volume of interest without excessively laborious point counting. Points were counted on every fifth slice (distance between MR images =5mm). Volume estimates for total brain volume are given in Table 4.6, separated by sex and handedness group.

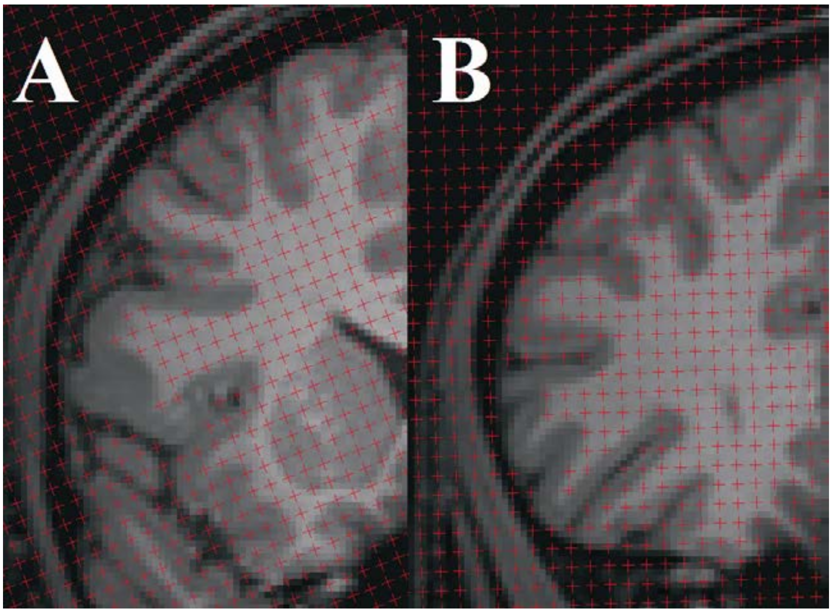


Figure 4.7. Point counting for stereological analysis of grey matter PO (A) and grey matter PTR (B) in the left hemisphere. Red crosses represent points not counted. Points removed on the structure of interest are shown on the left hemisphere. The same process was performed on the right hemisphere and on white matter.

Table 4.6. Mean stereological volume estimates (standard deviations in parenthesis) for the eight PFC sub-fields, total brain volume and PO and PTR sub-fields for participants (separated by sex and handedness). Left=left hemisphere, Right=right hemisphere, PFC=prefrontal cortex, DL=dorsolateral, DM=dorsomedial, OL=orbitolateral, OM=orbitomedial, PO=pars opercularis, PTR=pars triangularis. Note: PFC volume estimates are from all 82 participants, whereas PO and PTR volume estimates are for 79 participants (see Chapter 5).

Stereological volume estimates (cm^3)	**Total**	**Males**	**Females**	**Right-handers**	**Left-handers**	**Right-handed males**	**Right-handed females**	**Left-handed males**	**Left-handed females**
Total brain	1032 (114)	1127 (71.6)	971 (93.7)	1028 (128)	1036 (99)	1150 (77)	955 (96)	1108 (63)	989 (91)
Left DL PFC	25.6 (5.3)	27.7 (5.4)	24.0 (4.8)	25.7 (5.3)	25.4 (5.3)	29.7 (5.3)	23.3 (3.5)	25.6 (4.7)	25.2 (5.7)
Right DL PFC	29.1 (5.8)	32.1 (5.6)	27.1 (5.0)	29.0 (5.7)	29.2 (6.0)	32.9 (5.2)	26.5 (4.5)	31.4 (6.2)	27.7 (5.6)
Left DM PFC	30.3 (4.9)	32.7 (4.3)	28.7 (4.7)	30.5 (4.9)	30.0 (4.9)	33.3 (5.2)	28.8 (3.9)	32.1 (3.1)	28.6 (5.5)
Right DM PFC	29.3 (4.7)	31.3 (4.7)	28.0 (4.3)	29.2 (4.6)	29.4 (5.0)	32.2 (4.3)	27.4 (3.7)	30.4 (5.1)	28.8 (4.9)
Left OL PFC	12.7 (3.6)	14.4 (3.3)	11.7 (3.4)	13.0 (3.4)	12.5 (3.8)	15.3 (2.6)	11.6 (3.1)	13.5 (3.8)	11.8 (3.8)
Right OL PFC	12.1 (3.8)	13.7 (4.1)	11.0 (3.2)	12.4 (3.9)	11.7 (3.8)	14.2 (4.2)	11.3 (3.2)	13.3 (4.1)	10.6 (3.2)
Left OM PFC	15.6 (3.8)	17.7 (3.5)	14.2 (3.4)	15.8 (4.1)	15.4 (3.5)	18.5 (3.6)	14.2 (3.6)	17.0 (3.4)	14.3 (3.2)
Right OM PFC	14.7 (3.7)	16.8 (3.2)	13.6 (3.5)	14.7 (3.8)	15.0 (3.6)	17.3 (3.2)	13.1 (3.3)	16.3 (3.1)	14.2 (3.7)
Left PO GM	4.4 (1.4)	4.7 (1.5)	4.2 (1.3)	5.0 (1.5)	3.7 (1.0)	5.7 (1.4)	4.6 (1.3)	3.6 (0.7)	3.9 (1.2)
Right PO GM	4.7 (1.2)	5.0 (1.2)	4.5 (1.2)	4.8 (1.3)	4.6 (1.1)	5.2 (1.5)	4.6 (1.2)	4.8 (0.9)	4.4 (1.3)
Left PO WM	3.1 (1.1)	3.4 (1.2)	2.6 (1.0)	3.6 (1.1)	2.6 (0.9)	4.2(1.1)	3.3 (1.0)	2.5 (0.7)	2.6 (1.0)
Right PO WM	3.3 (1.0)	3.4 (1.2)	3.2 (0.9)	3.4 (1.1)	3.1 (0.8)	3.6 (1.5)	3.3 (0.9)	3.2 (0.6)	3.0 (0.9)
Left PTR GM	5.3 (1.9)	5.6 (1.8)	5.1 (1.9)	6.2 (1.8)	4.2 (1.4)	6.6 (1.3)	5.6 (2.0)	4.5 (1.6)	4.0 (1.2)
Right PTR GM	4.8 (1.5)	4.9 (1.4)	4.8 (1.6)	5.5 (1.5)	4.0 (1.2)	5.8 (1.0)	5.3 (1.7)	3.9 (1.2)	4.1 (1.2)
Left PTR WM	3.3 (1.2)	3.5 (1.2)	3.2 (1.1)	3.8 (1.1)	2.8 (1.0)	4.0 (1.0)	3.6 (1.2)	3.0 (1.2)	2.7 (0.8)
Right PTR WM	3.0 (1.1)	3.1 (1.1)	3.0 (1.0)	3.4 (0.9)	2.5 (0.9)	3.6 (0.8)	3.3 (1.0)	2.5 (0.9)	2.6 (0.9)

4.4.4 Sulcal contours of Broca’s area

MR sections viewed in BrainVoyager software in conjunction with rendered surfaces of cerebral hemispheres visualised in MRIcro (www.mricro.com, University of South Carolina, Columbia, SC, USA) were used to assess the sulcal contours of the PO and PTR. Orthogonal sections were referred to in BrainVoyager as the full extent of intrasulcal anatomy cannot be appreciated from the surface of the brain alone (Germann *et al*., 2005; Keller *et al*., 2007). Morphology of five sulci (or rami) was assessed: the inferior frontal sulcus (IFS); inferior precentral sulcus (IPCS); anterior ascending ramus (AR) of the Sylvian fissure; horizontal ascending ramus (HR) of the Sylvian fissure; and diagonal sulcus (DS). (For a full description of the variability of the length, continuity and connections of these sulci see Keller *et al*., 2007).

Inferior frontal sulcus: The posterior portion of the IFS is defined using the first ventral horizontal frontal sulcus extending from the IPCS (either connected or separated by a bridge of cortex). The IFS can be defined as continuous or discontinuous (Ono *et al*., 1990; Petrides and Pandya, 2004). When the IFS is continuous, it normally terminates at approximately the mid-portion of the dorsal edge of the PTR (Petrides and Pandya, 2004). When the IFS is discontinuous (composed of two or more segments) the anterior segment of the IFS can be difficult to distinguish from anterior frontal sulci. Reliable assessment of intrasulcal connectivity requires using orthogonal MR sections. An example of a continuous and a discontinuous IFS can be seen in Figure 4.8 on the left and right respectively.

Connections between the posterior IFS and the ventral IPCS can be broadly classified into one of four profiles (Germann *et al*., 2005; Ono *et al*., 1990): (i) a true long connection in which the IFS flows fully into the IPCS, (ii) a true short connection in which the IFS flows fully into the IPCS but is discontinuous in its length composed of two or more segments (Ono *et al*., 1990), (iii) a superficial connection, which appears as a connection on the surface of the brain but a submerged bridge of cortex interrupts this connection, or (iv) no connection.

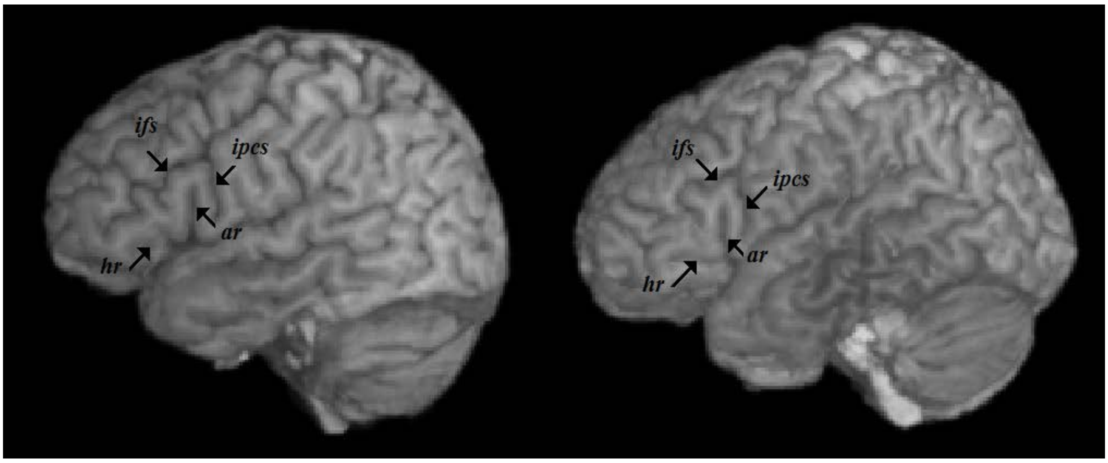


Figure 4.8. Connections between the posterior IFS and the ventral portion of the IPCS. A continuous connection is presented on the left and a discontinuous connection can be seen on the right.

Inferior precentral sulcus: The ventral most region of the IPCS marks the posterior border of the PO and is identified as the first descending sulcus immediately anterior to the central sulcus. It may occasionally flow into the Sylvian fissure (Ono *et al*., 1990).

Anterior ascending ramus: The AR of the Sylvian fissure is commonly located where the temporal lobe turns downwards to form the temporal pole. The AR ascends into the inferior frontal gyrus (IFG) and is located anterior to the DS, marking the division between the PO and PTR.

Anterior horizontal ramus: The HR appears as a continuation of the Sylvian fissure in the lateral-orbital frontal lobe. It demarcates the PTR from the more ventrally located pars orbitalis and it may: (i) be situated along the orbital margin or over the orbital surface, (ii) share a common trunk with the AR or (iii) be absent (Ono *et al*., 1990).

Diagonal sulcus: The DS is positioned between the IPCS and AR of the Sylvian fissure on the IFG, within the PO. It may: (i) extend from the IFS (Figure 4.9A), (ii) extend from the IPCS (Figure 4.9B), (iii) merge with the AR of the Sylvian fissure (Figure 4.9C) or (iv) not merge with any surrounding sulci and adjoin the Sylvian fissure (Figure 4.9D).

The following sulcal features were recorded for each cerebral hemisphere:

IFS: continuous or discontinuous; connection with the IPCS: true long, true short, superficial connection or no connection

IPCS (ventral most region): single or dual; connection or no connection with the Sylvian fissure.

AR of the Sylvian fissure: present or absent

HR of the Sylvian fissure: present or absent; common or separate origin from the AR.

DS: present or absent; connection to either IFS, IPCS, AR or no connection to these sulci.

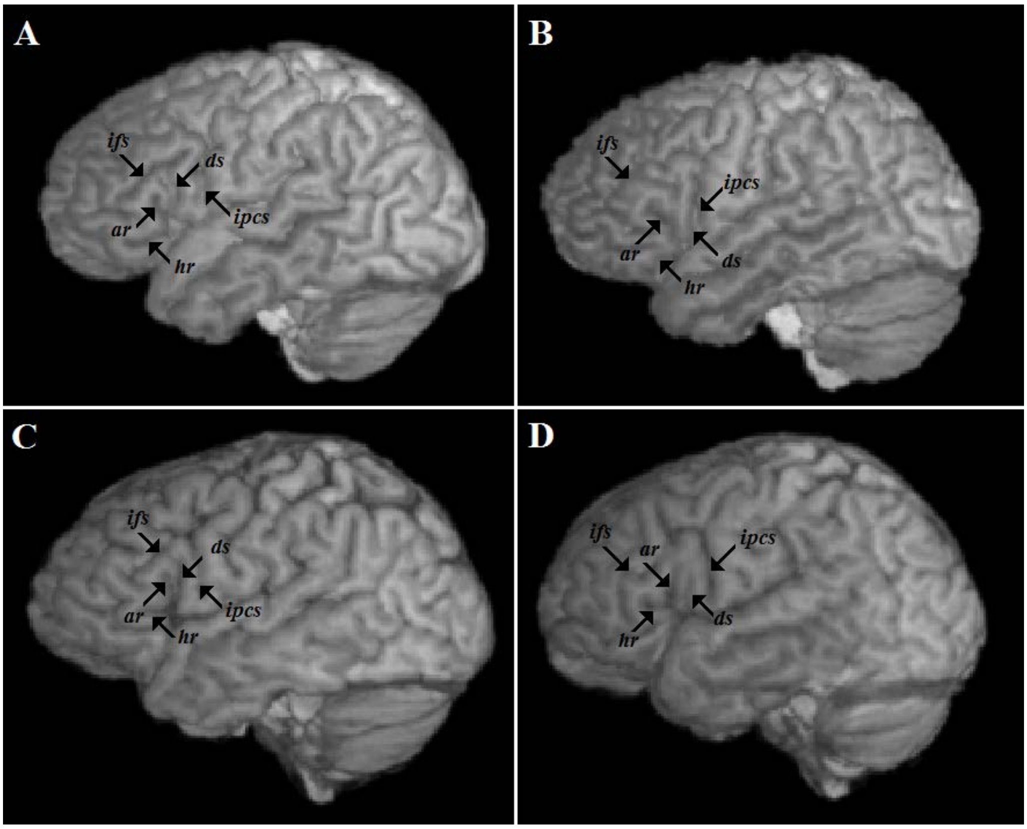


Figure 4.9. The four connections of the DS: A=connection with the IFS, B=connection with the IPCS, C=connection extending from the AR and D=no connection with surrounding sulci.

4.4.5 Automated MR image analysis techniques

Voxel-based morphometry (VBM) is an automated, computerized, quantitative image analysis technique developed to detect brain differences *in vivo* between two groups of subject's (Ashburner and Friston, 1997, 2000, 2003, 2005). The aim of VBM is to identify differences in the local composition of brain tissue, while discounting large scale differences in gross anatomy and position. This is achieved by firstly, transforming all the images to a common 3D stereotaxic space, through a process called spatial normalisation, so that corresponding brain structures can be compared between individuals. Normalised images are then segmented into partitions of GM, WM and cerebrospinal fluid (CSF), which are then smoothed with an Isotropic Gaussian Kernel (IGK) to compensate for normal inter-individual variation in brain morphology (e.g. gyral convolutions), rendering the data as normally distributed. Finally statistical analysis is performed to localize significant differences in GM or WM density or concentration between two or more participant cohorts. The output is a statistical parametric map (SPM) showing regions where GM or WM differs significantly among the groups.

Unified segmentation

VBM analysis was carried out using the VBM toolbox (VBM5) (http://dbm.neuro.uni-jena.de/software/) in the Statistical Parametric Mapping software package (SPM5), available at: Welcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm. The current version of SPM5 uses a new VBM method for segmenting brain images called "unified segmentation" (Ashburner and Friston, 2005). Unified segmentation deploys a framework where tissue classification, bias correction, and image registration are integrated within the same model (Segall *et al.*, 2009). This provides better results than simple serial applications of each component (Ashburner and Friston, 2005). All T_1-weighted MR images in this thesis were segmented without the use of priors.

Normalisation and segmentation

The ICBM tissue probabilistic atlases (International Consortium for Brain Mapping, http://www.Ioni.ucla.edu/ICBM/ICBMTissueProb.html John C. Mazziotta and Arthur W. Toga) derived from 452 T_1-weighted MR scans, which were aligned into an atlas space, corrected for scan inhomogenieties, and classified into GM, WM and CSF are provided as the tissue-specific templates in SPM5 and are used as the templates for normalisation of MR images in this thesis.

In order to preserve the true volume (GM/WM signal intensity within a voxel) of brain structures prior to normalisation, spatially normalised images can be modulated (or multiplied) by their Jacobian determinants, which are deformation parameters that contain information of the transformation of images from their native space into standard space. By modulating normalised and segmented images by Jacobian determinants, resulting analysis tests for regional differences in the absolute amount of GM (i.e. GM volume: correction for nonlinear normalisation), whereas analysis of unmodulated normalised images tests for regional differences in the local distribution of GM (i.e. GM concentration: no correction for nonlinear normalisation).

Following co-registration of the study images, the normalised images are segmented into partitions of GM, WM and CSF probability maps. The ICBM data set typically serves as the a priori information in SPM5. Volume estimates of the segmented partitions for GM, WM, CSF and intracranial volume (ICV: the total of GM, WM and CSF) obtained from VBM for left- and right-handed participants are given in Table 4.7.

Smoothing

After segmentation, the normalised GM and/or WM tissue probability maps are smoothed, or ‘blurred’, using an isotropic Gaussian kernel (IGK) with full width-half maximum. The process of smoothing satisfies two main criteria. Firstly, since cortical morphology is inherently variable between individuals, convolving the data with a smoothing kernel allows for the high variability of inter-individual gyral anatomy and compensates for the inexact nature of spatial normalisation (Ashburner and Friston, 2000; Mechelli *et al*., 2005). Secondly, smoothing conditions the data to conform to the random Gaussian field model underlying statistical analysis by rendering the data as normally distributed for subsequent voxel-based analysis (Ashburner and Friston, 2000; Salmond *et al*., 2002). Determining the size of the smoothing kernel is subjective and ultimately reflects the size of the effect of between group differences.

Voxel-wise statistical analysis of GM images

The final step in VBM analysis involves voxel-wise statistical analysis of the GM and/or WM images. Statistical analysis employs the general linear model (GLM), a flexible framework that allows many different tests to be applied (Ashburner and Friston, 2000; Keller and Roberts, 2008). Hypotheses are tested using standard parametric statistical procedures (t-tests and F-tests). A voxel-wise statistical parametric map (SPM) comprises the result of many statistical tests, and it is necessary to correct for these multiple dependent comparisons. Corrections for multiple comparisons are made using the theory of Gaussian random fields (Friston *et al*., 1995a,b; Worsley and Friston, 1995; Worsley *et al*., 1997). Further details of the statistical analysis performed on the GM images in this thesis can be found in Section 8.1.

Table 4.7. Mean volumes (standard deviations in parenthesis) are given for VBM segmentations based on the cohort of 42 right-handers and 40 left-handers investigated in this thesis: GM=grey matter, WM=white matter, CSF=cerebrospinal fluid, ICV=intracranial volume (the sum of GM, WM and CSF volume). Volume is given in cm^3.

Region	**Total**	**Males**	**Females**	**Right-handers**	**Left-handers**	**Right-handed males**	**Right-handed females**	**Left-handed males**	**Left-handed females**
VBM segmentation volumes									
GM	597 (66)	644 (63)	566 (48)	602 (74)	592 (57)	658 (73)	567 (49)	631 (49)	566 (47)
WM	452 (53)	493 (35)	426 (45)	457 (566)	447 (50)	504 (37)	428 (45)	483 (30)	423 (47)
CSF	439 (67)	490 (57)	406 (49)	443 (69)	433 (64)	505 (61)	406 (43)	476 (50)	405 (57)
ICV	1488 (159)	1628 (107)	1398 (115)	1503 (166)	1472 (151)	1667 (114)	1401 (96)	1589 (87)	1395 (134)

4.4.6 Voxel-wise analysis of diffusion images

Voxel-wise analysis was performed on diffusion-weighted MR images in this thesis to investigate the effect of handedness on WM anisotropy and anisotropy asymmetry (for study see Chapter 6). Following data acquisition raw diffusion-weighted images were imported into DTIStudio (http://www.mristudio.org/) for tensor calculation within each dataset. For each individual FA maps and average non-diffusion weighted images (b=0s/mm^2) were obtained using the tensor calculation option. Prior to tensor calculation motion correction was performed using Automatic Image Registration (AIR). Background noise level was adjusted for by checking image intensity of each diffusion-weighted image and selecting a masking threshold based on the noise level in the images. All B_0 images were averaged as a reference for tensor calculation.

Comparing WM integrity and asymmetry between left- and right-handers

WM anisotropy analysis: The averaged non-diffusion weighted images were spatially normalised to the MNI EPI template supplied by SPM5. These estimated parameters were then applied to the FA maps in native space. FA images were averaged from all participants creating an average FA template using the ImCalc function in SPM5. A binary mask was then created from the averaged template using the Masking toolbox (Ridgway *et al*., 2009) using the total sample of subjects and was entered as an explicit mask in the first design matrix. This masking strategy involves thresholding the mean of all 82 FA sets of images: voxels in the images exceeding this intensity value are included within the mask. Normalised FA maps were smoothed with an IGK of 10 mm FWHM which was chosen following experimentation using an 8mm IGK and a 10mm IGK. An 8mm IGK was too small for the size difference observed between the handedness groups.

To compare WM anisotropy the smoothed FA images for left- and right-handers were entered into the first full-factorial design matrix, with the explicit mask. Handedness was entered as a factor with two levels. Age and sex were entered as covariates along with the interaction between the binary variables handedness and sex. No global normalisation was applied to the analysis. Significant differences in FA between left and right-handers were tested by using t-tests, with a threshold set to $P<0.05$, corrected for multiple comparisons using the false-discovery-rate (FDR).

Anisotropy asymmetry analysis: A separate analysis was performed to investigate FA asymmetry in left- and right-handers. The averaged template, generated from the normalised FA images (without smoothing), was flipped and a symmetric FA template was created by averaging these two images i.e. the flipped and unflipped FA image. This symmetric template was then smoothed with a 10mm IGK. Individual FA images in native space were normalised to the symmetric FA template and flipped, producing flipped and unflipped normalised FA images for each individual. A binary mask was created using the flipped and unflipped normalised FA images from each participant with the Masking toolbox, resulting in a binary mask based on the total sample of participants. This binary mask was included in the second design matrix as an explicit mask. FA asymmetry images were created for each subject by subtracting the flipped from the unflipped normalised FA image using the ImCalc function in SPM5. FA asymmetry images were then smoothed with a 10mm FWHM Gaussian kernel, which matched the smoothing kernel of the symmetric template and to match the size difference expected between the handedness groups.

The smoothed normalised asymmetric FA images for both left- and right-handers were entered into the second full-factorial design matrix masked by the symmetric explicit mask, with age and sex as covariates. Handedness was entered as a factor with two levels. The interaction between sex and handedness group was also included. No global normalisation was applied within this full-factorial design matrix. FA asymmetry was explored in left- and right-handers separately using t-tests with a threshold set to $P<0.05$, corrected for multiple comparisons using the family-wise-error (FWE). The FDR yielded highly significant results, the FWE was chosen as a more conservative option to correct for multiple comparisons. Direct comparisons between the handedness groups were explored using t-tests (FDR, $P<0.05$). The voxel size was $2 \times 2 \times 2$ mm^3 and only voxels with an FA value greater than 0.2 were included. Only clusters of at least 10 voxels are reported. The results for this study are presented in Chapter 6.

4.5 FUNCTIONAL MR IMAGE ANALYSIS TECHNIQUES

4.5.1 Principles of fMRI data analysis

fMRI is used to detect brain activity related to blood volume changes. A number of pre-processing steps are performed on the data prior to statistical analysis, including, spatial realignment, spatial coregistration, spatial normalisation and spatial smoothing. Each step is explained below.

Spatial realignment

The main result of head movements is that the same voxel does not necessarily represent the same location in the brain throughout time. Spatial realignment is performed on each participant separately. The mean image of the time series was chosen as the reference volume and all other volumes in the same time series were repositioned until they were in the same position. Only the position of the brain is changed and not the size or shape. This repositioning treats the head as a rigid object and is known as a rigid body transformation. Realignment also adjusts for apparent movement: as the fMRI scanner heats up during a session it appears as though the head drifts slightly.

Spatial normalisation

Following spatial realignment the MR images are spatially normalised, or co-registered, into a common stereotaxic (standard) space (Ashburner and Friston, 2000, 2003). The target image is a neuroanatomical template, constructed from a large database of control images. The standard brain most commonly used is the MNI 152 template, which is based on the coordinate system described by Talairach and Tournoux (1988). Spatially normalising different brains to make them more alike in size and shape is performed to ensure that the same voxels in the brain of each participant represent the same anatomical location, enabling comparisons over and between different participants. (For details see Ashburner and Friston, 2000, 2003).

Spatial co-registration

Co-registration can sometimes help with spatial normalisation. In the current study each individual's low resolution EPI fMRI scan was aligned to their high resolution T_1-weighted scan. The high resolution anatomical scan is more detailed than the fMRI scans, so normalisation of the high resolution anatomical scan to a standard brain often leads to better results than matching the fMRI scans to the standard brain. If the high resolution anatomical scan and the fMRI scans are first co-registered, the parameters that are used to match the anatomical scan to the standard brain can then be applied to the fMRI dataset (Ashburner and Friston, 2003; Jenkinson, 2001) and this is what was performed on the MR images obtained in this thesis.

Spatial Smoothing

This pre-processing step is performed for a number of reasons. Firstly, smoothing the dataset increases the signal-to-noise ratio (SNR) in the fMRI signal by removing the high spatial frequencies. Secondly, smoothing removes small frequency differences, facilitating comparisons across participants. Thirdly, smoothing the dataset helps to satisfy the requirements for applying Gaussian Field Theory to correct for multiple comparisons in the ensuing statistical analysis by making the data more normally distributed (Smith, 2001).

4.5.2 fMRI activation tasks

Two tasks were used in the current study: a word generation task to assess language lateralization and a Landmark task to assess spatial lateralization. The word generation task is based on the Controlled Word Association Test (Lezak, 1995), which has been used routinely previously to establish language lateralization (Deppe *et al*., 2000; Flöel *et al*., 2001, 2002, 2005; Knecht *et al*., 1998a, 1998b, 2001, 2003; Pujol *et al*., 1999) and is particularly successful in eliciting fMRI activation in classical language areas of the left hemisphere including the inferior frontal gyrus and somewhat more variably, in superior temporal regions (Benson *et al*., 1999; Deppe *et al*., 2000; Flöel *et al*., 2001, 2002, 2005; Gaillard *et al*., 2000, 2002, 2003; Hertz-Pannier *et al*., 1997; Knecht *et al*., 1998a, 1998b, 2001, 2002, 2003; Pujol *et al*., 1999).

Cerebral dominance for visuospatial processing was assessed using the Landmark task (Flöel *et al*., 2001, 2005, Jansen *et al*., 2004), which is frequently used in the assessment of spatial neglect (Harvey *et al*., 1995) and has consistently been used to activate visuospatial associated cortex in normal healthy participant’s, including predominantly parietal cortex (Fink *et al*., 2001; Marshall *et al*., 1997). This task allows for robust brain perfusion-sensitive functional imaging (Fink *et al*., 2001; Flöel *et al*., 2001, 2005) and has shown high test-retest reliability (Flöel *et al.*, 2002) and cross-method validity (Jansen *et al.*, 2004).

The presentation of task stimuli for both tasks is performed using 'Presentation' software (https://nbs.neuro-bs.com).

Word Generation task

A fixation cross is first presented for 6 seconds followed by a single letter, which is presented for 15 seconds. Participants silently generate as many words as possible starting with the displayed letter. Ten different letters are used in balanced random order, and no letter is displayed more than once. Each letter is then followed by a control condition lasting 15 seconds. During the control condition a fixation cross is presented in the centre of the screen and participants silently repeat a pseudo word "bababa". This control condition is taken from Knecht *et al* (2003). Each epoch lasts 30 seconds (15 seconds of word generation and 15 seconds of "bababa" repetition).

Landmark Task

A cross is first presented for 6 seconds followed by a set of instructions which is presented for 6 seconds. In the task condition participants decide whether a small vertical line (referred to in the experiment as a 'mark') is bisecting a longer horizontal line at midline (i.e. "Is the mark in the centre of the line?"). In the control condition the horizontal line is presented and participants decide whether the mark is present or absent (i.e. "Is there a mark on the line?"). Participants are also told whether to respond using either their right or left hand, and conditions are balanced for hand response.

In both the task and control conditions the horizontal line is presented for 2 seconds. The horizontal line (17cm) is bisected by a vertical line (i.e. mark) either in the exact middle or deviating to the right or left of the middle by 1.5 or 3cm. A total of 24 horizontal lines are presented during each block, which therefore lasted 44 seconds. Following presentation of the horizontal line, subjects indicate their response via a button press (the forefinger was used to indicate yes and middle finger to indicate no, on either the left or the right hand). A fixation cross is presented for 15 seconds between each condition, on which subjects are asked to fixate. Each task and control condition is presented 8 times and the sequence of conditions is randomised.

4.5.3 fMRI data analysis performed

The Statistical Parametric Mapping software package (SPM5), available at: Welcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm was used for realignment, normalization, smoothing and statistical analysis of the fMRI scans to create statistical parametric maps of significant regional BOLD response changes (Friston *et al*., 1995a, 1995b).

The first two images of each experimental run, during which the MR signal reaches a steady state, were discarded. The image time series was realigned to the first image (of the remaining time series) to correct for head movement between scans. Sinc interpolation was used in the transformation. A mean functional image volume was constructed for each participant from the realigned images. The 3D anatomical data set was then coregistered to the mean functional image. The T_1-weighted image was then segmented using the VBM toolbox (VBM5) http://dbm.neuro.uni-jena.de/software. The GM segment was then normalized to the a priori GM template supplied by SPM5 created by the Montreal Neurological Institute (MNI). The resulting parameters were then applied to normalise the functional images and T_1-weighted image into MNI space (Friston *et al*., 1995a). The resulting pixel size in standard stereotaxic coordinates was 2 x 2 mm, with an interplane distance of 2mm. The normalized images were subsequently smoothed with an isotropic 6 FWHM Gaussian kernel to compensate for normal variations in brain size and individual gyral pattern.

4.5.4 Statistical analysis of fMRI data

Following stereotaxic normalisation and smoothing, statistical analysis was performed on individual data. The time series was filtered with a bandpass filter, this was a high-pass filter of 128 s to remove participant-specific low-frequency drifts in signal. Any slow signal drifts with a period longer than this are therefore removed. The experimental conditions (e.g. landmark task, control task) were modelled using a boxcar function convolved with a hemodynamic response function (HRF) (Friston *et al*., 1994) in the context of the general linear model employed by SPM5. Fitting the boxcar function to the time series at each voxel results in a parameter estimate image, which indicates how strongly the waveform fits the fMRI data at each voxel. By dividing the parameter estimate by its standard error, the parameter estimate image is converted to a t-statistic image (a t-statistic is given for each voxel). These t-statistics constitute a statistical parametric map (SPM) and can be interpreted by referring to the probabilistic behaviour of Gaussian random fields. For the description of differences between activation and control conditions in single-participant data, a height threshold of $P<0.001$, uncorrected for multiple comparisons was chosen for the first level analysis following the approach taken by others (e.g. Everts *et al*., 2010).

Individual contrast images were then imported into a 2nd level analysis to obtain group results for each of the tasks. Two full-factorial models were employed to see the overall pattern of activation for each of the tasks and the pattern of activation for each handedness group for both the landmark and word generation task. The statistical parametric maps were interpreted after applying a FWE ($P<0.05$). Regions of significant association were identified using the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/cms/software#PickAtlas) using Talairach coordinates of most significant voxel (x,y,z mm). Only clusters of at least 30 voxels are reported.

4.5.5 Calculation of the Laterality Index

Within fMRI, a laterality index is often calculated to establish extent of activation in the dominant hemisphere with reference to the subdominant hemisphere. Generally speaking, a laterality index (LI) can be seen as representing the extent to which a ROI in one hemisphere is involved in a particular task of interest compared to the corresponding homologue ROI. Thus, despite language production for instance, being predominantly left hemispheric localised primarily to IFG the corresponding right hemisphere homologue always shows some degree of activation and therefore a lateralization index is calculated. The choice of the methods may significantly influence the LI, and is always based on a mathematical distinction between right and left hemisphere dominance. Categorisation of a leftward LI for instance, does not exclude involvement of the right hemisphere. There does not appear to be a straight forward solution here. One approach is to measure the magnitude of the fMRI signal change within a ROI (Adcock *et al*., 2003; Cohen and DuBois, 1999). However, most authors have counted active voxels above an arbitrary statistical threshold (e.g. Binder *et al*., 1996; Deppe *et al*., 2000; Desmond *et al.*, 1995). To overcome the obvious disadvantage that this makes LI scores highly dependent on the choice of threshold, one refinement is to calculate the LIs for several different thresholds and then use a weighted average to define the resulting LI. This has been further refined by Wilke and colleagues (Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006), who combines the weighted average approach with a bootstrap procedure to improve the robustness of the LI calculation, and this is the approach used here.

IFG and parietal lobe laterality indices

The word generation task is used to assess language production which is localised primarily to the IFG, whereas the landmark task is used to assess spatial processing and is localised primarily to parietal cortex (Badzakova-Trajkov *et al*., 2010; Deppe *et al*., 2000; Knecht *et al*., 2003; Jansen *et al*., 2004). Each ROI was selected using standardised predefined regions within the Wake Forest University Pickatlas (see above) rather than participant activation. Further details of the approach used to define the regions using the Wake Forest Pickatlas software can be found in Maldjian *et al* (2003, 2004). Thus ROIs were selected based on predefined regions (based on anatomical definitions) normalised to MNI space based on the Talairach Daemon (Lancaster *et al*., 1997, 2000) in the Wake Forest University Pickatlas. The Talairach Daemon is a web-based application that returns anatomic and Brodmann area information based on Talairach coordinates (Talairach and Tournoux, 1988) and is a widely used application for determining Brodmann areas (Maldjian *et al*., 2003).

The approach used in this study allows future studies to more easily replicate the results allowing for better comparison of results. For each participant a LI was computed to describe the laterality of activation over regions of interest (ROIs) for the word generation task (IFG) and the landmark task (parietal lobe). Therefore the term language laterality when referring to the results obtained in this thesis can be taken to refer to the lateralization of activation in response to the word production task within IFG as defined by the Pickatlas. Similarly spatial laterality refers to the lateralization of activation in response to the landmark task within parietal cortex as defined by the Pickatlas. These masks were then applied to the contrast file when calculating the LI.

Hemispheric laterality

In order to investigate whether hemispheric asymmetries, as compared to regional asymmetries, may explain differences in performance, an additional analysis was carried out involving LIs for whole hemispheres (excluding brain stem and cerebellum) for both the word generation task and the landmark task. Hemispheric laterality for both the word generation task (language) and the landmark task (spatial) is computed using the hemisphere mask provided by Wake Forest University Pickatlas.

Calculation of laterality indices

LI was calculated using the SPM5 LI-toolbox (Wilke and Lidzba, 2007) for each ROI, disregarding 5 mm left and right of the interhemispheric fissure using the nonthresholded correlation maps as input. The bootstrapping technique used to calculate LI (Wilke and Schmithorst, 2006) applies the concept of threshold-dependent laterality curves (Deblaere *et al*., 2004). This allows about 10,000 indices to be calculated at different thresholds, yielding a robust mean, maximum and minimum index. The final LI was based on a weighted mean computed for each ROI during interactive thresholding (Wilke and Schmithorst, 2006). Positive values represent right-hemisphere lateralization and negative values left-hemisphere lateralization. In principle, LI can vary between -1 and +1, i.e. from clear-cut left- to right-hemispheric dominance, although extreme values are highly unlikely in practice. Furthermore this bootstrapping approach, which includes a minimum size criterion in the algorithm, excludes clear-cut values of LI = ±1. LI scores for language and spatial processing can be found in Table 7.3 separated by sex and handedness.

4.5.6. Language activation in left and right IFG

In order to explore whether sex and handedness have a significant effect on activation within either the left or right IFG contrast scores (i.e. extent of activation) was obtained for each participant in the left and right hemisphere IFG. The region IFG was defined using the Wake Forest University Pickatlas (see above: this is the same mask used to define the IFG for the language laterality). Contrast values were defined in left and right IFG using MarsBaR software (Brett *et al*., 2002; http://marsbar.sourceforge.net/) for SPM. The result is a measure of the extent of activation in the left IFG and the right IFG for each participant. For study see Chapter 7.

CHAPTER 5:

BROCA'S AREA, SEX, HANDEDNESS AND OTHER BEHAVIOURAL LATERALITIES

5.1 METHODS

Participants (Parts one and two) and Image Acquisition (<u>Part one</u>): Information on the sex and handedness of the participants are given in Section 4.1. Participants were assessed for hand preference using the EHI (Oldfield, 1971). Degree of handedness for left- and right-handers is given in Table 4.2, separated by sex. For a description of the EHI see Section 4.2.1. Details of the imaging parameters used to acquire the T_1-weighted MR images in this study are given in Section 4.3.

Parental handedness and behavioural assessment (<u>Part two only</u>): Participants reported their foot preference for kicking and eye preference using the questions outlined on the EHI (see Section 4.2.1). Participants were asked by the researcher to indicate whether their parent uses their left or right hand to write with. Two participants (2.4% of the total sample) did not report parental handedness. Parental handedness fell into four different categories: (a) two right-handed parents, (b) left-handed mother and right-handed father, (c) right-handed mother and left-handed father, and (d) two left-handed parents. Eye and foot preference fell into three different categories: (a) right (eye or foot) preference, (b) left (eye or foot) preference, and (c) no preference.

Sulcal assessment and stereological measurements (<u>Part one</u>): Details of the approach used to pre-process and demarcate the structural MR images into PO and PTR subfields and assess intrasulcal anatomy are given in full in Section 4.4.3 and 4.4.4 respectively. Details of the stereological approach used in this study to measure PO and PTR volume estimates are given in Section 4.4.3.

Statistical Analysis

<u>Part one</u>: Statistical analysis was performed using R software (version 2.10.1, The R Foundation for Statistical Computing, http://www.r-project.org/). Mixed-effects logistic regression analysis was applied to explore the association of handedness and sex with sulcal contours defining the PO and PTR in the left and right hemisphere. Two mixed-effects logistic regression models were obtained using inferior frontal sulcus (IFS) connection (i.e. continuous/discontinuous) as the outcome variable in the first model and presence of the diagonal sulcus (DS) (i.e. present/absent) as the outcome variable in the second model. A random effect component was added into each model to take into account when measurements of the right and left hemisphere were from the same participant (paired data). Predictor variables were selected for inclusion in the logistic regression models using a stepwise approach (inclusion criteria $P<0.05$, exclusion criteria $P>0.1$).

Two linear mixed-effects models were fitted using relative PO volume and relative PTR volume as the outcome variables. Relative volume was calculated for each hemisphere by dividing the corresponding raw volume of PO (or PTR) by the average hemisphere volume (that is 2 * raw volume/(left hemisphere volume + right hemisphere volume). The relative volume was used instead of the absolute values in order to control for differences in overall brain size between participants. This is especially important for males and females who demonstrate large differences in overall brain size. A stepwise approach was used to select predictor variables and comparisons were made between handedness and sex groups for each of the four structures of interest, i.e. left and right hemisphere PO and left and right hemisphere PTR, using the esticon function within R software. Explanatory variables were: handedness, sex, grey matter/white matter (GM/WM), hemisphere side. Interaction terms of interest were between sex, hemisphere side and handedness.

***Part two*:** Statistical analysis of the data for the second part of the study was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software. Chi-Square tests were performed using the cross-tabs function in SPSS to investigate the association between the handedness direction of participants, eye preference and foot preference for kicking. Handedness was the dependent variable and the predictor variables were eye and foot preference. The relationship between participants' handedness and parental handedness was tested for using a logistic regression model with handedness as the outcome variable and the predictor variables: mother handedness, father handedness and the interaction between these two variables.

5.2 RESULTS

Sulcal contours *(<u>Part one</u>)*

Results for the morphology of the sulcal contours for each hemisphere are provided in Table 5.1, separated by handedness. Results were not separated by sex since the figures were similar for males and females.

In right-handers, the IFS was discontinuous more often in the right than in the left hemisphere (62% versus 43%) while in left-handers the IFS was discontinuous more often in the left than the right hemisphere (65% versus 47.5%). Mixed-effects logistic regression analysis was applied to test for differences in the proportion of cases with a discontinuous IFS between right- and left-handers, while taking into account the correlation within individuals (i.e., the correlation between the outcomes of the right and left hemisphere for the same participant). Sex was non-significant and was subsequently excluded from the model. Predictor variables included in the final model were handedness, hemisphere side and their interaction (see Table 5.2, first part).

Table 5.2 shows the results of the mixed effects logistic analysis for the IFS. The analysis revealed that left-handers (reference group) have approximately half the odds of having a discontinuous IFS in the right hemisphere than in the left hemisphere. Although this result was not statistically significant (coefficient= -0.82, Odds ratio (OR)=exp(-0.82)=0.44; *P*=0.08) it was close to the boundary of significance. By contrast right-handers have approximately twice the odds of having a discontinuous IFS in the right hemisphere than in the left hemisphere (coefficient=1.71-0.82=0.89, OR=exp(0.89)=2.4, *P*=0.05). Note that the group of left-handers is the reference group (handedness=0) and that the results for right-handers (handedness=1) were derived using contrasts since they cannot be directly obtained from the table. The fact that the interaction term handedness*hemisphere side is significant and positive (coefficient=1.71, *P*=0.009) indicates that while in right-handers the most common hemisphere with a discontinuous IFS is the right, in left-handers it is the left. Figure 5.1 illustrates this finding by showing the percentage of left and right-handed subjects with a discontinuous IFS in the left and right hemisphere. Statistical analysis showed that sex was not associated with connection pattern of the IFS.

Table 5.1. Sulci variability in the left and right hemispheres for right-handers (n=42), left-handers (n=40) and the total sample (n=82). Figures are given in number of cases (percentages). Significant differences between the hemispheres for right- and left-handers are highlighted in grey.

			Left Hemisphere			**Right Hemisphere**		
			Right-handers	**Left-handers**	**Total**	**Right-handers**	**Left-handers**	**Total**
IFS	**Continuous**		24 (57)	14 (35)	38 (46)	16 (38)	21 (52.5)	37 (45)
	Discontinuous		18 (43)	26 (65)	44 (54)	26 (62)	19 (47.5)	45 (55)
	Connection pattern	**Long**	14 (33)	27.5 (11)	25 (30.5)	10 (24)	13 (32.5)	23 (28)
		Short	9 (21)	13 (32.5)	22 (27)	13 (31)	6 (15)	19 (23)
		Superficial	11 (26)	4 (10)	15 (18)	7 (17)	11 (27.5)	18 (22)
		None	8 (19)	12 (30)	20 (24)	12 (29)	10 (25)	22 (27)
IPCS	**No connection with SF**		36 (86)	34 (85)	70 (85)	35 (83)	28 (70)	63 (77)
	Connection with SF		6 (14)	6 (15)	12 (15)	7 (17)	12 (30)	19 (23)
HR	**Absent**		0 (0)	3 (7.5)	3 (3)	0 (0)	0 (0)	0 (0)
	AR/HR common origin		16 (38)	15 (37.5)	31 (38)	16 (38)	18 (45)	34 (41.5)
	AR/HR separate origin		26 (62)	22 (55)	48 (59)	26 (62)	22 (55)	48 (58.5)
DS	**Absent**		23 (55)	29 (72.5)	52 (63)	15 (36)	15 (37.5)	30 (37)
	Present		19 (45)	11 (27.5)	30 (37)	27 (64)	25 (62.5)	52 (63)
	Present	**IFS**	1 (2.4)	1 (2.5)	2 (2.4)	6 (14)	5 (12.5)	11 (13)
		IPCS	2 (4.8)	5 (12.5)	7 (8.5)	4 (9.5)	4 (10)	8 (10)
		AR	6 (14)	4 (10)	10 (12)	9 (21)	7 (17.5)	16 (20)
		No connection	10 (24)	1 (2.5)	11 (13)	8 (19)	9 (22.5)	17 (21)

In left-handers, the DS was present more often in the right than in the left hemisphere (64% versus 28%) while in right-handers the difference was not so pronounced (64% in the right hemisphere versus 45% in the left hemisphere). A mixed-effects logistic regression model was fitted to the data (see Table 5.2, second part). Following a stepwise approach the variables handedness and hemisphere side were included in the final model. Statistical analysis showed that the odds of having a DS are higher in the right hemisphere than in the left-hemisphere for both right- and left-handers. While in left-handers the difference is statistically significant (coefficient=1.5, OR=exp(1.5)=4.48; *P*=0.002), in right-handers the result did not reach the significance level (coefficient=1.5-0.7=0.8, OR=exp(0.8)=2.22; *P*=0.08). The interaction term (handedness*hemisphere side) was non-significant (coefficient= -0.7, *P*=0.3) and this is consistent with the fact that the difference in odds of having a DS in the left compared to the right hemisphere did not differ significantly between left- and right-handers (see Figure 5.1, right panel). Statistical analysis showed that sex was not associated with connection pattern of the DS.

Table 5.2. Results of the mixed-effects logistic regression analyses for the IFS and DS. The predictor variables: handedness, hemisphere side and the interaction term between these two variables were included in the first model following the selection stepwise approach. In the second model the variables handedness and hemisphere side were included, however the results are included here for the interaction. Significant results are highlighted in grey.

Predictor variables	**Coefficient**	**SE**	**95% CI**	**P-value**
IFS				
Handedness *(0: Left, 1: Right)*	-1.04	0.5	(-2.4, -0.04)	0.04
Hemisphere side *(0: Left, 1: Right)*	-0.82	0.5	(-1.8, 0.2)	0.08
Handedness*Hemisphere side	1.71	0.7	(0.3, 3.1)	0.009
DS				
Handedness (*0: Left, 1: Right*)	0.78	0.5	(-0.2, 1.8)	0.1
Hemisphere side *(0: Left, 1: Right)*	1.5	0.5	(0.5, 2.5)	0.002
Handedness*Hemisphere side	-0.7	0.7	(-2.0, 0.6)	0.3

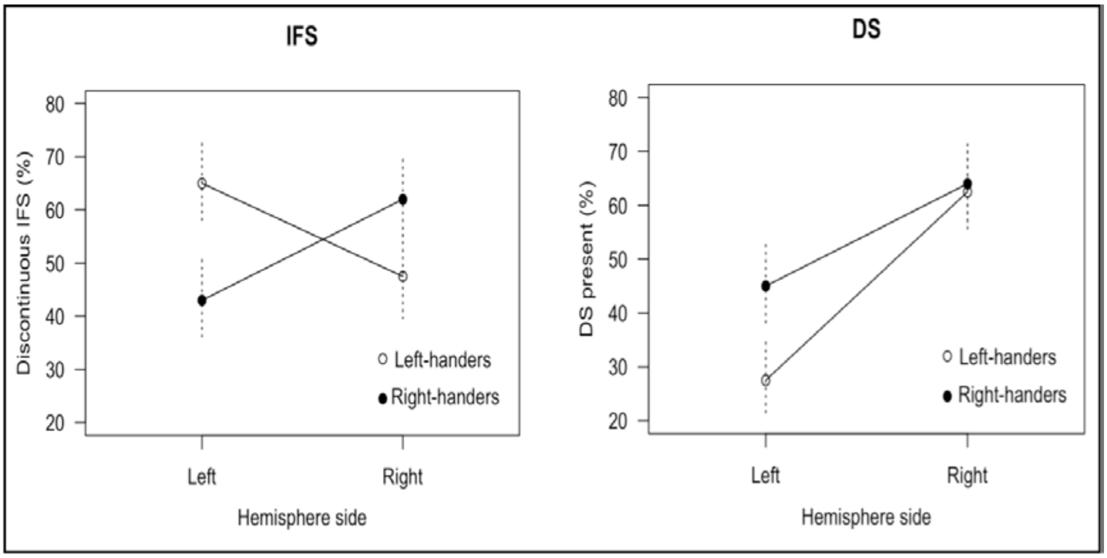


Figure 5.1. Percentage of cases with a discontinuous IFS and present DS in the left and right-hemisphere for left-handers (open circles) and right-handers (filled circles). The vertical broken line represents the percentage estimate ± standard error for each case. The standard error was here calculated as: $SE = \sqrt{p\,(1-p)}/\sqrt{n}$ where p represents the percentage of cases with either a discontinuous IFS or DS and n is the number of subjects in the sample.

The ventral IPCS of the right hemisphere was more likely to be connected with the Sylvian fissure in left-handers (30%) than in right-handers (17%). For the left hemisphere the percentages were very similar (15% in left-handers and 14% in right-handers). The AR and HR of the Sylvian fissure had a common trunk in 38% of left and right hemispheres for right-handers and slightly more often in the right (45%) than the left hemisphere (37.5%) for left-handers. None of the results for IPCS or HR/AR origin were statistically significant.

Stereological volume estimates *(Part one)*

Exclusion of cases for morphometry

Table 5.1 indicates the morphology of the sulcal contours defining the PO and PTR in the 82 brains. A double parallel IPCS was observed in 2 hemispheres. While absence of a single IPCS results in no posterior boundary for PO, when a double parallel IPCS was observed, the posterior boundary for PO was defined using the first IPCS posterior to the AR of the Sylvian fissure. The HR of the SF was absent in 3 hemispheres, resulting in no anterior boundary for PTR in 3 left-handers. These three brains were therefore removed from the volume analysis which was performed using the remaining 79 brains.

Volume of PO and PTR in right- and left-handers

Table 5.3 shows the descriptive statistics for raw and relative volume estimates for grey matter and white matter PO and PTR in the left and right hemispheres, separated by handedness and sex. Right-handed males had greater raw volume in all structures compared to right-handed females and left-handed males and females. In order to take into account the differences that exist in brain size among participants, relative volumes of PO and PTR (defined as the raw value divided by the average of the hemisphere volume) were considered for the statistical analysis.

Results for the two linear mixed models are presented in Table 5.4. For relative PO volume, the stepwise selection approach resulted in the inclusion of sex, handedness, grey/white matter, hemisphere side (i.e. left/right), and four interaction terms between sex, handedness and hemisphere side. Table 5.4 indicates that on average grey matter is significantly larger than white matter (2.7 cm^3 per 1000 cm^3 of hemisphere volume). The model does not include interaction terms involving the factor grey/white matter since the interaction terms were not significant, so volume comparisons between the two hemispheres for specific groups (e.g. female right-handers, male left-handers) apply equally to both grey and white matter.

Note that in the linear mixed-effects models male right-handers are the reference group. Right-handers tend to show larger PO relative volumes than left-handers (see Figure 5.2, upper left panel). For example, right-handed males (the reference group) show an average difference of approximately 3cm^3 of left PO volume per 1000 cm^3 of left hemisphere volume when compared to left-handed males: $P<0.001$, 95%CI: 1.6, 4.4 (see Tables 5.3 and 5.4). Results from the linear-mixed effects model show a right-greater-than-left (rightward) PO volume, for both grey and white matter, in left-handed males ($P<0.001$). Volume comparisons for the other groups (left-handed females and right-handers) can be derived based on contrast analyses from the fitted model (see coefficient estimates and their 95% confidence intervals in Table 5.4). In particular, results show that left-handed females also showed a rightward PO volume ($P<0.001$). In contrast, right-handed males show left-greater-than-right (leftward) PO volume (P=0.004). In right-handed females however, no significant difference was found between left and right PO volume (P=0.9).

Figure 5.2 (lower panels) show PO volume asymmetry for right-handed and left-handed males and females. Volume asymmetry is here defined as the difference in PO volume between the left and right hemisphere divided by the sum of the right and left PO volumes. While (on average) right-handed males show a leftward PO volume, right-handed females do not show PO volume asymmetry, and both male and female left-handers exhibit rightward PO volume. Further statistical analysis with volume asymmetry as the outcome variable confirms statistically significant differences in PO asymmetry between right- and left-handers for both males and females, although the comparison between males and females for each handedness group in volume asymmetry was not statistically significant (P>0.05).

A mixed effects linear regression model was also fitted for PTR relative volume. Although none of the interaction terms between sex, handedness and hemisphere side were significant, we have included them in the model to allow group comparisons in terms of handedness and sex. PTR grey matter is significantly larger than white matter (an average of 3.6 cm^3 per 1000 cm^3 of hemisphere volume, see Table 5.4). Similarly, as observed for PO relative volume, right-handers tend to show larger PTR volumes than left-handers (see Figure 5.2, upper right panel). For example, right-handed males, show a difference of 2.6cm^3 per 1000 cm^3 of left hemisphere volume larger than left-handed males: P<0.001, 95%CI: 1.1, 4.1) (see Table 5.4). Furthermore, right-handed males (P=0.01, coefficient= -1.0cm^3 per 1,000cm^3, 95%CI: -1.8,0.2) and females (P =0.002, coefficient= -1.0cm^3 per 1,000cm^3, 95%CI: -1.7, 0.4) show leftward PTR volume. Neither male (P=0.1) nor female (P=0.8) left-handers show differences in PTR volume between the right and left hemispheres (see Table 5.4 and Figure 5.2, lower right panel). Figure 5.2 (right lower panel) shows the differences in PTR asymmetry between left- and right-handed males and females.

Table 5.3. Raw volume estimates and relative volume estimates of grey and white matter PO and PTR (cm^3) for the left and right hemisphere, separated by sex and handedness (standard deviation is given in parenthesis). Relative volume estimates of PO and PTR are in cm^3 per 1000cm^3 of hemisphere volume.

		Raw volumes estimates (cm^3)						**Relative volume estimates (cm^3 per 1000cm^3 of hemisphere volume)**					
		Right-handers			**Left-handers**			**Right-handers**			**Left-handers**		
		Males	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Pars opercularis	***left hemisphere*** *grey matter*	5.7 (1.4)	4.6 (1.3)	5.0 (1.5)	3.6 (0.7)	3.9 (1.2)	3.7 (1.0)	10.0 (2.3)	9.7 (3.0)	9.8 (2.7)	6.6 (1.2)	7.7 (2.4)	7.3 (2.1)
	white matter	4.2(1.1)	3.3 (1.0)	3.6 (1.1)	2.5 (0.7)	2.6 (1.0)	2.6 (0.9)	7.4 (1.9)	7.0 (2.3)	7.1 (2.1)	4.7 (1.2)	5.1 (1.9)	5.0 (1.7)
	right hemisphere *grey matter*	5.2 (1.5)	4.6 (1.2)	4.8 (1.3)	4.8 (0.9)	4.4 (1.3)	4.6 (1.1)	9.0 (2.4)	9.7 (2.6)	9.4 (2.5)	8.7 (1.8)	8.9 (2.5)	8.8 (2.2)
	white matter	3.6 (1.5)	3.3 (0.9)	3.4 (1.1)	3.2 (0.6)	3.0 (0.9)	3.1 (0.8)	6.3 (2.4)	6.9 (2.0)	6.7 (2.1)	5.7 (1.2)	6.0 (1.7)	5.9 (1.5)
Pars triangularis	***left hemisphere*** *grey matter*	6.6 (1.3)	5.6 (2.0)	6.2 (1.8)	4.5 (1.6)	4.0 (1.2)	4.2 (1.4)	11.6 (2.4)	12.4 (3.6)	12.1 (3.2)	8.1 (3.0)	8.0 (2.2)	8.1 (2.5)
	white matter	4.0 (1.0)	3.6 (1.2)	3.8 (1.1)	3.0 (1.2)	2.7 (0.8)	2.8 (1.0)	7.0 (1.7)	7.6 (2.0)	7.4 (1.9)	5.4 (2.2)	5.4 (1.4)	5.4 (1.8)
	right hemisphere *grey matter*	5.8 (1.0)	5.3 (1.7)	5.5 (1.5)	3.9 (1.2)	4.1 (1.2)	4.0 (1.2)	10.2 (1.9)	11.1 (3.6)	10.7 (3.1)	7.3 (2.2)	8.2 (2.4)	7.8 (2.3)
	white matter	3.6 (0.8)	3.3 (1.0)	3.4 (0.9)	2.5 (0.9)	2.6 (0.9)	2.5 (0.9)	6.3 (1.4)	6.9 (2.1)	6.7 (1.8)	4.8 (2.1)	5.1 (1.7)	5.0 (1.8)

A Bonferroni correction is applied to take into account the number of hypotheses tested in each linear mixed-effects model, while maintaining an overall significance level of 0.05. A total of 4 hypotheses are tested for each model (see Table 5.4) resulting in the adjusted significance level of 0.0125 (=0.05/4). The significant *P*-values reported above therefore all remain significant even after applying the conservative Bonferroni correction.

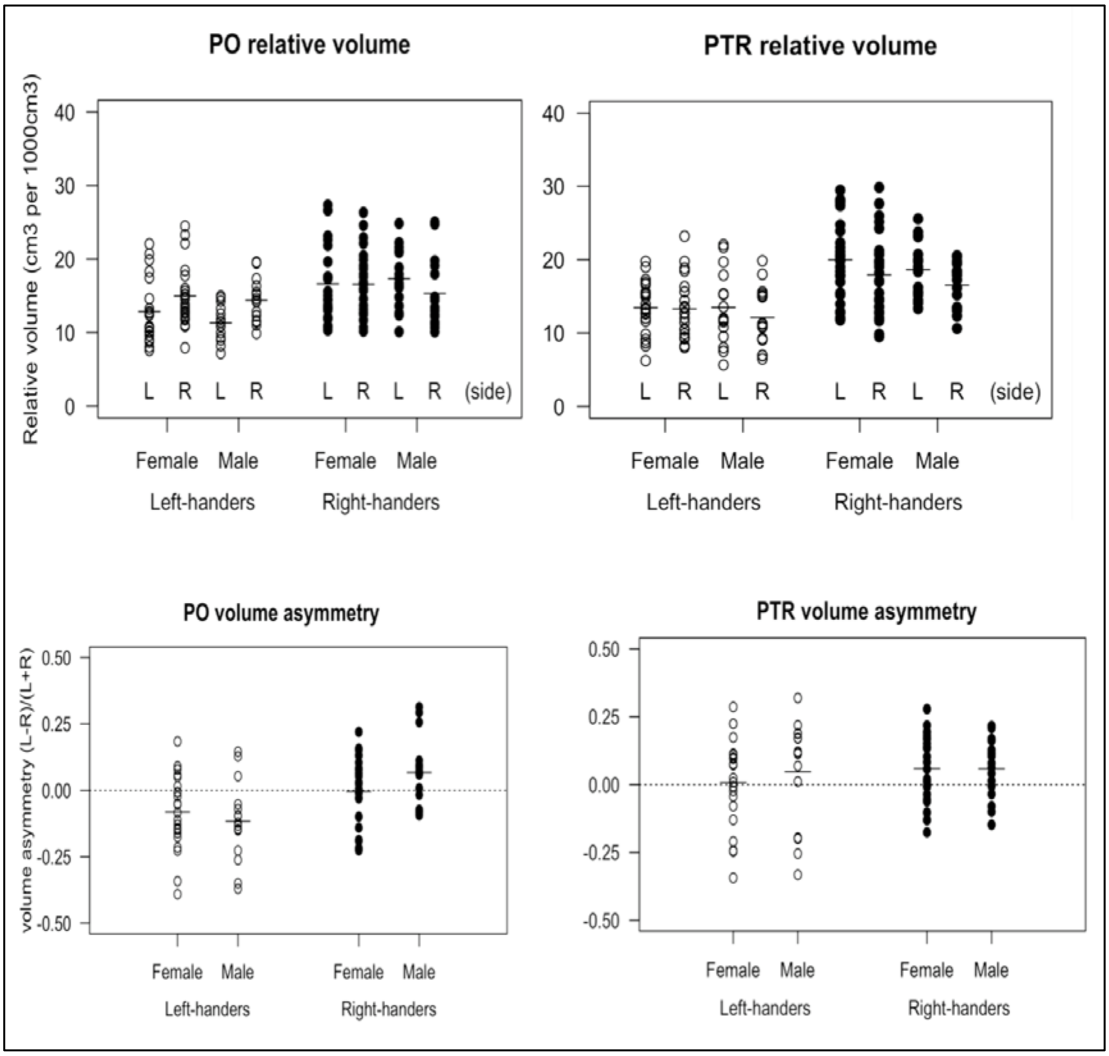


Figure 5.2. Upper panels: PO and PTR relative volume (in cm^3 per 1000 cm^3 hemisphere volume) of the right and left hemisphere for left- and right-handed males and females. Lower panels: PO and PTR volume asymmetry for left- and right-handed males and females. Note that volume estimates in this graphic are the sum of both grey and white matter.

Table 5.4. Results for the two linear mixed-effects models where PO and PTR relative volumes (in cm^3 per 1000 cm^3 of hemisphere volume) are the outcome variables. Comparisons between left and right hemisphere PO and PTR volumes, calculated using the esticon function in R software are also shown (significant results for comparisons are highlighted in grey). GM=grey matter, WM=white matter.

Predictor variables	Coefficient	St Error	95% CI (lower, upper)	P-value
Pars Opercularis Relative Volume				
Handedness *(0: Left, 1: Right)*	3.0	0.7	(1.6, 4.4)	<0.001
Sex *(0: Males, 1: Females)*	0.8	0.6	(-0.5, 2.0)	0.2
GM/WM *(0: GM, 1: WM)*	-2.7	0.2	(-3.0, -2.4)	<0.001
Hemisphere *(0: Left, 1: Right)*	1.5	0.4	(0.8, 2.2)	<0.001
Handedness*Hemisphere	-2.5	0.5	(-3.5, -1.6)	<0.001
Sex*Hemisphere	-0.5	0.5	(-1.3, 0.5)	0.3
Sex*Handedness	-1.1	0.9	(-2.9, 0.6)	0.2
Sex*Hemisphere*Handedness	1.5	0.6	(0.2, 2.7)	0.03
Comparisons right versus left hemisphere (right-left)				
Left-handed males	1.5	0.4	(0.8, 2.2)	<0.001
Left-handed females	1.1	0.3	(0.5, 1.7)	<0.001
Right-handed males	-1.0	0.3	(-1.7, -0.3)	0.004
Right-handed females	-0.1	0.3	(-0.6, 0.5)	0.9
Pars Triangularis Relative Volume				
Handedness *(0: Left, 1:Right)*	2.6	0.8	(1.1, 4.1)	0.001
Sex *(0: Male, 1: Female)*	-0.03	0.7	(-1.4, 1.4)	0.9
GM/WM *(0: GM, 1: WM)*	-3.6	0.2	(-4.0, -3.3)	<0.001
Hemisphere *(0: Left, 1: Right)*	-0.7	0.4	(-1.5, 0.1)	0.1
Handedness*Hemisphere	-0.4	0.6	(-1.5, 0.8)	0.5
Sex*Hemisphere	0.6	0.5	(-0.4, 1.7)	0.3
Sex*Handedness	0.7	1.0	(-1.2, 2.6)	0.5
Sex*Hemisphere*Handedness	-0.6	0.8	(-2.1, 0.9)	0.4
Comparisons right versus left hemisphere (right-left)				
Left-handed males	-0.7	0.4	(-1.5, 0.1)	0.1
Left-handed females	-0.07	0.3	(-0.8, 0.6)	0.8
Right-handed males	-1.0	0.4	(-1.8, 0.2)	0.01
Right-handed females	-1.0	0.3	(-1.7, -0.4)	0.001

Parental handedness and behavioural lateralities *(<u>Part two</u>)*

Table 5.5 shows eye and foot preference for right- and left-handed participants and their parent's writing hand preference. Numbers are given in percentages with the number of subjects bracketed. Results show that 85.7% of right-handers and 47.7% of left-handers had two right-handed parents. Substantially more left-handers had a left-handed father and right-handed mother than right-handers i.e. 34.2% vs. 4.8% respectively. Figure 5.3 shows the number of left- and right-handed participants with each parental handedness category i.e. mother/father = LH/RH, RH/LH, RH/RH or LH/LH. Results for the logistic regression model can be found in Table 5.6. Results showed a significant association between handedness and father's handedness (coefficient=2.6, OR=exp(2.6)=13.4, *P*=0.001), indicating that the odds of being left-handed are approximately 13 times greater when the father is left-handed than when the father is right-handed. The model showed no significant association between the mother's handedness and the participants' handedness (coefficient=1.12, OR=exp(1.12)=3.1, *P*=0.1). The interaction between mother and father handedness was tested for in the model, however this was found to be non-significant (*P*>0.05) and was subsequently removed from the model.

The percentage of right-handers with a left eye preference is lower than that of left-handers (21.4% vs. 37.5% respectively). Additionally a larger percentage of right-handers have a right eye preference (52.4%) than left-handers (40%). The graphs presented in Figure 5.3 display the number of left- and right-handed participants with each preference category (i.e. right, left or none) for eye and foot behaviours. Pearson's Chi-Square showed no significant association between handedness and eye preference ($\chi^2_{(2)}$=2.6, *P*=0.3). A right foot preference for kicking was found in right-handers much more often than in left-handers (78.6% vs. 50% respectively), whereas a left foot preference was found more often in left-handers compared to right-handers (40% vs. 7.1% respectively). Pearson's Chi-Square revealed a significant association between handedness and foot preference for kicking ($\chi^2_{(2)}$=12.442, *P*=0.002) indicating that the handedness of participants is significantly associated with their foot preference for kicking. Consistent hand, foot and eye preference was found in 32% of participants overall. Right hand, eye and foot preference was found in 40% of right-handers, while 22.5% of left-handers showed consistent left hand, foot and eye laterality. Additionally only 2.4% of right-handers (n=1) presented left foot and eye preference whereas 25% of left-handers presented right foot and eye preference.

Table 5.5. Foot and eye preference for right- and left-handers and their parents writing hand preference. Numbers are given in percentages. The total percentage and number for each variable category is also given. Data were collected from 42 right-handers and 40 left-handers however, parental handedness is missing from 2 left-handed participants thus for left-handers n=38 for parental handedness and n=40 for eye and kick preference.

Variable	**Variable category**	**Right-handers**	**Left-handers**	**Total for variable category**
Parental handedness	Both right-handed	85.7% (36)	47.4% (18)	67.5% (54)
	Mother left, Father right	9.5% (4)	15.8% (6)	12.5% (10)
	Mother right, Father left	4.8% (2)	34.2% (13)	18.8% (15)
	Both left-handed	0 % (0)	2.6% (1)	1.3% (1)
Eye preference	Right eye preference	52.4% (22)	40 % (16)	46.3% (38)
	Left eye preference	21.4% (9)	37.5% (15)	29.3% (24)
	Either eye	26.2% (11)	22.5% (9)	24.4% (20)
Kick preference	Right foot preference	78.6% (33)	50 % (20)	64.6% (53)
	Left foot preference	7.1% (3)	40 % (16)	23.2% (19)
	Either foot	14.3% (6)	10 % (4)	12.2% (10)

Table 5.6. Results of the logistic regression model fitted for participant's handedness. The predictor variables are mother and father writing and preference. The significant result is highlighted in grey.

Predictor variables	**Coefficient**	**SE**	**95% CI**	**P-value**
Outcome variable: **Participant handedness** (*0: right, 1: left*)				
Mother hand *(0: right, 1: left)*	1.12	0.7	0.78, 12.13	0.12
Father hand *(0: right, 1: left)*	2.6	0.8	2.75, 65.34	0.001

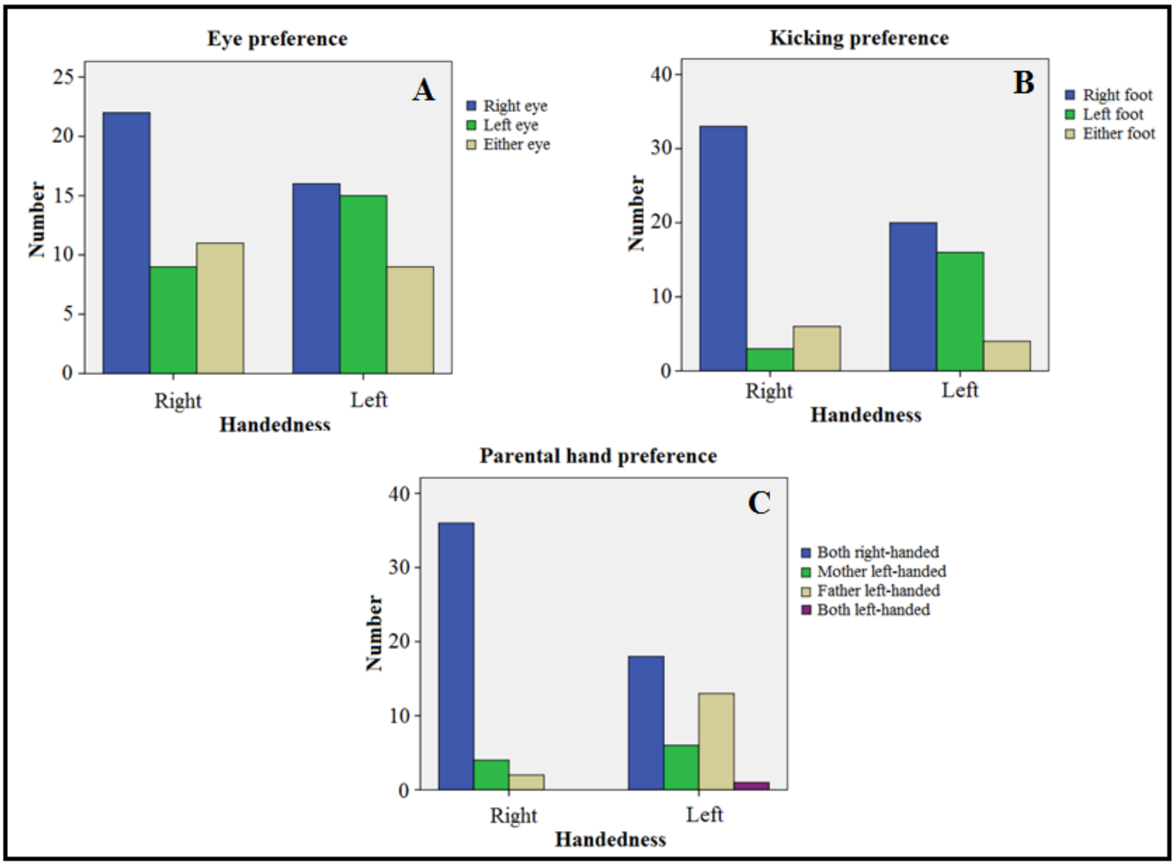


Figure 5.3. Number of right- and left-handers presenting each category of (A) eye preference, (B) kick preference and (B) parental handedness.

5.3 PRELIMINARY DISCUSSION

Part one: The present study makes two additional novel findings to the handedness and Broca's area literature: firstly, by showing an association between handedness and hemisphere side and connection pattern of the IFS and the presence of the DS; and secondly by showing an effect of handedness and sex in PO asymmetry and an effect of handedness on PTR asymmetry. Additionally, only the left PO was found to contribute to the observed asymmetry differences between the handedness groups, suggesting that the left PO is more heterogeneous whilst the right PO is a less variable structure.

Quantification of asymmetry of the anterior speech regions is complicated by the large inter-individual differences in sulco-gyral contours defining these regions within and between handedness groups. The study suggests that both handedness and sex should be taken into account when considering both the degree and direction of asymmetries of the posterior IFG and that there is a need to consider the interaction between sex and handedness when exploring asymmetries in language associated cortex.

Part two: Results from the second part of this study indicate a relationship between parental and offspring handedness, with the handedness of the father being significantly associated with offspring left-handedness. The results also indicate a significant association between handedness and foot preference for kicking. Right-handers show a right foot preference more often than left-handers whereas left-handers reported a left foot preference more often than right-handers. Consistent eye preference was not however significantly associated with participant handedness. Overall the results indicate that right-handers present consistent lateralities more often than left-handers, which may reflect a greater degree of cerebral dominance in right-handers than left-handers.

CHAPTER 6:

HANDEDNESS AND WHITE MATTER ANISOTROPY

6.1 METHODS

Participants and image acquisition: Information on these participants can be found in Section 4.1. Descriptive statistics for the participants are given in Table 4.2. Details of the imaging parameters used to acquire the diffusion-weighted MR images used in this study are given in Section 4.3.

Image Analysis: Details of approach used to analyse the diffusion data including the pre-processing steps and the voxel-wise statistical analysis performed on the FA images are given in Section 4.4.6.

Statistical Analysis: Full details of the voxel-wise statistical analysis performed on the two sets of FA images are given in Section 4.4.6.

6.2 RESULTS

The effect of handedness on white matter anisotropy

Testing for greater anisotropy in right-handers than left-handers (Table 6.1A) revealed large regions residing in the WM of the limbic region, prefrontal lobe, medial frontal lobe and inferior frontal gyrus (IFG) in the left hemispheres, and orbital lobe, medial frontal lobe, and inferior frontal lobe in the right hemisphere (Figure 6.1). On testing for greater anisotropy in left-handers than right-handers no voxels survived correction for multiple comparisons using the FDR. Additionally when sex and age were tested for no voxels survived correction for multiple comparisons using the FDR $P<0.05$.

The effect of handedness on anisotropy asymmetry

Anisotropy asymmetry was assessed for left- and right-handed groups. Leftward anisotropy is defined as those voxels were anisotropy is greater in the left hemisphere than corresponding voxels in the right hemisphere whereas the opposite is true for rightward anisotropy: here voxels show greater anisotropy in the right hemisphere than the left. Leftward anisotropy is shown in Figures 6.2 and 6.3 and Table 6.2 and rightward anisotropy is shown in Figure 6.4, and in Table 6.2. The number and percentage of leftward and rightward anisotropy voxels is given in Table 6.3.

Table 6.1. Anisotropy differences between right-handers and left-handers in the (A) left hemisphere and (B) right hemisphere. Results are for greater anisotropy in right-handers than left-handers. Talairach coordinates of the most significant voxel (x,y,z mm) are given. UF=uncinate fasciculus, SLF=superior longitudinal fasciculus, PO=pars opercularis, IFG=inferior frontal gyrus.

Description of cluster	**Cluster volume (mm^3)**	**T-score**	**z-score**	**x,y,z**	***P*-value (FDR)**
A. Left hemisphere					
Limbic region (UF)	3112	5.49	5.03	-28 -4 -26	0.006
Prefrontal lobe	665	4.88	4.54	-14 44 2	0.008
Medial frontal gyrus/ Anterior cingulate	597	4.45	4.18	-14 40 16	0.013
IFG/PO	215	4.43	4.17	-34 30 -12	0.013
Parietal lobe (SLF)	174	3.86	3.68	-20 -52 56	0.019
Superior parietal lobule/Precuneus	91	3.02	2.82	-6 -64 48	0.017
B. Right hemisphere					
Orbital lobe (superior occipito-frontal fascicle)	2909	4.35	4.10	24 20 10	0.014
Medial frontal gyrus/ Anterior cingulate	616	4.08	3.87	12 46 10	0.017
IFG/PO	223	4.03	3.83	34 4 40	0.017
Frontal lobe (cortico-spinal tract)	116	3.51	3.83	36 -6 36	0.017
Frontal lobe (SLF)	292	3.51	3.37	22 -42 38	0.023

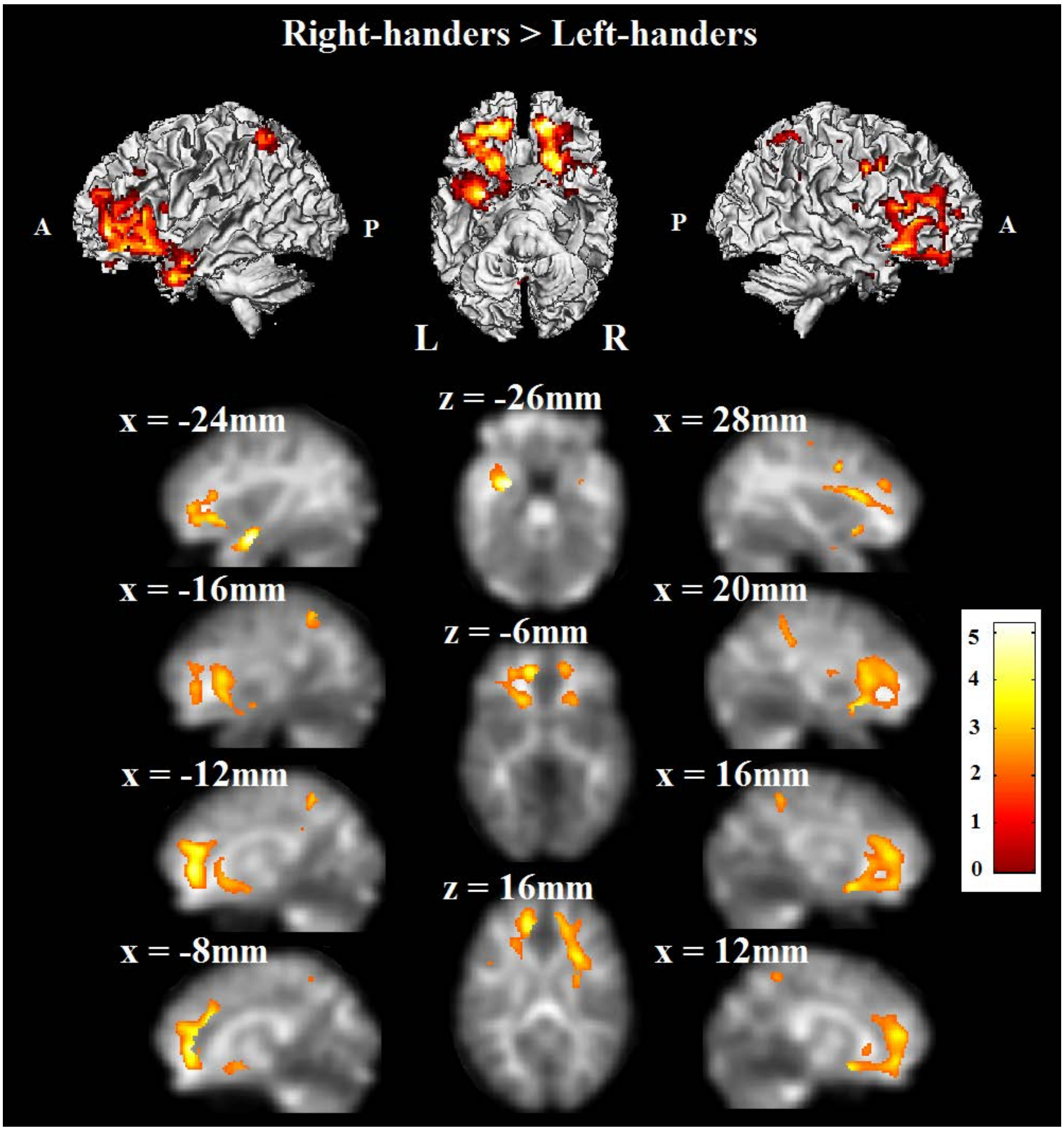


Figure 6.1. Greater anisotropy in right- than left-handers is shown. In the top row of images results are displayed on the WM surface of a single participant from the study on lateral and inferior views. The surface was extracted using the VBM toolbox (http://dbm.neuro.uni-jena.de/software/) in SPM5 from a T_1-weighted structural image. Beneath this, results of the anisotropy differences between groups are displayed on sections of a smoothed normalised anisotropy image from the same subject at selected Talairach coordinates where differences between the groups were at their maximum. Colour intensity in the figure and side bar corresponds to T-scores. L=left hemisphere, R=right hemisphere, A=anterior, P=posterior.

Both groups presented leftward FA in regions of the inferior frontal gyrus (IFG), uncinate fasciculus (UF), and AF within the superior temporal gyrus and rightward anisotropy in the middle temporal cortex, posterior cingulum and the genu of the corpus callosum. Direct comparisons between the handedness groups for leftward anisotropy and rightward anisotropy revealed no significant voxels when using a cluster size cut-off of 50 voxels. Overall the results demonstrate similar asymmetries in both handedness groups in the left hemisphere (see Figures 6.2 and 6.3) and the right hemisphere (see Figure 6.4 and Table 6.2). However Table 6.3 indicates that right-handers present more leftward anisotropy voxels than left-handers i.e. 6,866 vs. 5,251 respectively, although both handedness groups report the same proportion of leftward asymmetric voxels i.e. 95%. Table 6.2 shows that while left- and right-handers show leftward and rightward anisotropy in similar WM regions, the T-scores are higher in right-handers. The effect of sex on anisotropy asymmetry was tested for in each handedness group however no voxels survived correction for multiple comparisons (FDR, $P<0.05$). The covariate age was tested for in the model, results yielded no cluster size greater than 50 voxels.

Leftward FA asymmetry was observed throughout medial and lateral regions (Figure 6.2) including the prefrontal, frontal and temporal lobes (Table 6.2). A notable leftward C-shaped structure can be seen extending from frontal to parietal cortex and from parietal to superior temporal cortex in both handedness groups. This structure represents the AF, and can be seen in its full extent in Figure 6.3 (right column, indicated by black arrows at x = -36 mm). The AF is a language-associated WM tract originating in the posterior inferior frontal cortex, particularly the IFG extending posteriorly to the inferior parietal lobe where it arches around the lateral fissure to terminate in the posterior part of the superior and middle temporal gyrus (Catani *et al.*, 2005). Asymmetry of the AF extends the length of the superior temporal gyrus to temporal pole and limbic lobe from medial to lateral regions (x = -30 to -50 mm, Figure 6.2). However, the significant voxels in the clusters representing the dorsal portion of the AF which extends from frontal to parietal cortex is slightly more fragmented in left-handers (see Figure 6.3).

Table 6.2. Left-greater-than-right (leftward) anisotropy and right-greater-than-left (rightward) anisotropy in right- and left- handers. Talairach coordinates of most significant voxel (x,y,z mm) are given. AF=arcuate fasciculus, SLF=superior longitudinal fasciculus, UF=uncinate fasciculus, IFG=inferior frontal gyrus, PO=pars opercularis, PTR=pars triangularis.

Description of cluster	**Cluster size (mm^3)**	**T-score**	**z-score**	**x,y,z**	***P*-value (FWE)**
A. Right-handers: *Leftward anisotropy*					
Superior temporal gyrus (AF)	2033	13.62	Inf	-42 -30 8	<0.001
Temporal pole/UF	644	11.53	Inf	-32 4 -32	<0.001
Parietal lobe/SLF	421	10.61	Inf	-22 -38 26	<0.001
IFG/PO	2530	9.91	7.89	-46 32 -8	<0.001
Pars orbitalis/PTR	488	9.40	7.65	-38 36 -2	<0.001
Prefrontal lobe	474	9.27	7.50	-20 50 18	<0.001
IFG	235	7.61	6.54	-46 -2 24	<0.001
IFG/PO	61	5.41	4.89	-56 6 4	<0.001
B. Right-handers: *Rightward anisotropy*					
Medial temporal gyrus	148	8.65	7.31	42 -34 -4	<0.001
Posterior cingulum	139	7.84	6.71	12 -54 18	<0.001
Corpus callosum (genu)	69	7.35	6.35	4 24 8	<0.001
C. Left-handers: *Leftward anisotropy*					
Superior temporal gyrus (AF)	1346	11.90	Inf	-42 -30 8	<0.001
Parietal lobe/SLF	268	8.74	7.30	-24 -36 26	<0.001
IFG/PO	2309	9.47	7.68	-46 32 -8	<0.001
Cingulum	194	8.09	6.80	-8 14 -4	<0.001
Pars orbitalis/PTR	76	8.00	6.78	-38 38 -4	<0.001
Cerebellum posterior lobe	312	8.40	7.01	-30 -64 -36	<0.001
Cerebellum anterior lobe	229	6.32	5.69	-20 -58 -30	<0.001
Limbic region/UF	368	7.87	6.73	-28 0 -16	<0.001
Temporal pole/UF	77	7.71	6.62	-34 4 -32	<0.001
Corticospinal tract	72	6.39	5.70	-24 -8 16	<0.001
D. Left-handers: *Rightward anisotropy*					
Corpus callosum (genu)	65	7.89	6.74	4 22 12	<0.001
Medial temporal gyrus	98	7.19	6.32	40 -36 -2	<0.001
Medial temporal lobe	56	5.54	4.92	44 -24 -12	<0.001
Posterior cingulum	63	6.31	5.67	12 -54 18	<0.001

Leftward FA asymmetry was observed in the UF in both handedness groups (Figure 6.3; left column: indicated by black arrows), which can be seen in its full extent at x = -28 mm. The UF is a structure extending from the limbic lobe within the temporal pole curving upward behind the external capsule projecting inward from the insular cortex in a hook shape, terminating in the orbital frontal cortex (Kier *et al*., 2004; Rodrigo *et al*., 2007). Right-handers presented leftward FA asymmetry along the full length of the UF including subinsular, anterior and posterior extrainsular portions of the UF. In left-handers all segments were present; however, the anterior extrainsular segment did not extend as far into orbital cortex compared to that of right-handers. Leftward FA asymmetry was also observed in the pars opercularis (BA44) and pars triangularis (BA45) and along the subinsular segment and posterior extrainsular portion of the UF (x = -28 mm, Figure 6.2) in both handedness groups.

Significant rightward FA asymmetry in both right- and left-handers is presented in Figure 6.4 and Table 6.2. Both handedness groups demonstrated significant rightward FA asymmetry in WM within posterior middle temporal gyrus, posterior cingulum and the genu of the corpus callosum (Table 6.2).

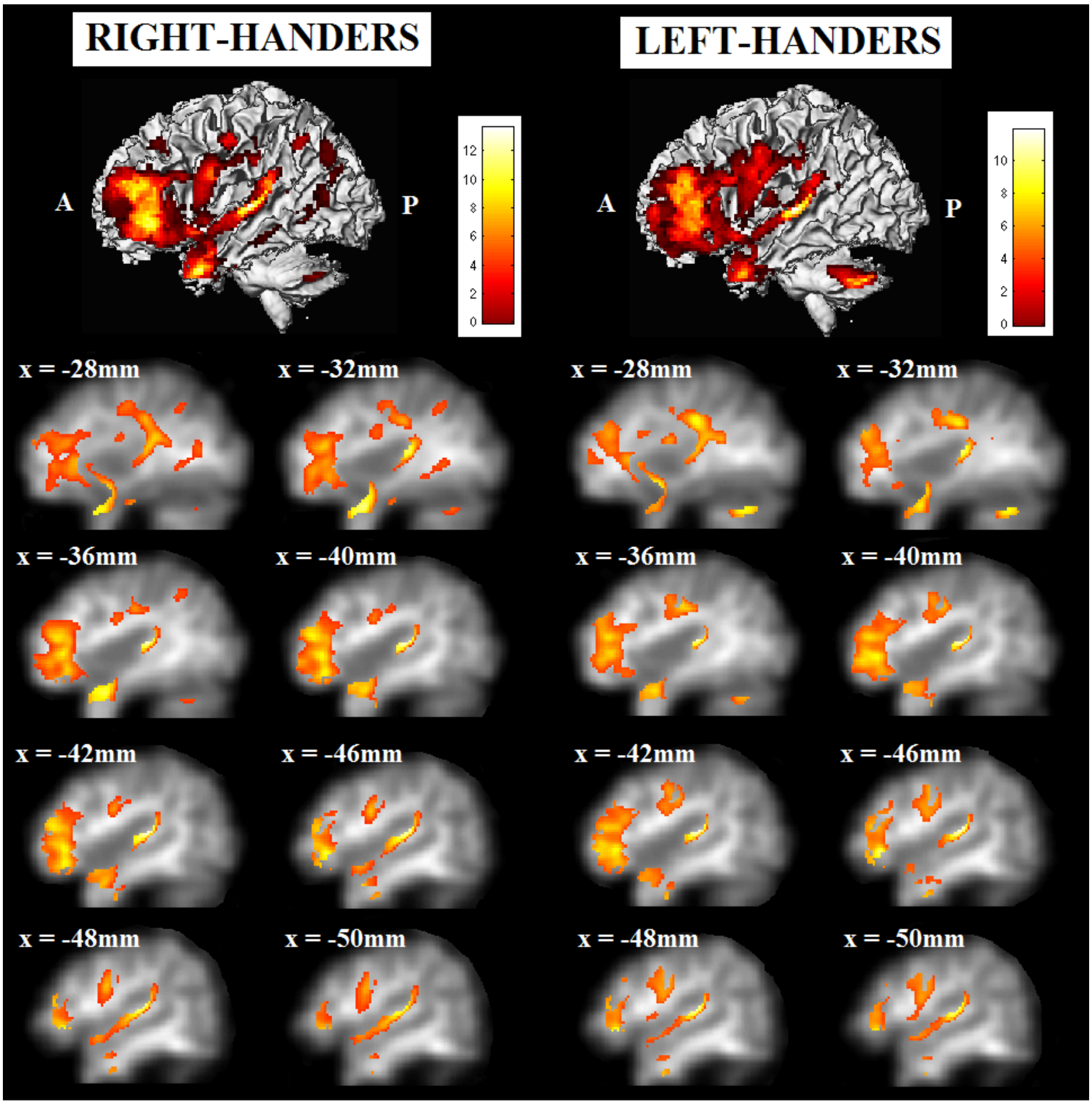


Figure 6.2. Left-greater-than-right (leftward) anisotropy asymmetry results in left- and right-handers rendered on the surface of a WM segment in lateral view. The WM segment was obtained from a T_1-weighted MR image of one participant and was segmented using the VBM toolbox within SPM5. Results are also displayed on sections of a smoothed normalised anisotropy image from the same subject at selected Talairach coordinates. Colour intensity in the figure and side bar corresponds to T-scores. A=anterior, P=posterior.

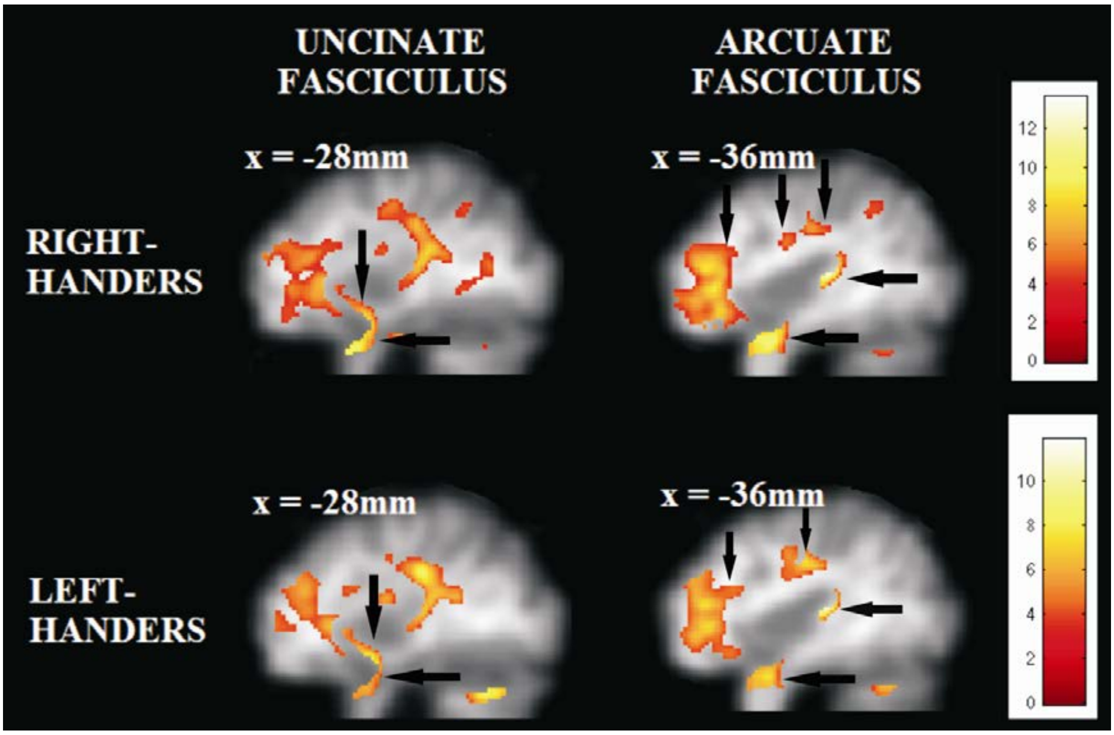


Figure 6.3. Results demonstrate leftward FA asymmetry of the UF at x = -28 mm (first column, indicated by black arrows) and leftward anisotropy of the AF at x = -36 mm (second column, indicated by black arrows) for both right-handers and left-handers. Results are presented on a smoothed normalised FA map of one participant. Colour intensity in the figure and side bar corresponds to T-scores.

Table 6.3. Number of clusters, number of voxels and proportion of voxels for leftward and rightward FA asymmetry for right- (A) and left- (B) handed groups.

	Leftward FA	**Rightward FA**	**Total**
A. Right-handers			
Number of clusters	8	3	11
Number of voxels	6886	356	7242
% of total voxels	95	5	100
B. Left-handers			
Number of clusters	10	4	14
Number of voxels	5251	282	5533
% of total voxels	95	5	100

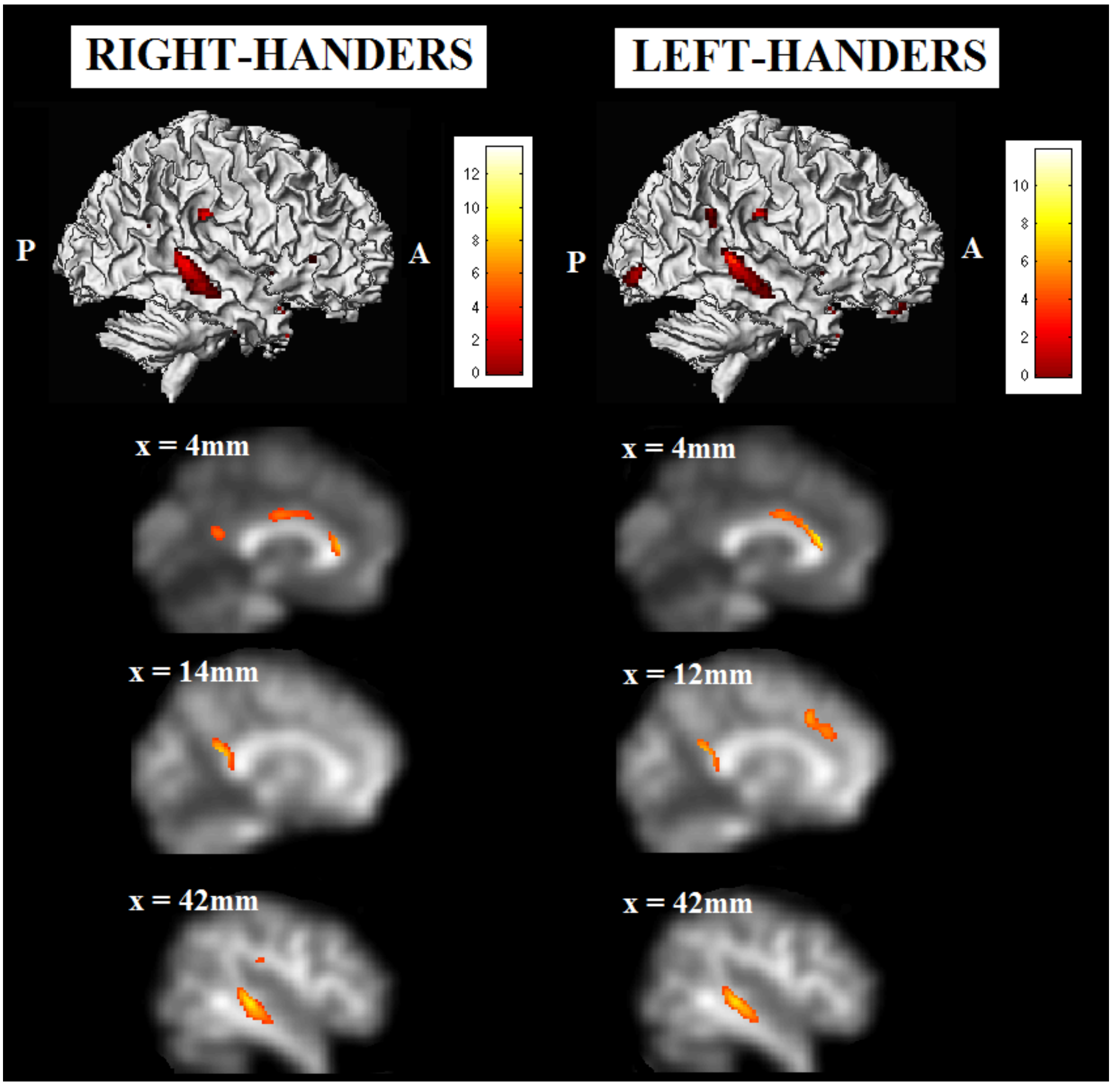


Figure 6.4. Right-greater-than-left (rightward) anisotropy asymmetry results in left- and right-handers rendered on the surface of a WM segment in lateral view. The WM segment was obtained from a T_1-weighted MR image of one participant which was segmented using the VBM toolbox within SPM5. Results are also displayed on sections of a smoothed normalised anisotropy image from the same subject at selected Talairach coordinates. Colour intensity in the figure and side bar corresponds to T-scores. A=anterior, P=posterior.

6.3 PRELIMINARY DISCUSSION

The findings indicate significantly greater diffusion anisotropy in the frontal lobe (particularly prefrontal lobe), and middle temporal gyrus in right-handers compared with left-handers. Leftward FA asymmetry of the AF and UF was found in both left- and right-handers. Both groups presented leftward FA in regions of the IFG, UF, and AF within the superior temporal gyrus and rightward FA in middle temporal cortex, posterior cingulum and the genu of the corpus callosum. The leftward FA asymmetry of the superior temporal gyrus and rightward asymmetry of the medial temporal gyrus observed in both left- and right-handers may support the AF terminations proposed by Glasser and Rilling (2008).

The present study is based on young adults and findings may be influenced by differences in the developmental trajectory of WM pathways in right- and left-handers. Although both groups show FA asymmetry in similar WM regions more leftward FA voxels are observed in right-handers than left-handers, and FA asymmetry was stronger (although not statistically significant) in right-handers as shown by the higher T-scores. Overall however, there is no clear evidence to suggest any significant difference between the handedness groups for WM anisotropy asymmetry. The only significant effect for handedness is on the underlying WM anisotropy, with right-handers showing greater FA than left-handers, particularly in frontal areas of the brain.

CHAPTER 7:

HANDEDNESS, LANGUAGE LATERALITY, SPATIAL LATERALITY AND EXECUTIVE FUNCTIONS

7.1 METHODS

Participants and image acquisition: Information on the participants used in this study including descriptive statistics is given in Section 4.1. Details of the imaging parameters used to acquire the functional MR images and the T_1-weighted MR images used in this study are given in Section 4.3.

fMRI activation tasks: Two fMRI tasks were used in the current study: a verbal fluency task called the word generation task to assess language laterality and a landmark task to assess spatial lateralization. The word generation task is used to assess language production and is the task most commonly used in the literature to establish language laterality. The landmark task has additionally been used in a number of studies to elicit spatial activation, particularly in regions of the parietal lobe (see Section 4.5.2 for further details on the fMRI tasks).

Neuropsychological protocol: Seven sub-tests from the Wechsler Adult Intelligence Scale (WAIS-III) were used to calculate three index scores: verbal comprehension; working memory; and perceptual organisation. Verbal reasoning, including semantic knowledge was assessed using the sub-tests vocabulary and comprehension. Working memory is a measure of auditory short-term memory and was measured using the sub-tests digit-span and letter-number sequencing. Perceptual organisation is a measure of visual reasoning skills and includes the sub-tests: picture completion; block design; and matrix reasoning. Details of the WAIS-III sub-tests used to assess verbal comprehension, working memory and perceptual organisation including the scoring of the WAIS-III are given in Section 4.2.2. Raw scores were converted into percentages for the purposes of interpretation.

MRI data analysis: The Statistical Parametric Mapping software package (SPM5; available from the Welcome Department of Cognitive Neurology, London, UK at http://www.fil.ion.ucl.ac.uk/spm) was used for realignment, normalization, smoothing and statistical analysis to create statistical parametric maps of significant regional BOLD response changes (Friston *et al*., 1995a, 1995b). Principles of the fMRI data analysis are given in Section 4.5.1. Details of the fMRI data analysis performed for this study are given in Section 4.5.3.

Statistical analysis of fMRI data: Following stereotaxic normalisation and smoothing, statistical analysis was performed on individual data. A full description of the statistical analyses performed on the smoothed fMRI images are given in detail in Section 4.5.4. Briefly, the time series was filtered with a high-pass filter of 128 s to remove subject-specific low-frequency drifts in signal. The experimental conditions (e.g. landmark task, control task) were modelled using a boxcar function convolved with a hemodynamic response function (HRF) (Friston *et al*., 1994) in the context of the general linear model employed by SPM5. For the description of differences between activation and control conditions in single-subject data, a height threshold of $P<0.001$, uncorrected for multiple comparisons, was chosen. Testing uncorrected for multiple comparisons was chosen for the first level analysis following the approach taken by others (e.g. Everts *et al*., 2010). Individual contrast images were then imported into a second level analysis to obtain group results for each task. Two full-factorial models were employed to establish the overall pattern of activation for each task, and the pattern of activation for each handedness group. The statistical parametric maps were interpreted across subjects and for each handedness groups after applying a family-wise error (FWE) correction with $P<0.05$: t-tests were used. The effect of sex and age on language and spatial processing were tested for using t-tests (FDR, $P<0.05$). The effect of handedness on language processing and spatial processing was tested for using an F-test (FDR, $P<0.05$).

Laterality Index and activation: A laterality index (LI) was computed for each participant to describe the laterality of activation over ROIs for the word generation task (IFG) and the landmark task (parietal lobe) based on findings from prior research (Badzakova-Trajkov *et al*., 2010; Deppe *et al*., 2000; Knecht *et al*., 2003; Jansen *et al*., 2004). The LI was calculated using the SPM5 LI-toolbox (Wilke & Lidzba, 2007) for each ROI. Details of the method used to calculate the LIs for both tasks are given in

Section 4.5.5. Negative values are associated with greater leftward lateralization of activation and positive values are associated with greater rightward laterality. Neuronal activation in response to the word generation task in left and right IFG were computed for each participant. For the method used to calculate activation see Section 4.5.6.

Statistical analysis of laterality indices: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software. Two multivariate models were performed to explore the association between the predictor variables: handedness, sex and age and the outcome variables: language laterality (IFG), spatial laterality (parietal lobe) in the first model and the outcome variables left and right IFG activation in response to the word generation task in the second model. Two-tailed *P*-values are reported throughout. Pearson's product correlation coefficients were performed to explore the relationship between language laterality and spatial laterality in left- and right-handers separately. An alpha level of $P<0.05$ was used to identify statistical significance.

Statistical analysis of cognitive ability data: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software. A multivariate analysis was performed to investigate the association between neuropsychological performance (defined as a three-dimensional vector composed by working memory, verbal reasoning and perceptual organisation scores) and the explanatory variables: handedness, language laterality and spatial laterality and an interaction term between language and spatial laterality to take into account the association between these two variables on cognitive ability scores. The covariates age and sex were also considered in the model as possible explanatory variables. The multivariate statistical approach was chosen to account for the co-dependence among the three outcome variables, and the factor handedness was regarded as a binary variable (i.e., which takes into account handedness direction and not magnitude) to facilitate the interpretation. Two-tailed *P*-values are reported throughout.

7.2 RESULTS

Language and spatial activation in left- and right-handers

Group-level activations for the landmark and word generation tasks are shown in Figure 7.1. Anatomical regions showing significant activation during each of these tasks are presented in Table 7.1 for the word generation task and Table 7.2 for the landmark task. The co-ordinates in both tables indicate the most significant voxel within the activated cluster. Briefly, for both right- and left-handers the word generation task yielded greatest activation in the left hemisphere, with significant activations in the superior frontal gyrus, PO, PTR, inferior occipital gyrus and cerebellum. T-scores show this activation to be stronger in right-handers than left-handers. Activations can also be seen in the inferior and superior parietal lobe and parahippocampal gyrus in right-handers and in cingulate gyrus and middle frontal gyrus in left-handers. Right hemisphere activation was greater in left-handers than right-handers (see Figure 7.1). Direct comparisons across the whole brain however revealed no significant differences in activation for the word generation task between left- and right-handers for either the right hemisphere or the left hemisphere following correction for multiple comparisons (FDR, $P<0.05$).

For the landmark task, greater activation was seen overall in the right-hemisphere for both left- and right-handers (Figure 7.1). Significant activations (Table 7.2) were found in the lingual gyrus, middle frontal gyrus, insula cortex, and inferior parietal lobule in the left hemisphere in both left and right-handers. In the right hemisphere significant activations were found in the inferior and medial frontal gyrus, precuneus and inferior parietal lobule. The regional activation overlap in response to the word generation task and landmark task for left- and right-handers, as can be seen at the bottom of Figure 7.1 (regional overlap). Direct comparisons across the whole brain did not show significant differences in activation for the landmark task ($P>0.05$) between left- and right-handers for either the right hemisphere or the left hemisphere following correction for multiple comparisons (FDR).

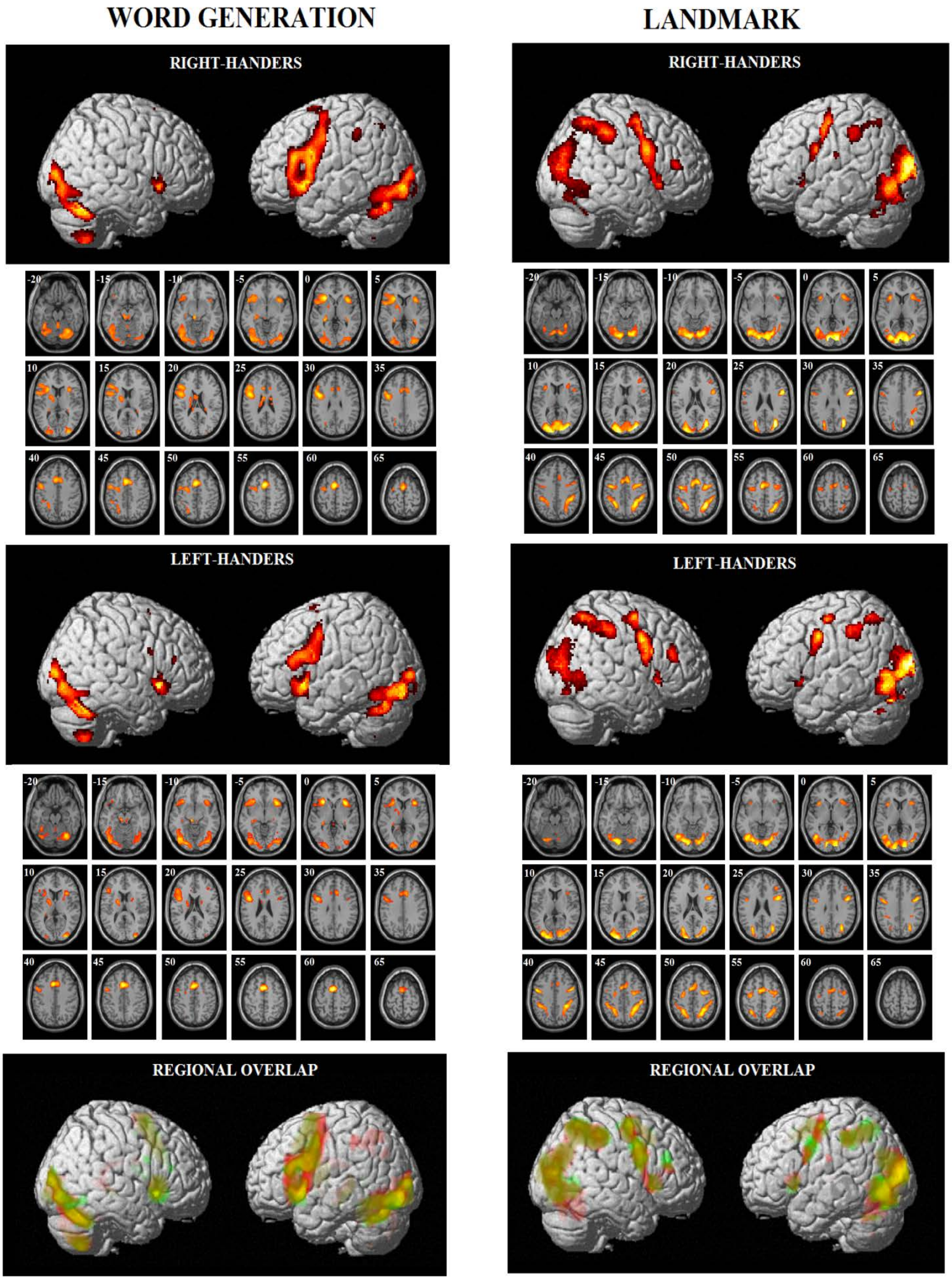

WORD GENERATION
LANDMARK
RIGHT-HANDERS
RIGHT-HANDERS
-20
-15
-10
-5
0
5
10
15
20
25
30
35
40
45
50
55
60
65
LEFT-HANDERS
LEFT-HANDERS
REGIONAL OVERLAP
REGIONAL OVERLAP

Figure 7.1. Group activation for the word generation task (left column) and landmark task (right column) in left- and right-handers. Results show significant regions of cortical activation for both the tasks. Activations are displayed laterally on a cortical surface rendered brain and through axial slices. Regional overlap represents regions of activation seen in right-handers (red) and left-handers (green) for both the word generation task (left column) and landmark task (right column). Displayed results are significant at $P<0.05$ corrected for multiple comparisons using the family-wise error (FWE).

Descriptive statistics for laterality indices and language task activation can be seen in Table 7.3, separated by handedness and sex groups. The largest mean differences in language laterality are observed between right- and left-handers, with right-handers showing greatest leftward laterality (this is evident whether laterality is calculated in the IFG only or across the hemisphere). Spatial laterality (both parietal lobe and hemisphere) is similar across all groups. Males show greater language activation in both the left and right IFG than females. Left-handers show greater language activation in right hemisphere IFG than right-handers however both groups show similar language activation in left hemisphere IFG.

Table 7.1. Brain regions showing significant activations for the word generation task for left- and right-handers in the left hemisphere (A) and right hemisphere (B). Talairach coordinates of most significant voxel (x,y,z mm) are given, along with the corresponding brain region for this voxel and the closest Brodmann Area (BA) corresponding with that region. PO=pars opercularis, PTR=pars triangularis.

RIGHT-HANDERS				**LEFT-HANDERS**			
Brain Region	**BA**	**x,y,z**	**T-score**	**Brain Region**	**BA**	**x,y,z**	**T-score**
A. Left hemisphere							
Superior Frontal Gyrus	6	-4 6 56	14.14	Insula	13	-30 22 0	12.21
Inferior Frontal Gyrus (PO)	44	-44 6 28	12.99	Superior Frontal Gyrus	6	-6 8 54	11.55
Declive cerebellum		-42 -64 -26	11.96	Cingulate gyrus	32	-2 14 46	11.32
Inferior Frontal Gyrus (PTR)	45	-48 26 24	9.75	Declive cerebellum		-42 -64 -26	10.17
Inferior occipital gyrus	18	-42 -82 -6	9.29	Inferior Frontal Gyrus (PO)	44	-42 6 28	10.15
Superior parietal lobule	7	-24 -64 48	7.47	Inferior occipital gyrus	19	-42 -74 -10	9.38
Inferior parietal lobule	40	-42 -38 46	6.94	Inferior Frontal Gyrus (PTR)	45	-46 28 16	8.25
Parahippocampal gyrus		-32 -16 -14	5.95	Middle Frontal Gyrus	6	-50 4 42	8.14
				Inferior Frontal Gyrus (PTR)	45	-42 18 -6	7.48
B. Right hemisphere							
Culmen cerebellum		32 -58 -28	16.55	Culmen cerebellum		34 -54 -30	13.29
Insula	13	36 16 0	10.36	Superior Frontal Gyrus	6	2 8 58	12.03
				Insula	47	34 18 0	10.78

Table 7.2. Brain regions showing significant activations for the landmark task for left- and right-handers in the left hemisphere (A) and right hemisphere (B). Talairach coordinates of most significant voxel (x,y,z mm) are given, along with the corresponding brain region for this voxel and the closest Brodmann Area (BA) corresponding with that region. PO=pars opercularis, PTR=pars triangularis.

RIGHT-HANDERS				LEFT-HANDERS			
Brain Region	**BA**	**x,y,z**	**T-score**	**Brain Region**	**BA**	**x,y,z**	**T-score**
A. Left hemisphere							
Lingual Gyrus	17	-12 -88 0	11.09	Cuneus	18	-18 -96 18	10.93
Medial Frontal Gyrus	6	-6 -2 54	10.13	Lingual Gyrus	17	-26 -76 -8	9.22
Middle Frontal Gyrus	6	-38 -6 48	8.42	Precentral Gyrus	6	-50 0 40	8.52
Insula	13	-32 18 6	7.64	Precuneus	7	-28 -56 52	7.97
Inferior Parietal Lobule	40	-42 -38 42	7.45	Middle Frontal Gyrus	6	-6 4 52	7.92
				Inferior Parietal Lobule	40	-42 -40 40	7.38
				Insula	13	-34 16 4	6.59
				Declive Cerebellum		-40 -64 -30	6.21
				Culmen Cerebellum		-28 -54 -30	5.72
B. Right hemisphere							
Lingual gyrus	17	14 -84 -2	11.07	Cuneus	18	14 -92 2	9.95
Inferior Frontal Gyrus (PO)	44	50 6 28	10.70	Inferior Frontal Gyrus (PO)	44	46 6 24	9.06
Middle Occipital Gyrus		30 -72 30	10.50	Inferior Frontal Gyrus	6	46 0 36	8.72
Precuneus	7	32 -50 50	10.43	Precuneus	7	32 -50 50	8.57
Medial Frontal Gyrus	6	8 8 48	8.78	Inferior Parietal Lobule	40	46 -39 43	8.27
Inferior Parietal Lobule	40	44 -38 46	8.54	Medial Frontal Gyrus	6	4 0 56	7.44
Middle Frontal Gyrus	6	30 -6 50	8.27	Insula	13	32 20 4	6.61
				Cingulate Gyrus	32	12 20 42	5.72

Table 7.3. Mean scores (standard deviations) for laterality indices and language activation scores separated by sex and handedness groups; square brackets give minimum and maximum values. Language refers to results for the word generation task and spatial refers to results from the landmark task.

Functional measure	**Regions of interest**	**Right-handers** (n=42)	**Left-handers** (n=40)	**Males** (n=32)	**Females** (n=50)
Language laterality	**IFG**	-0.74 (0.18) [-0.97, -0.10]	-0.42 (0.51) [-0.93, 0.92]	-0.58 (0.4) [-0.97, 0.87]	-0.59 (0.42) [-0.96, 0.92]
Spatial laterality	**Parietal lobe**	0.18 (0.42) [-0.71, 0.79]	0.18 (0.44) [-0.71, 0.71]	0.22 (0.4) [-0.65, 0.76]	0.15 (0.44) [-0.71, 0.69]
Language laterality	**Whole hemisphere**	-0.52 (0.34) [-0.93, 0.33]	-0.25 (0.46) [-0.8, 0.67]	-0.33 (0.45) [-0.86, 0.67]	-0.44 (0.41) [-0.93, 0.66)
Spatial laterality	**Whole hemisphere**	-0.09 (0.44) [-0.93, 0.64]	0.05 (0.41) [-0.8, 0.65]	-0.004 (0.40) [-0.65, 0.65]	-0.04 (0.45) [-0.93, 0.65]
Language activation	**Left hemisphere IFG**	0.86 (0.4) [-0.28, 1.78]	0.83 (0.65) [-1.2, 2.35]	1.0 (0.56) [0.34, 2.35]	0.7 (0.5) [-1.2, 1.96]
Language activation	**Right hemisphere IFG**	0.44 (0.43) [-0.54, 1.33]	0.66 (0.58) [-1.1, 2.16]	0.72 (0.56) [-0.54, 2.16]	0.39 (0.44) [-1.1, 1.67]

Figure 7.2 shows group activations for the word generation task and landmark task across all subjects within each ROI. Laterality indices are calculated for the word generation across the IFG while laterality indices for the landmark task are calculated across the parietal lobe. Details of each ROI used to calculate the laterality indices for the landmark and word generation task is given in Table 7.4. The results show that the parietal lobe encompasses a much larger region to that of the word generation task.

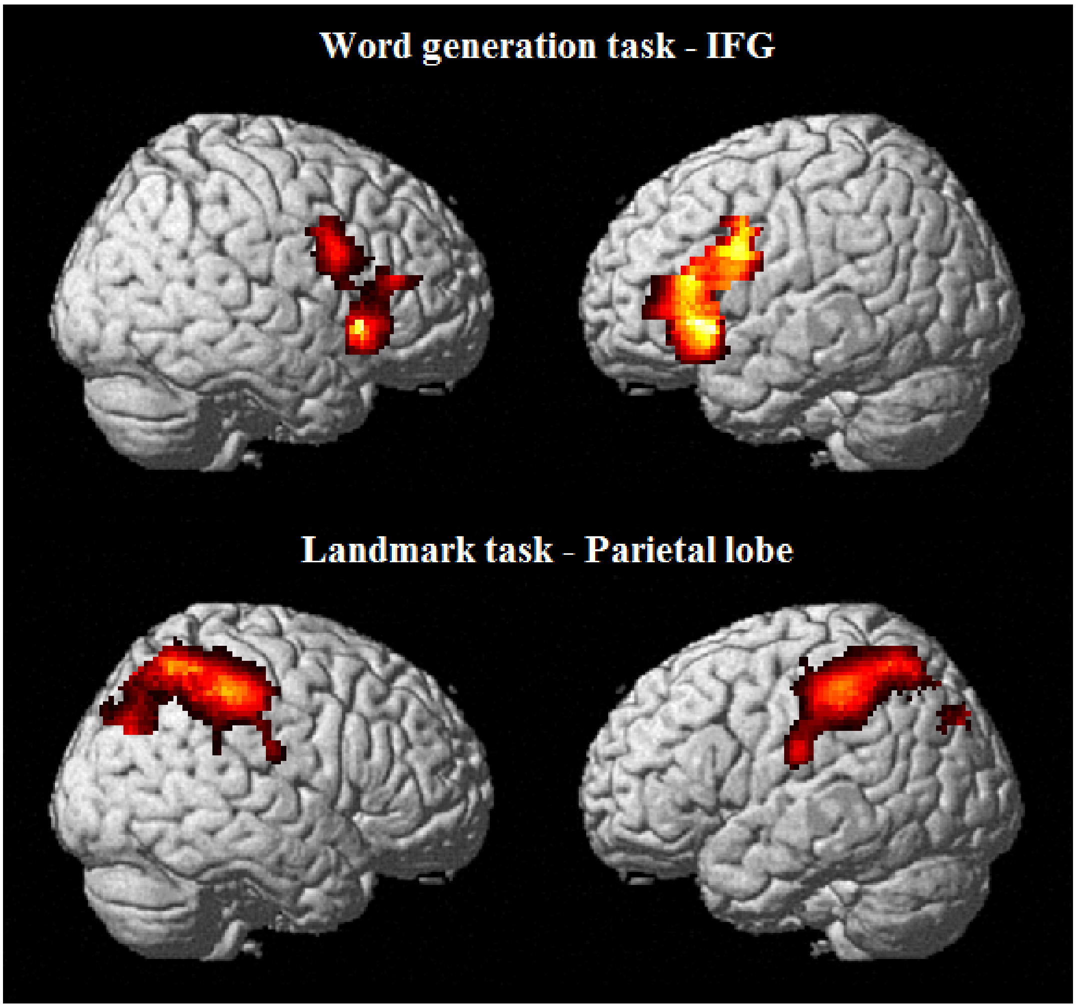


Figure 7.2. Group activations for the word generation task and landmark task across all subjects within each ROI are shown. Laterality indices are calculated for the word generation across the IFG while laterality indices for the landmark task are calculated across the parietal lobe. Results show significant regions of cortical activation for both the tasks. Activations are displayed laterally on a cortical surface rendered brain. Displayed results are significant at $P<0.05$ corrected for multiple comparisons (FDR).

Table 7.4. Details of each ROI used to calculate the laterality indices for the landmark task and word generation task. Volume of the ROI is given along with the Talairach coordinates of the centre of the ROI and coordinates of the maximum and minimum boundary along x, y and z coordinates.

	Landmark task		**Word generation task**	
	Left Parietal lobe	**Right Parietal lobe**	**Left IFG**	**Right IFG**
Volume of ROI (mm^3)	107176	107608	37856	38272
Talairach coordinates (x, y, z mm)	-33, -48, 43	34, -48, 43	-44, 24, 4	46, 24, 4
Max/Mix X(mm)	-68, 0	0, 70	-64, -12	12, 66
Max/Mix Y(mm)	-88, -4	-88, -6	-4, 60	-4, 60
Max/Mix Z(mm)	14, 82	14, 82	-26, 40	-26, 40

The effect of handedness on language (IFG) and spatial (parietal lobe) laterality

The distribution of language (IFG) and spatial (parietal lobe) lateralization scores in left- and right-handers can be seen in Figure 7.3. There is leftward language lateralization in 32 (80%) left-handers and 42 (100%) right-handers, and rightward spatial lateralization in 25 (63%) left-handers and 28 (67%) right-handers (Table 7.3). No significant linear relationship is found between language and spatial lateralization for either left-handers (r=0.026, *P*=0.9) or right-handers (r=0.106, *P*=0.5) (see Figure 7.4).

The results presented in Figure 7.3 demonstrate a greater variance in language lateralization in left-handers than right-handers: language laterality in right-handers in strongly left-lateralized whereas in left-handers scores range between the extremes i.e. strong leftward and strong rightward laterality. Given this smaller variance in language lateralization in right-handers the correlation between language lateralization and degree of handedness was explored only in left-handers, and no significant correlation was found (r= -0.2, *P*=0.2).

The proportion of individuals showing associated and dissociated language and spatial lateralization are shown in Table 7.5. Twenty five (30%) subjects presented leftward language and spatial LIs and 4 (5%) subjects presented rightward language and spatial LIs. Approximately two-thirds of subjects presented dissociated LIs: 49 (60%) leftward language and rightward spatial laterality and 4 (5%) leftward spatial and rightward language laterality. Thus when language is lateralized to the right hemisphere, 50% present right hemisphere spatial dominance; in contrast, when language is lateralized to the left hemisphere, two-thirds (66%) present rightward spatial laterality.

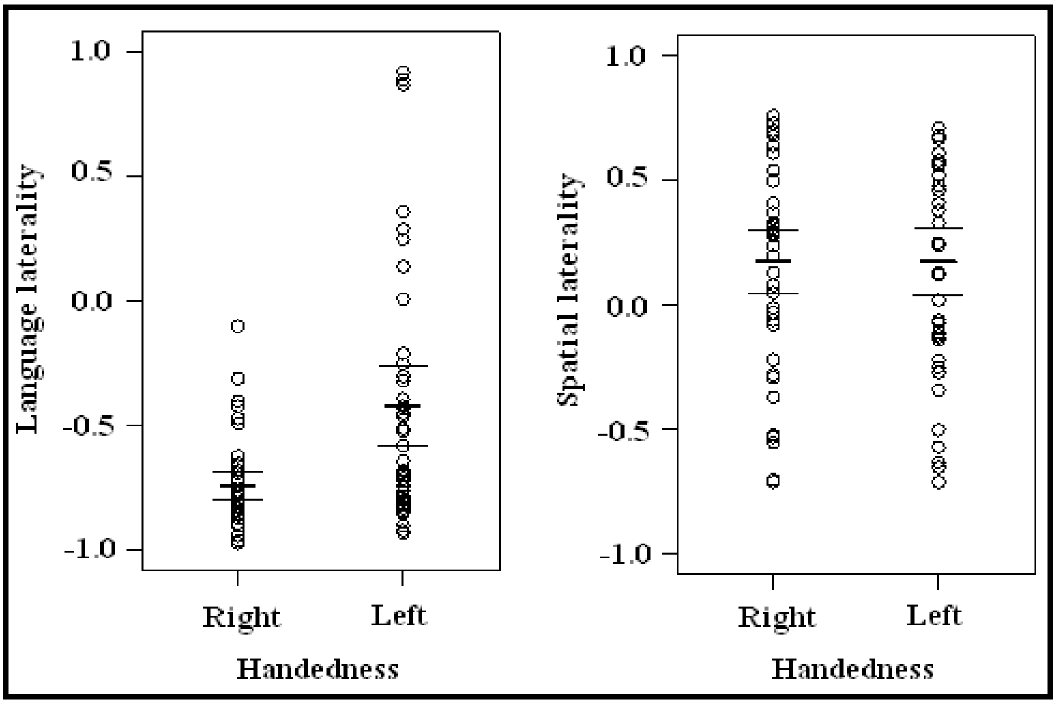


Figure 7.3. Language and spatial laterality scores for right- and left-handers. Sample means are represented by the short line segments, and the upper and lower bounds of the 95% confidence interval are represented by the longer, outer pair of lines.

Table 7.5. The proportion of participants displaying dissociated and associated language laterality and spatial laterality for the total sample and each handedness group. Figures are given as number of cases (percentage).

	Leftward spatial	**Rightward spatial**
Total (n=82)		
Leftward language	25 (30%)	49 (60%)
Rightward language	4 (5%)	4 (5%)
Right-handers (n=42)		
Leftward language	14 (33%)	28 (67%)
Rightward language	0 (0%)	0 (0%)
Left-handers (n=40)		
Leftward language	11 (28%)	21 (53%)
Rightward language	4 (10%)	4 (10%)

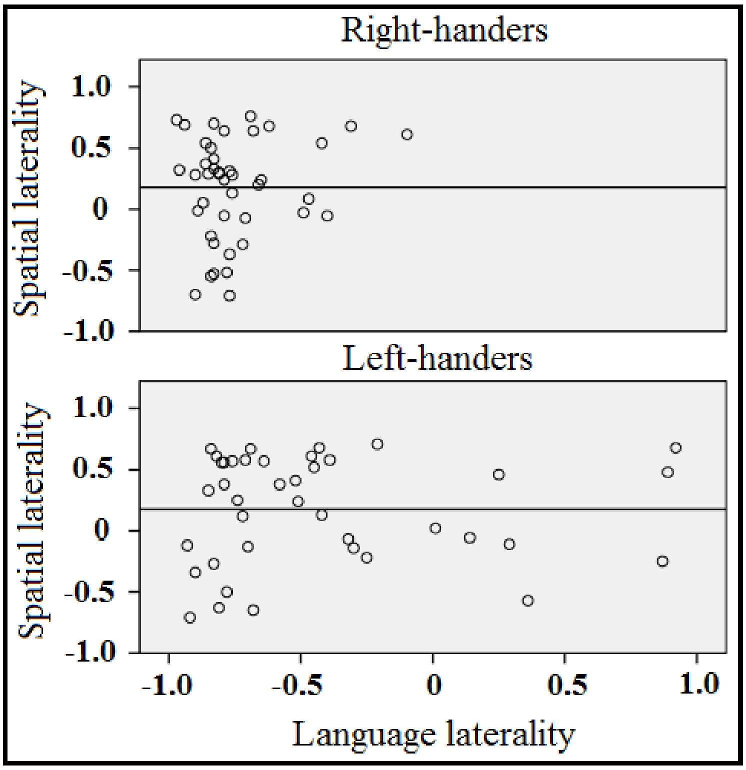


Figure 7.4. Scatter plot of language versus spatial lateralization scores and fitted least-square regression lines in right- and left-handers.

The effect of handedness sex and age on language and spatial processing

Results from the two multivariate models can be seen in Table 7.6. An overall significant effect was found for handedness in the first multivariate model ($F_{(2,77)}$=6.46, P=0.003). Univariate results based on the marginal distributions showed a significant effect of handedness specifically on language laterality across the IFG (P=0.001, coefficient= -0.31, 95%CI: -0.47,-0.14) with right-handers showing significantly greater leftward language laterality than left-handers. No significant effect was found for any of the predictor variables on spatial laterality. This was expected based on the fact that left- and right-handers obtained similar mean scores for spatial laterality (see Table 7.3) and the proportion of left- and right-handers presenting rightward spatial laterality was very similar. In order to explore whether differences in activation in left and right hemisphere IFG may have contributed to the difference in language laterality indices (as calculated across the IFG), contrast values were calculated in left and right IFG separately in response to the word generation task.

Handedness ($F_{(2,77)}$=3.47, P=0.036) and sex ($F_{(2,77)}$=5.039, P=0.009) were both found to be significant in the second multivariate model. Specifically, the univariate results presented in Table 7.6B showed that left-handers present significantly greater activation in right IFG than right-handers (P=0.046, coefficient= -0.22, 95%CI: -0.44,-0.004) and that males show significantly greater activation in response to the word generation task than females in both left IFG (coefficient=0.30, 95%CI: 0.07,0.53) and right IFG (coefficient= 0.33, 95%CI: 0.11,0.55). No overall significant effect was found for age in the multivariate model ($F_{(2,77)}$=2.686, P=0.075), however results from the univariate analysis showed that an increase in age is associated with an increase in activation in response to the word generation task in the left IFG (P=0.025, coefficient=0.05, 95%CI: 0.01,0.08).

Note that if Bonferroni corrections were applied to each outcome variable in order to maintain an overall significance level of 0.05, the significance level would be equal to 0.05/2=0.025. Therefore, the P-values provided in Table 7.6 would be close to significance for the univariate analyses even using the conservative Bonferroni correction for the association between sex and IFG activation and for the effect of handedness on language laterality. However, the effect of handedness on right IFG activation is close to the boundary of significance using a significance level of *P*=0.05 indicating that the effect of handedness on right IFG is weak.

Table 7.6. Results based on the univariate marginal distributions from the multivariate analyses with: (A) language and spatial laterality as the outcome variables in the first model, and (B) neuronal activation in left and right hemisphere IFG in response to the word generation task entered as the outcome variables in the second model. IFG=inferior frontal gyrus. Significant results are highlighted in grey.

Outcome variable	**Predictor variable**	**Coefficient**	**SE**	**P-value**	**Lower 95% CI**	**Upper 95% CI**
A. Model 1: Laterality						
Language laterality: IFG	**Sex** (*F=0, M=1*)	0	0.09	>0.9	-0.17	0.17
	Hand (*R=0, L=1*)	-0.31	0.09	**0.001**	-0.47	-0.14
	Age	-0.02	0.01	0.17	-0.05	0.01
Spatial laterality: parietal lobe	**Sex** (*F=0, M=1*)	0.08	0.1	0.4	-0.12	0.28
	Hand (*R=0, L=1*)	-0.002	0.1	>0.9	-0.19	0.19
	Age	0.01	0.02	0.7	-0.03	0.04
B. Model 2: Language activation						
Left IFG activation	**Sex** (*F=0, M=1*)	0.3	0.12	0.01	0.07	0.53
	Hand (*R=0, L=1*)	0.03	0.11	0.8	-0.2	0.26
	Age	0.05	0.02	0.025	0.01	0.08
Right IFG activation	**Sex** (*F=0, M=1*)	0.33	0.11	0.004	0.11	0.55
	Hand (*L=0, R=1*)	-0.22	0.11	0.046	-0.44	-0.004
	Age	0.02	0.02	0.4	-0.02	0.05

Cognitive ability and laterality

Descriptive statistics for all cognitive ability tests can be seen in Table 4.2, separated by handedness and sex groups. Graphs displaying the results for verbal comprehension, perceptual organisation and working memory can be seen in Figure 7.5. A multivariate analysis of covariance was performed to assess the relationship between the predictor variables: handedness, language LI, spatial LI, age, sex and the outcome variables: verbal comprehensions, working memory and perceptual organisation. Sex and age were not significantly associated with any of the three outcome variables (P>0.05) and were subsequently removed from the model. The three-dimensional variable neuropsychological performance is significantly associated with both handedness ($F_{(3,75)}$=4.3, P=0.007) and the interaction term language LI*spatial LI ($F_{(3,75)}$=4.1, P=0.01).

The results for each of the outcome variables are shown in Table 7.7. Working memory is significantly associated with handedness (coefficient= -6.1, P=0.001, 95%CI: 0.7,11.5), such that left-handedness is associated with a 6.1% decrease in working memory score. Rightward language lateralization is also associated with a reduction in working memory score (coefficient= -8.2, P=0.025, 95%CI: -15.4,-1.1). Roughly speaking, this means that an increment in language laterality of 1 unit in the rightward direction is associated with an 8.2% reduction in working memory score (this is strictly so when the spatial LI is equal to zero; for a more precise interpretation of the model the value of the interaction term should also be considered).

The interaction between language and spatial laterality is significantly associated with verbal comprehension (coefficient= -14.7, P=0.016, 95%CI: -29.3,-3.2) and with perceptual organisation (coefficient= -12.0, P=0.016, 95%CI: -21.7,-2.3), indicating that verbal comprehension and perceptual organization are higher when language and spatial lateralization are dissociated.

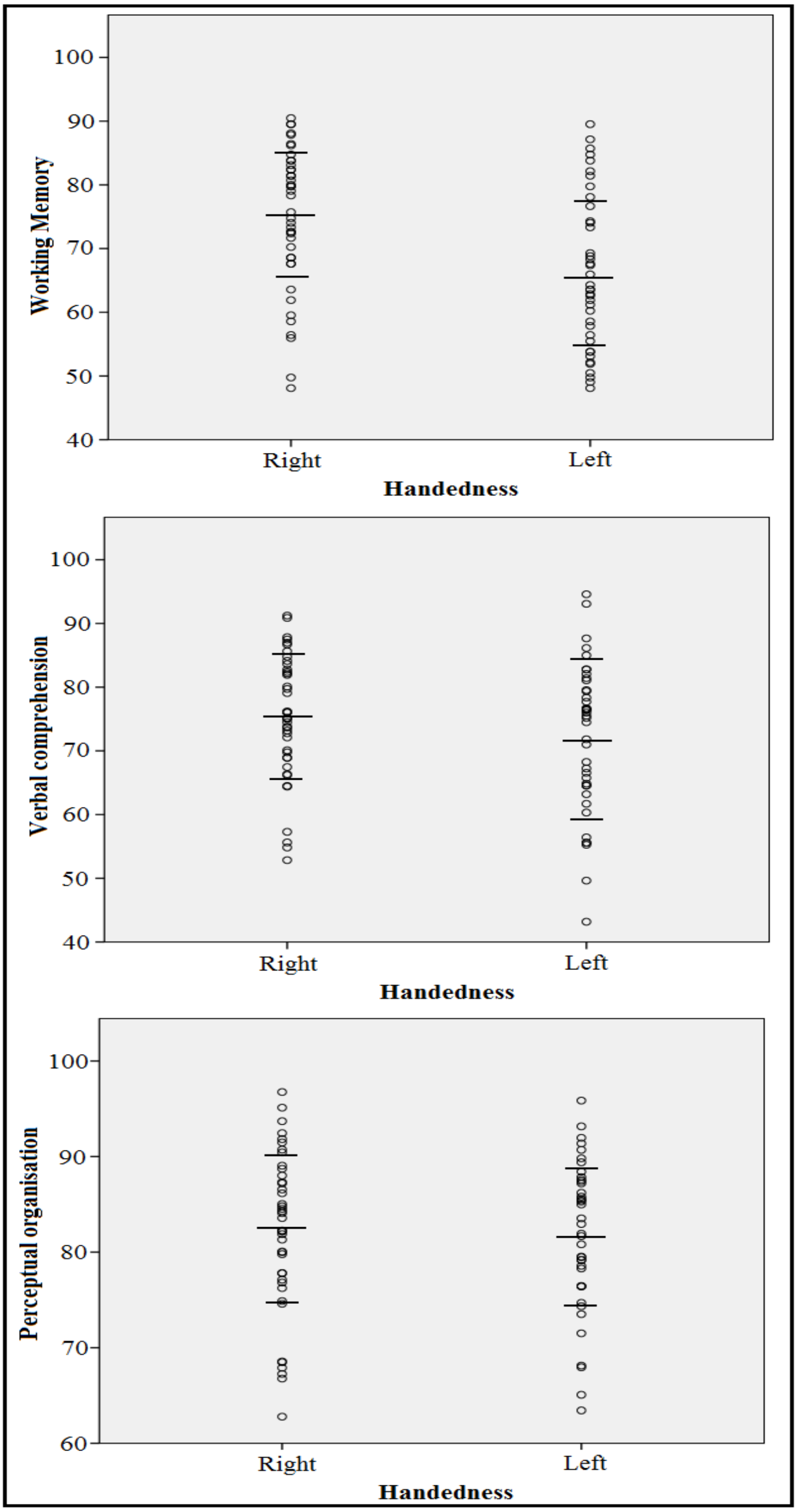


Figure 7.5. Graphs displaying the mean (± standard deviations) for each cognitive ability measure, separated by handedness group. The longer horizontal lines represent mean scores for each of the three subtests the smaller outer dashes represent ± standard deviations.

Overall the results from the multivariate model (including the corresponding univariate analyses) show that neither language laterality nor spatial laterality per se is significantly associated with either verbal comprehension (*P*=0.8 and *P*=0.4, respectively) or perceptual organisation (*P*=0.6 and *P*=0.1, respectively); instead large values of language LI with opposed laterality for the spatial task are associated with an increase in both performances (this follows from the significant interaction term with a negative coefficient). In the case of working memory the interaction term is not significant (*P*=0.6), and an increase in leftward language laterality is directly associated with an increase in working memory.

A Bonferroni correction is applied to each outcome variable in order to maintain an overall significance level of 0.05, resulting in a significance level equal to 0.05/3=0.016. The significant results reported above would therefore reach the adjusted significance level. However, the effect of language laterality would be slightly over the boundary of significance (i.e. *P*=0.025). Strictly speaking this would mean that this variable is not significant although close to the boundary of significance.

Figure 7.6 shows the associations between cognitive ability scores and laterality indices. Least square regression lines are included to show the trend between cognitive ability scores and laterality indices for each handedness group: the exact associations between these variables can be taken from the model presented in Table 7.7.

Table 7.7. Results from the multivariate analysis with the outcome variables: working memory, verbal comprehension and perceptual organisation and the predictor variables handedness, language laterality, spatial laterality and the interaction between language and spatial laterality. A negative LI indicates left-hemispheric dominance and positive LI indicates right-hemispheric dominance, so negative values of the interaction term Language LI * Spatial LI indicate dissociated hemispheres. The coefficients of the model that are statistically significant are highlighted in grey.

	Coefficient	**Std Error**	**P-value**	**Lower 95% CI**	**Upper 95% CI**
Working memory					
Handedness (R=0, L=1)	-6.1	2.7	0.001	-0.7	-11.5
Language LI	-8.2	3.6	0.025	-15.4	-1.1
Spatial LI	3.4	5.3	0.5	-7.1	14.0
Language LI * Spatial LI	3.3	7.1	0.6	-10.8	17.4
Verbal Comprehension					
Handedness (R=0, L=1)	-3.8	2.6	0.2	-8.5	1.5
Language LI	2.5	3.4	0.8	-2.9	10.4
Spatial LI	-12.6	5.0	0.4	-22.3	-2.9
Language LI * Spatial LI	-14.7	6.6	0.016	-29.3	-3.2
Perceptual Organisation					
Handedness (R=0, L=1)	-0.1	1.9	0.8	-3.9	3.6
Language LI	1.0	2.5	0.6	-4.0	5.9
Spatial LI	-4.1	3.6	0.1	-11.4	3.1
Language LI * Spatial LI	-12.0	4.9	0.016	-21.7	-2.3

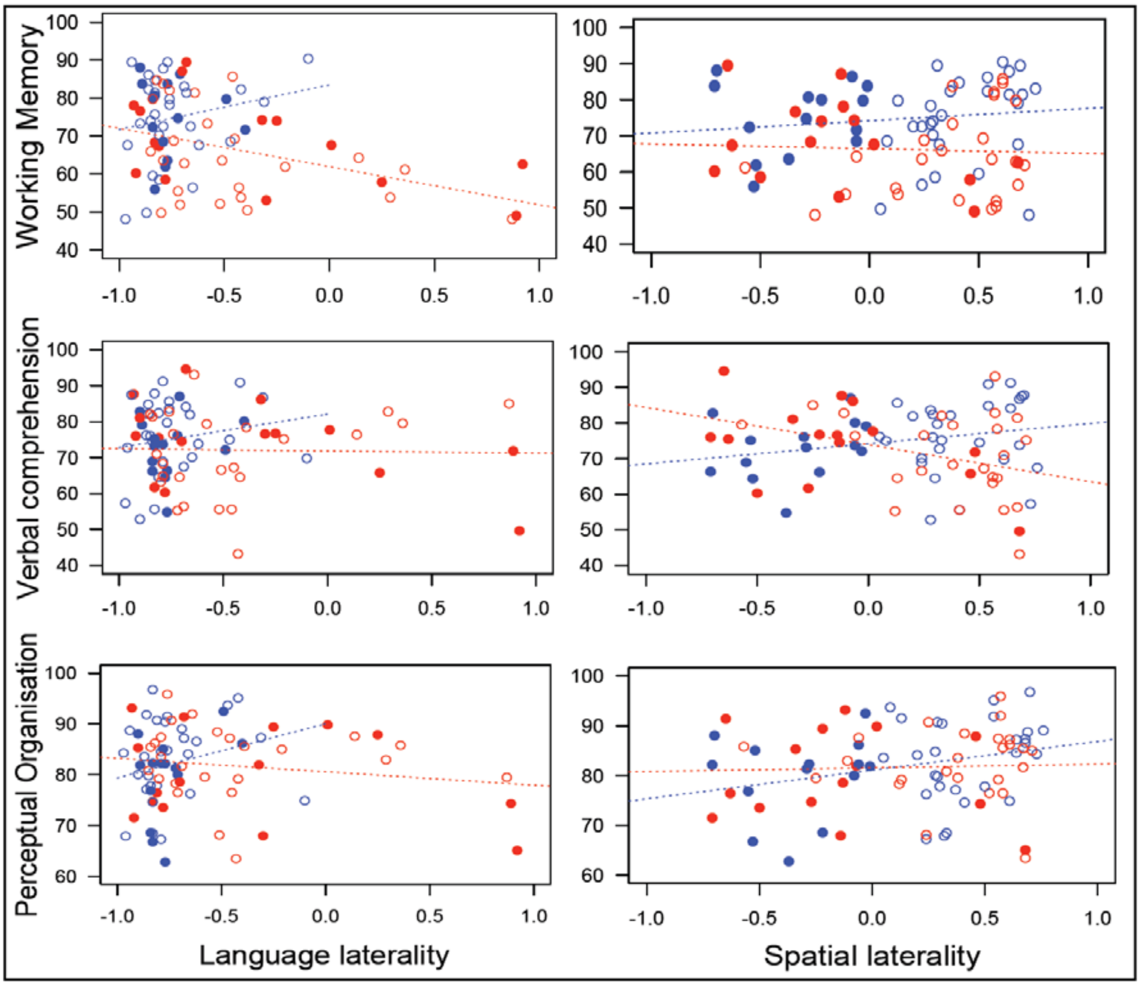


Figure 7.6. Associations between cognitive ability score and laterality indices across regions of interest. Laterality indices range from -1.0 (leftward laterality) to +1.0 (rightward laterality). Blue and red circles represent right-handers and left-handers, respectively. Empty and filled circles are used to indicate, respectively, disassociation and association of the hemispheres for the language and spatial tasks. Least square regression lines are shown for each handedness group to illustrate the trends: the exact associations can be taken from the fitted model presented in Table 7.7.

7.3 PRELIMINARY DISCUSSION

Language lateralization differed significantly between left- and right-handers, with right-handers showing greater leftward language laterality. Results showed that this difference in laterality may be due to greater activation in right hemisphere IFG as left-handers showed significantly greater activation than right-handers in this region in response to the word generation task, while no difference was observed between handedness groups in the left IFG.

Three novel findings emerged from this study, specifically results show: (i) a relationship between handedness and auditory working memory; (ii) a relationship between increased rightward language lateralization and decreased working memory performance, which is suggested to relate to the involvement of frontal speech areas in subvocal rehearsal during working memory tasks; and (iii) an effect of associated language and spatial LI's on cognitive ability. Specifically the interaction between language and spatial lateralization is associated with performance on verbal comprehension and perceptual organisation, such that when language and spatial lateralization are associated to the same hemisphere (especially when both showed rightward laterality indexes), verbal comprehension and perceptual organisation performance is significantly decreased. This interaction is interpreted in relation to the 'hemispheric crowding' hypothesis, which proposes increased cognitive ability performance when language and spatial lateralization are dissociated.

Understanding the quantitative relationships between language and spatial lateralization, handedness, and the demographic factors that influence these asymmetries of function in the normal population, is of clinical relevance for three reasons: (i) these relationships might be useful for predicting the risk of postoperative language disturbance in patients undergoing brain surgery for adult-onset disease; (ii) such knowledge could lead to an improved understanding of the biological basis of language lateralization, leading to novel therapeutic strategies for patients with impaired language processing, and; (iii) understanding the brain's organisation within the healthy population for language and spatial processing, and its relationship with cognitive ability, will provide evidence of an optimal brain state and the possible advantages of laterality for our species and will further our understanding of the factors which have driven brain evolution.

CHAPTER 8:

HANDEDNESS, GREY MATTER VOLUME AND INTELLIGENCE

8.1 METHODS

Participants and imaging parameters: Information on the participants used in this study is given in Section 4.1. Descriptive statistics for the sample used in this study are given in Table 4.2. Details of the imaging parameters used to acquire the T_1-weighted MR images, which were used in this study, are given in Section 4.3.

Neuropsychological testing: Verbal comprehension was assessed in this study using two subtests from the Wechsler Adult Intelligence Scale (WAIS-III): vocabulary and comprehension. This is taken here as a measure of crystallised intelligence. Fluid intelligence comprised the WAIS-III subtests used to assess perceptual organisation (i.e. picture completion; block design; and matrix reasoning), and auditory working memory (i.e. digit-span and letter-number sequencing) and the Imposing Memory Task (IMT) used to assess intentionality. Details of the WAIS-II sub-tests and the IMT are given in Section 4.2.2 and Section 4.2.3 respectively. Results for each handedness group are shown in Table 4.2.

Voxel-based morphometry (VBM): VBM was applied to identify brain areas where working memory correlated with GM volume separately for left- and right-handed groups. Details of the VBM procedure used in this study are given in Section 4.4.5. An isotropic Gaussian kernel (IGK) of 10mm was chosen to smooth the normalised segmented GM images.

Statistical analysis of MR images and neuropsychological data: Briefly the smoothed normalised GM segments (without priors) were entered into a full-factorial design matrix with the covariates: hand degree, verbal comprehension, auditory working memory, perceptual organisation, intentionality, age, sex, total intracranial volume (IVC: the sum of GM, WM and CSF segments) and an interaction term between hand direction and the four measures of cognition. Hand direction was entered in the model as a factor with two levels. Associations between GM volume and crystallised intelligence (i.e. verbal comprehension) and between GM volume and fluid intelligence (i.e. the sum of auditory working memory, perceptual organisation, and intentionality) were tested for across all subjects using t-tests with a threshold set to $P<0.05$, corrected for multiple comparisons using the false-discovery-rate (FDR). A direct comparison was performed to examine significant differences in GM correlates between fluid and crystallised measures of intelligence using an *F*-test (FDR, $P<0.05$). F-tests were used to test the effect of handedness on fluid intelligence and crystallised intelligence. Locations of significant clusters are reported as the closest Brodmann area (BA) where possible. Regions of significant association are identified using the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/cms/software#PickAtlas). Only clusters of at least 10 voxels are reported.

A multivariate model was fitted using intentionality and short-term memory scores as the outcome variables and age, sex and hand direction as the predictor variables. This was to test for the effect of hand direction on intentionality and short-term memory. The multivariate statistical approach was chosen to account for the dependence between intentionality and memory. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software. The effect of age, sex and handedness on verbal comprehension, working memory and perceptual organisation score was tested for in Chapter 7: results are presented in Section 7.2.

8.2 RESULTS

Descriptive statistics for participant information and neuropsychological data are given in Table 4.2 separated by sex and handedness groups. Descriptive statistics of VBM segmentation volumes are given in Table 4.7. Results from the multivariate model showed that the variables age, sex and handedness group were not significantly associated with intentionality or short-term memory score (P>0.05). This indicates that there is no evidence from the data to suggest a significant difference in intentionality or short-term memory score between left- and right-handed groups or between males and females. Graphs displaying the means and standard deviations for intentionality and short-term memory score for each handedness group are given in Figure 8.1.

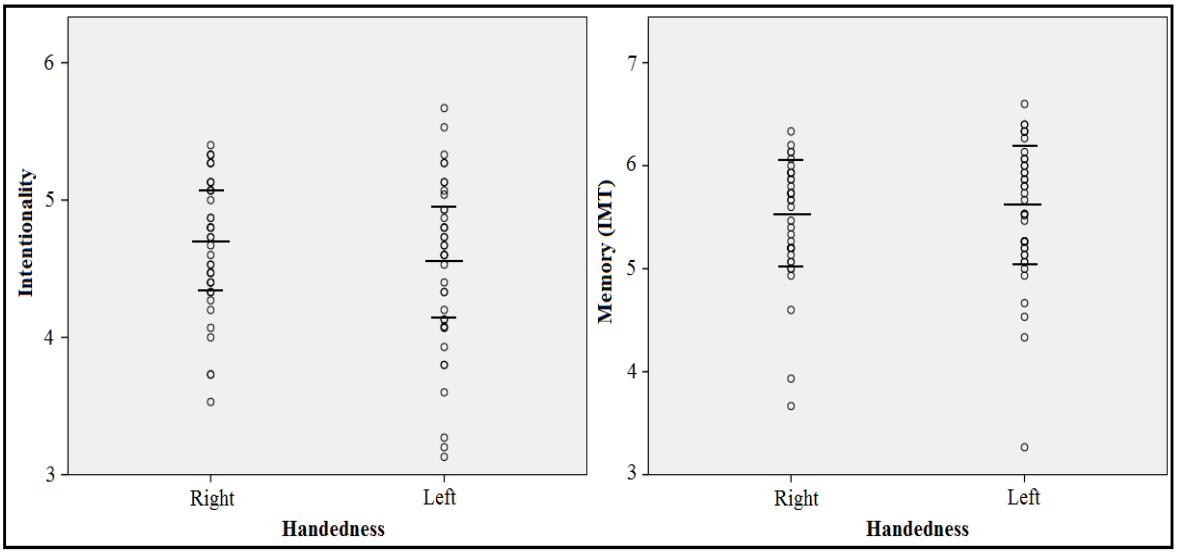


Figure 8.1. Graphs displaying means and standard deviations for intentionality and short-term memory, separated by left- and right-handed group. The longer horizontal lines (centre line) represent mean scores for each of the three subtests and the smaller (outer) dashes represent ± standard deviations.

The difference in GM volume, across the whole brain, between right- and left-handers was first tested for. Results shown in Table 8.1 indicate significant differences in GM volume between the two handedness groups in middle frontal gyrus (BA10 and BA11) and fusiform gyrus (BA20).

Table 8.1. Differences in GM volume between the two handedness groups. Talairach coordinates of most significant voxel (x,y,z mm) are given, along with the corresponding brain region for this voxel and the closest BA. The number of surviving voxels, peak z-value, and *F*-values are also shown for each region.

Nearest grey matter region	**BA**	**Talairach coordinates (x,y,z)**	***F*-score**	**Z-score**	**Cluster size (mm^3)**
Middle frontal gyrus	10	-29, 48, -6	16.24	3.63	51
Fusiform gyrus	20	48, -39, -29	13.99	3.37	55
Middle frontal gyrus	11	-15, 53, -15	13.53	3.31	46

The relationship between fluid intelligence and GM volume and between crystallised intelligence and GM volume was tested for across the whole brain for all subjects. Results are shown in Table 8.2 and Figure 8.2. Significant relationships were found between crystallised intelligence and increased GM volume in medial (BA6) and superior (BA8) frontal gyrus and superior parietal gyrus (BA7) in the left hemisphere and superior frontal gyrus (BA9) in the right hemisphere across all subjects. Increased fluid intelligence correlated with GM volume in middle frontal gyrus (BA8 and BA11) in the left hemisphere and middle (BA8), medial (BA9) and inferior (BA47) frontal gyrus, posterior cingulate (BA31) inferior temporal (BA37) and lingual (BA18) gyrus.

Direct comparisons were performed to test whether the relationship with GM volume differed for fluid and crystallised intelligence: results are shown in Table 8.3 (part A) and Figure 8.3. Direct comparisons were performed to investigate which voxels associated with fluid and crystallised intelligence differed significantly between the handedness groups: results are presented in Table 8.3 (parts B and C, respectively) and Figure 8.4. The results show significant differences the GM correlates between fluid and crystallised intelligence in inferior (BA47) and middle (BA8) frontal gyrus, lingual gyrus (BA18), precuneus (BA7), posterior cingulate (BA31) and inferior temporal gyrus (BA37) in the right hemisphere and middle frontal (BA8 and BA11) and temporal (BA21) gyrus in the left hemisphere.

Results show differences in GM correlates between the handedness groups for crystallised intelligence in the superior temporal gyrus (BA38) bilaterally, left hemisphere middle frontal gyrus (BA8 and BA11), and precuneus (BA7). Differences in the GM correlates between the handedness groups for fluid intelligence were found in left hemisphere inferior (BA20) and superior (BA22) temporal gyrus.

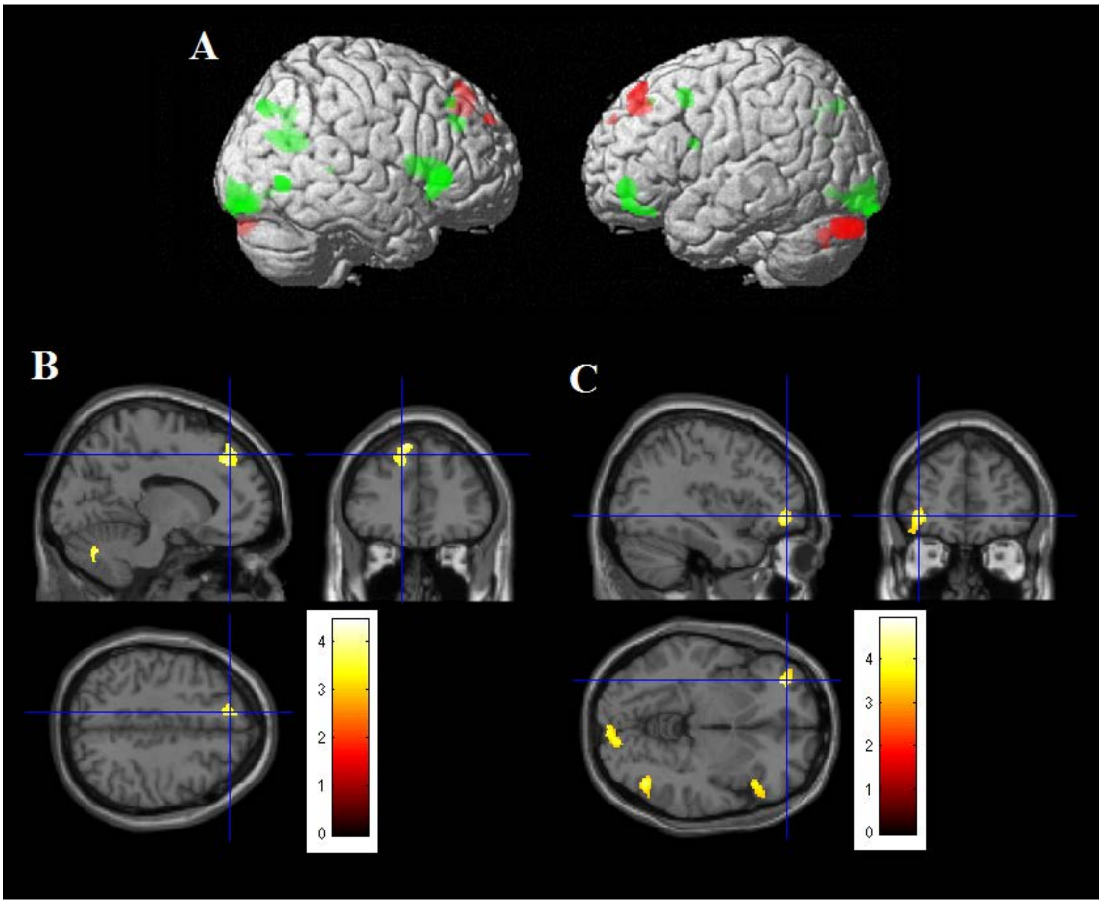


Figure 8.2. Significant correlations between GM volume and crystallised intelligence (red) and between GM volume and fluid intelligence (green) are rendered on the surface of a single T_1-weighted image supplied by SPM5 (A). Correlations between crystallised intelligence and GM volume in the superior frontal gyrus are shown in B: the cross-hairs in sagittal, coronal and axial images mark the Talairach coordinates (x, y, z mm) -9, 41, 52. Correlations between fluid intelligence and GM volume in the middle frontal gyrus are shown in C: the cross-hairs in sagittal, coronal and axial images mark the Talairach coordinates (x, y, z mm): -33, 44, -6. Colour intensity in the side bars correspond to T-scores.

Table 8.2. Correlations between GM volume and crystallised intelligence and fluid intelligence across all subjects are given. Talairach coordinates of most significant voxel (x,y,z mm) are given, along with the corresponding brain region for this voxel, the closest BA, the number of surviving voxels, peak z-scores, and T-scores for the region. R=right-hemisphere, L=left-hemisphere.

Region	**BA**	**Talairach coordinates (x,y,z)**	**T-score**	**Z-score**	**Cluster size (mm^3)**
Crystallised intelligence					
Superior parietal gyrus (L)	7	-26, -85, 27	4.45	4.15	915
Superior frontal gyrus (L)	8	-9, 41, 52	4.12	3.87	312
Medial frontal gyrus (L)	6	-12, 35, 40	3.85	3.73	100
Uvula, cerebellum posterior lobe (L)		-14, -69, -32	3.75	3.56	176
Superior frontal gyrus (R)	9	18, 54, 36	3.41	3.27	19
Fluid intelligence					
Lingual gyrus (R)	18	14, 91, -14	4.94	4.55	1958
Middle frontal gyrus (L)	11	-33, 44, -6	4.46	4.16	513
Inferior temporal gyrus (R)	37	44, -67, -3	4.36	4.08	280
Inferior frontal gyrus (R)	47	51, 26, 0	3.93	3.71	1318
Posterior cingulate (R)	31	14, -63, 21	3.92	3.71	1316
Middle frontal gyrus (L)	8	-23, 11, 45	3.80	3.61	169
Middle frontal gyrus (R)	8	18, 32, 43	3.69	3.51	57
Medial frontal gyrus (R)	9	23, 36, 31	3.50	3.34	68

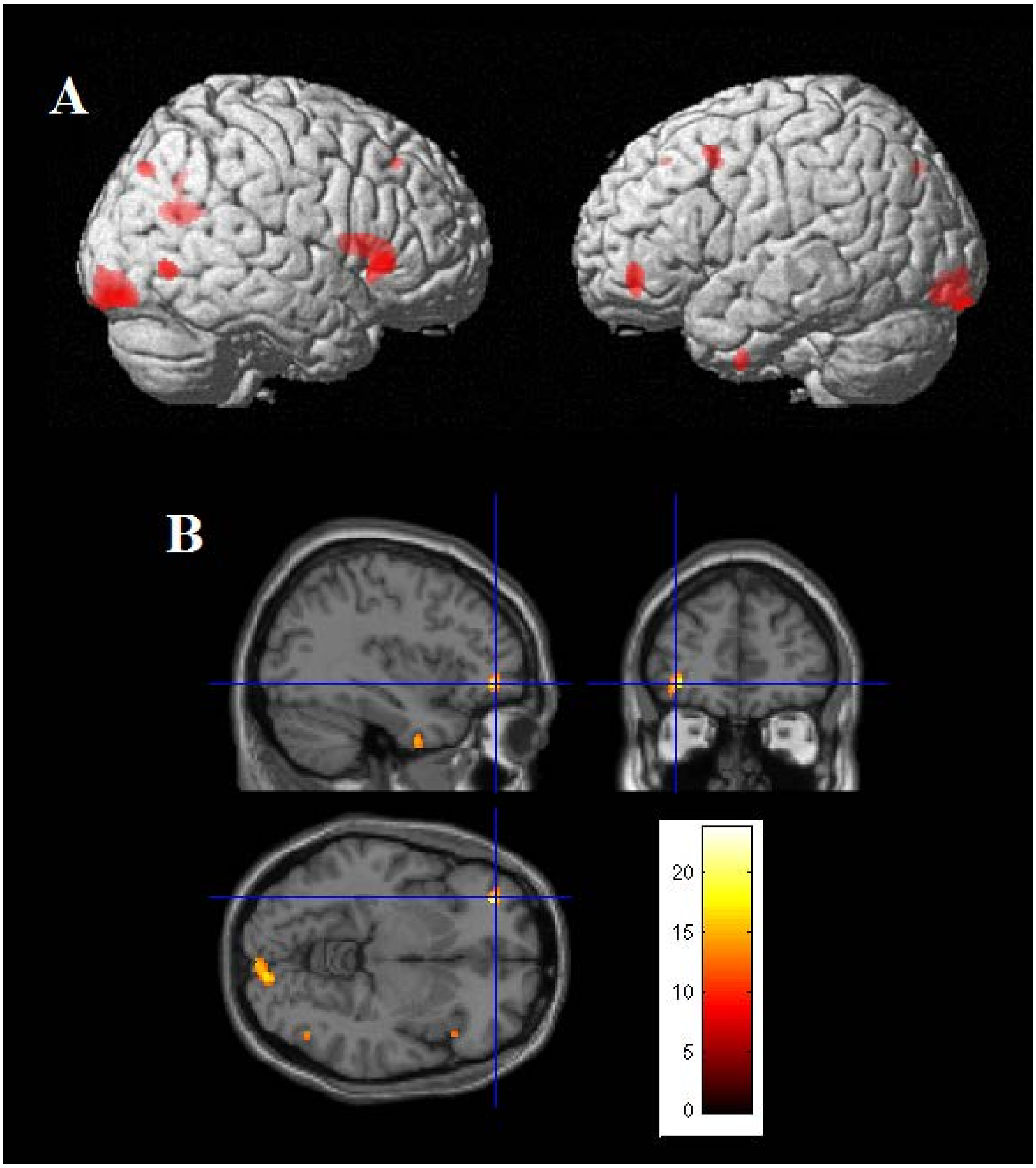


Figure 8.3. Differences in GM correlates between crystallised and fluid intelligence, rendered on the surface of a structural MR image supplied by SPM5 (A). This difference in shown in the middle frontal gyrus (B): the cross-hairs in sagittal, coronal and axial images mark the Talairach coordinates (x,y,z): -33, 44, -6. Colour intensity in the side bar corresponds to T-scores.

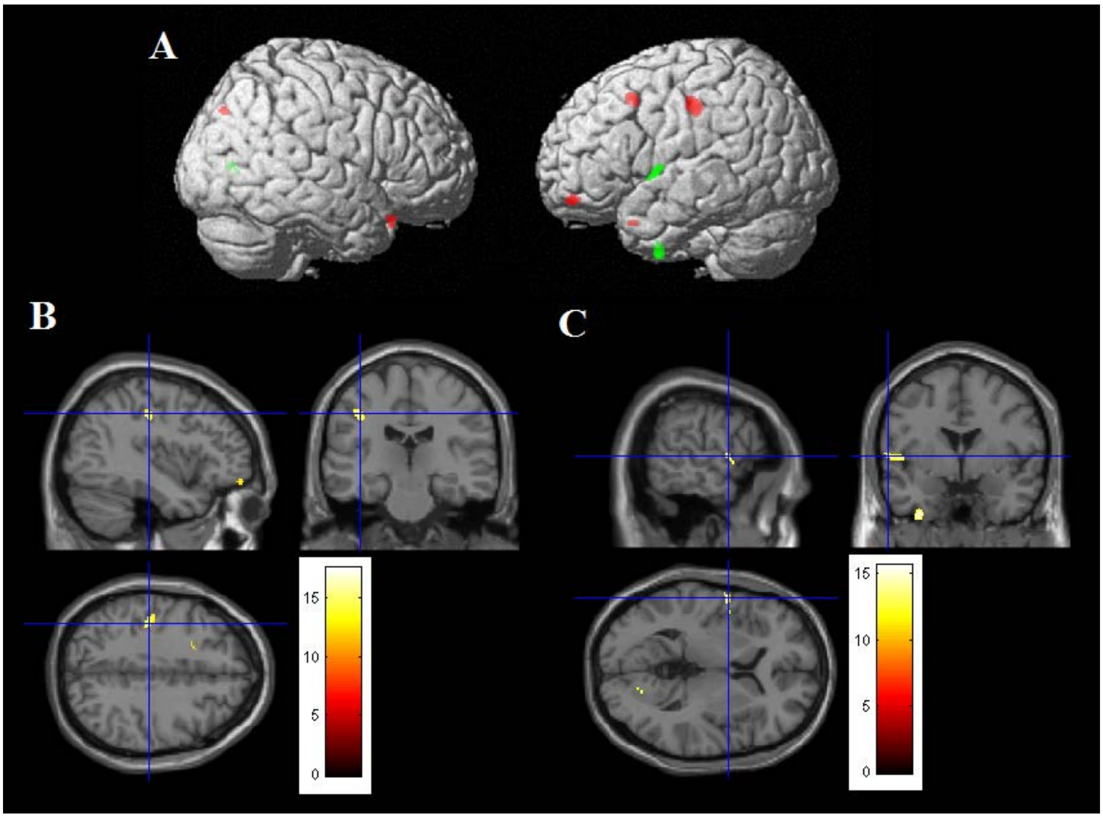


Figure 8.4. Significant differences in the GM correlates of crystallised intelligence between the hand groups (red) and differences in the GM correlates of fluid intelligence between the hand groups (green) rendered on the surface of a single T_1-weighted MR image supplied by SPM5 are shown in A. Differences in the GM correlates of crystallised intelligence between the hand groups in the superior temporal gyrus is shown in B: the cross-hairs in sagittal, coronal and axial images mark the Talairach coordinates (x,y,z mm): -29, 15, -29. Difference in the GM correlates of fluid intelligence between the handedness groups in the inferior temporal gyrus is shown in C: cross-hairs in sagittal, coronal and axial images mark the Talairach coordinates (x,y,z mm): -33, -1, -44. Colour intensity in the side bars correspond to T-scores.

Table 8.3. Differences in the GM correlates between fluid and crystallised intelligence (A), differences in the GM correlates of crystallised intelligence between the hand groups (B) and differences in the GM correlates of fluid intelligence between the hand groups (C) is given (based on direct comparisons). R=right-hemisphere, L=left-hemisphere.

Region	**BA**	**Talairach coordinates (x,y,z)**	***F*-score**	**Z-score**	**Cluster size (mm^3)**
A. Differences between fluid and crystallised GM correlates					
Lingual gyrus (R)	18	14, -91, -14	23.81	4.35	1372
Middle frontal gyrus (L)	11	-33, 44, -6	18.92	3.91	150
Inferior temporal gyrus (R)	37	44, -67, -3	18.49	3.86	145
Inferior frontal gyrus (R)	47	51, 26, 0	15.64	3.56	698
Posterior cingulate (R)	31	14, -63, 21	15.31	3.52	511
Middle frontal gyrus (L)	8	-23, 11, 45	14.76	3.46	104
Middle temporal gyrus (L)	21	-36, -1, -41	14.62	3.44	58
Precuneus (R)	7	20, -76, 40	14.08	3.38	78
Middle frontal gyrus (R)	8	18, 32, 43	13.38	3.29	20
B. The effect of handedness on the GM correlates of crystallised intelligence					
Superior temporal gyrus (R)	38	35, 23, -27	17.54	3.77	37
Postcentral gyrus (L)	3	-39, -24, 39	16.85	3.69	135
Middle frontal gyrus (L)	8	-17, 15, 45	16.61	3.67	99
Precuneus (R)	7	23, -76, 39	12.97	3.24	14
Middle frontal gyrus (L)	11	-38, 51, -15	12.96	3.24	39
Superior temporal gyrus (L)	38	-29, 15, -29	12.47	3.18	15
C. The effect of handedness on the GM correlates of fluid intelligence					
Inferior temporal gyrus (L)	20	-33, -1, -44	15.62	3.56	80
Superior temporal gyrus (L)	22	-59, 0, 4	13.94	3.36	106
Cuneus (R)	17	20, -70, 4	12.77	3.22	10

8.3 PRELIMINARY DISCUSSION

The present study shows that crystallised intelligence is correlated with GM volume primarily in the medial-superior frontal gyrus (including BA6, BA8 and BA9) and cuneus (BA7) in the occipital lobe across all subjects. Fluid intelligence is correlated with GM volume primarily in lateral and inferior frontal lobe (BA8, BA9, BA11 and 47), inferior temporal gyrus (BA37), posterior cingulate cortex (BA31) and lingual gyrus (BA18). The majority of these regions (i.e. BA6, BA7, BA9, BA18, BA37 and BA47) correspond to those regions which are correlated with better performance on measures of intelligence and reasoning in the P-FIT model of intelligence proposed by Jung and Haier (2007).

Significant differences in the GM correlates of crystallised intelligence between the handedness groups was found in bilateral superior temporal gyrus (BA38) and left middle frontal gyrus (BA8 and BA11) and right precuneus (BA7). Results showed significant differences in the GM correlates of fluid intelligence between the handedness groups in left inferior (BA20) and superior (BA22) temporal gyrus. Fluid intelligence was composed of the scores working memory, perceptual organisation and intentionality. Only working memory score differed significantly between the handedness groups with right-handers showing superior performance.

The general basis of correlations between cognitive ability scores and regional brain volume is not well understood. Larger brains have more neurons which may benefit both cognitive capacity and synaptic connectional complexity (Pakkenberg and Gundersen, 1997). However, increased GM volume reflects not only neuronal number, but also the number of glial cells which contribute to neurovascular regulation (Iadecola and Nedergaard, 2007) and integration of synaptic information (Haydon, 2001; Perea *et al.*, 2009); the proportion of these two cell types differs with region (Azevedo *et al* (2009).

Overall the results from this study suggest that it is important to consider differences in the neuroanatomical correlates of cognitive ability between groups known to differ in brain organisation and structure. Understanding differences in the neuroanatomical correlates of cognitive functioning in different groups within the healthy population may help shed light on individual differences in cognitive performance.

CHAPTER 9:

HANDEDNESS, PREFRONTAL VOLUME AND INTENTIONALITY

9.1 METHODS

Participants and Image Acquisition: The imaging parameters used to acquire the T_1-weighted MR images are given in Section 4.3. Information on the participants involved in this study including descriptive statistics are given in Section 4.1.

Neuropsychological protocol: An Imposing Memory Task (IMT) (Powell *et al*., 2010; Stiller and Dunbar, 2007), was used to assess intentionality capacity and short-term memory (Appendix 1). A description of this questionnaire, including information on the scoring system is given in Section 4.2.3.

Imaging analysis: Volume estimates of eight PFC subfields and left and right hemispheres were made from T_1-weighted MR images using the Cavalieri method of stereology in combination with point counting. Details of the approach used to demarcate and estimate the PFC subfields as well as left and right hemispheres are given in Section 4.4. Volume estimates were used to explore the relationship between intentionality and PFC volume in left- and right-handers. Details of the VBM approach used in this study to segment the T_1-weighted MR images are given in Section 4.4.5.

Statistical analysis of PFC volume estimates: Statistical analysis was performed using R software (version 2.10.1, The R Foundation for Statistical Computing, http://www.r-project.org/). A linear mixed-effects model was performed with PFC volume as the outcome variable to investigate whether a relationship exists between regional PFC volume and intentionality in left- and right-handers after adjusting for other covariates (see West *et al* (2007) for a description of mixed-effects models). The linear-mixed model allows for the inclusion of both fixed factors (e.g. sex, hemisphere side and handedness) and a random factor to account for the within-subject correlation (i.e., to take into consideration the dependence between the volume estimates from the right and left hemisphere of the same participant). In particular, intentionality, short-term memory, handedness (right/left), age, sex, region (lateral/medial), dorsal/orbital region, hemisphere side (left/right) and hemisphere volume were considered as predictor variables in the analysis. To take account of the effect of overall brain volume on raw orbital or dorsal PFC volume, hemisphere volume was included in the model as a predictor variable. Relevant interaction terms were considered in the model by adding the product of the corresponding two variables as an additional explanatory variable. For example, direct comparisons between right- and left-handers in the association between PFC volume and intentionality can be carried out by including the interaction term intentionality*handedness in the model. The significance of each interaction term was therefore tested following the same procedure as with the individual explanatory variables of the model. Predictor variables included in the final model were selected using a stepwise selection procedure. The relationship between intentionality, orbital PFC volume and dorsal PFC volume was tested for in left- and right-handers separately using the esticon function within R software.

A Pearson product-moment correlation coefficient was used to explore the correlation between short-term memory and intentionality in left- and right-handers separately, and Bonferroni correction was applied to maintain an overall 0.05 significance level. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.17) software.

9.2 RESULTS

Descriptive statistics for all variables used in the analysis, separated by handedness, are summarised in Table 9.1. Correlation analysis revealed a positive significant relationship between intentionality and short-term memory in left-handers (r=0.39, *P*=0.015) but not right-handers (r=0.24 *P*=0.12). Although the result for left-handers remains significant after applying Bonferroni correction, i.e. *P*<0.025, a Fisher r-to-z transformation indicates that this correlation between intentionality and short-term memory does not significantly differ between left- and right-handers, i.e. the difference between the two correlation coefficients was non-significant (z=0.73, *P*=0.5).

Table 9.1. Mean (SD) scores for intentionality and short-term memory, raw and relative prefrontal cortex (PFC) volume (cm^3 and %, respectively), total brain volume (cm^3) and age separated by handedness group.

Variable	Total	Right-handers	Left-handers
Age	21.4 (3.0)	21.8 (3.1)	21.0 (2.8)
Intentionality	4.6 (0.6)	4.7 (0.5)	4.5 (0.6)
Short-term Memory	5.5 (0.6)	5.5 (0.6)	5.6 (0.7)
Orbital Volume (cm^3)	55.2 (13.6)	55.9 (13.6)	54.6 (13.8)
Dorsal Volume (cm^3)	114.1 (16.7)	114.4 (16.9)	114.6 (16.2)
Relative Orbital Volume (%)	5.3 (1.0)	5.4 (1.0)	5.3 (1.1)
Relative Dorsal Volume (%)	11.1 (1.3)	11.2 (1.3)	11.0 (1.2)
Total Brain Volume (cm^3)	1032 (114)	1028 (128)	1036 (99)

Stereological volume estimates and intentionality

A linear mixed-effects model was fitted using PFC volume as the outcome variable. Predictor variables included in the final model were: intentionality, hemisphere volume, hemisphere side (left/right), handedness (right/left), region1 (dorsal/orbital), region2 (lateral/medial), and the following interaction terms: hemisphere side*region1, handedness*intentionality, handedness* region1, region1*intentionality and a three-term interaction between intentionality*handedness*region1 to take into account the effect of handedness on the association between intentionality and orbital and dorsal

PFC volume. These variables were selected for inclusion following a stepwise selection approach. The factors age, sex, short-term memory and interactions between intentionality, short-term memory, hemisphere side and region2 did not significantly improve the model fit (*P*>0.05) and were subsequently excluded from the final model.

Results for the mixed-effects model can be seen in Table 9.2. Handedness is significantly associated with dorsal PFC volume (cm^3) (*P*=0.003, coefficient= -11.83, 95%CI: -19.51,-4.14) with right-handers showing significantly greater PFC volume than left-handers. Hemisphere volume is significantly associated with dorsal PFC volume (*P*<0.001, coefficient=0.04, 95%CI: 0.04,0.05), indicating that an increase of, for example, 100cm^3 in hemisphere volume is associated with an increase of 4cm^3 in dorsal PFC volume, for each hemisphere side and for each lateral and medial region. Note that since there are no interaction terms involving hemisphere volume, the effect of hemisphere volume mentioned above also applies to the orbital region. The interaction between intentionality, region1 and handedness is significant (*P*<0.001, coefficient= -4.8, 95%CI: -7.0,-2.6), suggesting an effect of handedness on the association between intentionality and dorsal/orbital PFC volume.

Specific associations were tested for using the esticon function in R software (see Table 9.2, part B). Left-handers show a significant positive association between dorsal PFC volume and intentionality score (*P*=0.004, coefficient=1.57, 95%CI: 0.53,2.6), such that an increase in 1 intentionality score is associated with an increase in 6.28cm^3 of dorsal PFC volume (6.28cm^3=1.57cm^3 x 4 subfields left DL, right DL, left DM and right DM). Right-handers however, show no significant association between dorsal PFC volume and intentionality (*P*=0.15, coefficient= -0.96, 95%CI: -2.27,0.35). Furthermore, the association between dorsal PFC volume and intentionality differed significantly between the handedness groups (*P*=0.004, coefficient= 2.52, 95%CI: 0.87,4.18).

Contrary, following statistical analyses for the region orbital, right-handers instead show a significant relationship between orbital PFC volume and intentionality (*P*=0.01, coefficient= 1.74, 95%CI: 0.44,3.06): an increase in 1 intentionality score is associated with an increase in 6.96cm^3 of orbital PFC volume (6.96cm^3=1.74cm^3 x 4 subfields left OL, right OL, left OM and right OM). No relationship was found between orbital PFC volume and intentionality in left-handers (*P*=0.3, coefficient= -0.54, 95%CI: -1.56, 0.51). Additionally, the association between orbital PFC volume and intentionality differed significantly between the handedness groups (*P*=0.008, coefficient= -2.28, 95%CI: -3.94,-0.61).

Table 9.2. Results for the linear mixed-effects model with PFC volume (cm^3) as the outcome variable. SE= standard error. Results for each variable in the model are shown in part A. Contrasts for each ‘question’ asked using the esticon function in R software are given in part B. Significant results are highlighted in grey. LH=left-handers, RH=right-handers.

	Predictor variables	**Coefficient**	**SE**	***P*-value**	**95% CI**	
					Lower	**Upper**
A. Predictor variables in the model						
	Intentionality	-0.96	0.66	0.15	-2.26	0.34
	Handedness (*0: right, 1: left*)	-11.83	3.9	0.003	-19.51	-4.14
	Region 1 (*0: dorsal, 1: orbital*)	26.29	4.19	<0.001	-34.43	-18.14
	Region 2 (*0: lateral, 1: medial*)	2.65	0.3	<0.001	2.07	3.24
	Side (*0: left, 1: right*)	1.15	0.42	0.007	0.33	1.97
	Hemisphere volume	0.04	0.003	<0.001	0.04	0.05
	Handedness*Intentionality	2.52	0.84	0.004	0.87	4.18
	Region 1*Hand	21.87	5.26	<0.001	11.63	32.11
	Region 1*Intentionality	2.7	0.89	0.002	0.98	4.43
	Region 1*Side	-1.98	0.6	0.001	-3.14	-0.82
	Region 1*Hand*Intentionality	-4.8	1.13	<0.001	-7.0	-2.6
B. Associations between PFC volume and intentionality for each dorsal/orbital region and handedness group.						
Dorsal	**Left-handers**	1.57	0.52	0.004	0.53	2.6
	Right-handers	-0.96	0.66	0.15	-2.27	0.35
	Differences in association between LH and RH	2.53	0.84	0.004	0.87	4.18
Orbital	**Left-handers**	-0.54	0.52	0.3	-1.56	0.51
	Right-handers	1.74	0.66	0.01	0.44	3.06
	Differences in association between LH and RH	-2.28	0.84	0.008	-3.94	-0.61

Bonferroni correction can be applied to take into account the number of hypotheses tested from the linear mixed-effects model, while maintaining the overall significance level to 0.05. Bearing in mind that 6 hypotheses have been tested regarding the association with intentionality (see Table 9.2B) the adjusted significance level becomes 0.008 (=0.05/6). The *P*-values obtained are therefore significant after correcting for multiple comparisons for most of the cases (the *P*-value corresponding to the association between orbital PFC volume and intentionality in right-handers is above 0.008, but nevertheless very close to the significance boundary).

Figure 9.1 illustrates intentionality scores against orbital and dorsal PFC volume in both left- and right-handers. Trend lines show a positive association between orbital PFC volume and intentionality in right-handers, but no association between orbital PFC volume and intentionality in left-handers; conversely a positive association can be seen between dorsal PFC volume and intentionality in left-handers, but not in right-handers. This illustration provides visual support for the results of the linear mixed-effects models (see Table 9.1 for statistical significance of these associations), although the associations shown in Figure 9.1 do not control for overall brain volume.

Pearsons product-moment correlations were performed to test the strength and direction of the relationship between raw orbital PFC volume and intentionality in separate groups of left- and right-handers and the relationship between raw dorsal PFC volume intentionality in separate groups of left- and right-handers. These associations can be seen in Figure 9.1. A Fisher r-to-z transformation was applied to test the difference in the correlations between raw orbital PFC volume and intentionality and between raw dorsal PFC volume and intentionality in right-handers: results were significant (z=1.67, *P*=0.048). A second Fisher r-to-z transformation was performed to test the difference in the correlations between raw orbital PFC volume and intentionality and between raw dorsal PFC volume and intentionality in left-handers: results were significant (z=1.78, *P*=0.038).

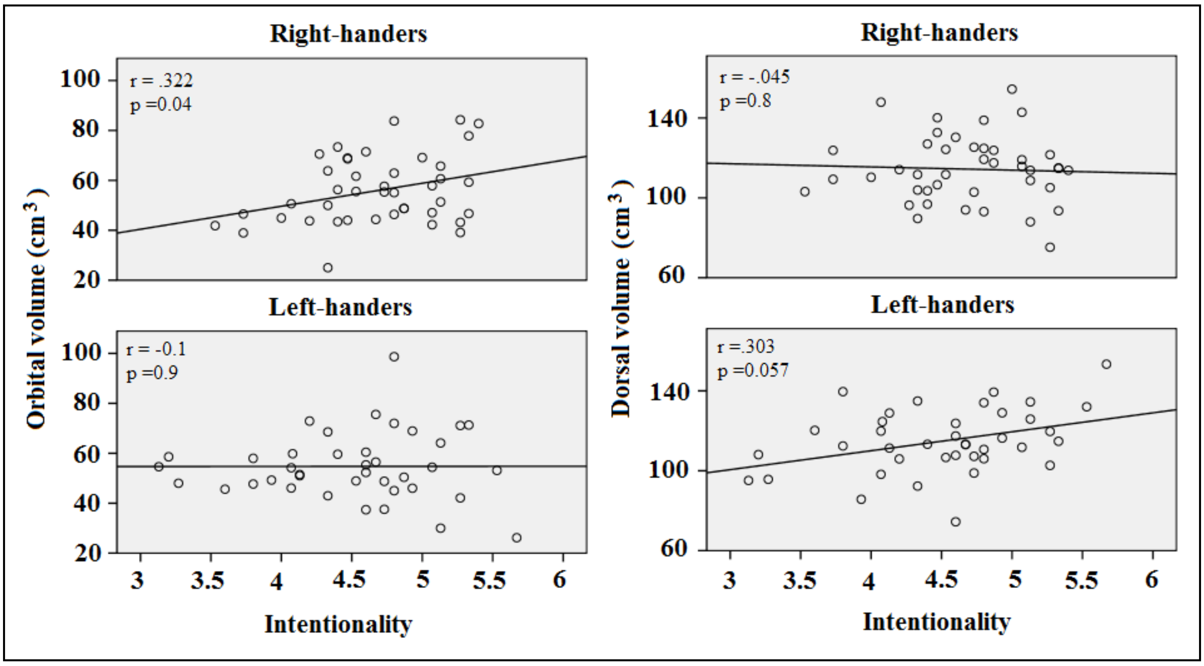


Figure 9.1. Correlations between intentionality scores and both raw orbital PFC volume (cm^3) and raw dorsal PFC volume (cm^3), separated by handedness group. Pearsons product-moment correlational analysis was performed to test the relationship between orbital PFC volume and intentionality and dorsal PFC volume and intentionality in separate groups of left- and right-handers. Results from the correlational analysis can be seen in each scatterplot.

9.3 PRELIMINARY DISCUSSION

The association found between orbital PFC volume and intentionality in right-handers was expected based on the findings from a previous study (Powell *et al.*, 2010). In left-handers an association between dorsal PFC volume and intentionality was found. These associations were found to be signficiantly different between the handedness groups. Also results showed that the association between intentionality and orbital PFC volume differed from the association between intentionality and dorsal PFC volume in both right-handers and left-handers. One explanation is that left- and right-handers show different neural organisation for intentionality, which might explain why they achieve similar intentionality score despite different localisation of intentionality. This localisation may however change in the course of development, although further research would be required to clarify this.

CHAPTER 10:

DISCUSSION AND CONCLUSION

10.1 SUMMARY OF RESULTS

The first aim of the thesis was to establish differences in brain structure and function between left- and right-handed individuals and the second main aim was to explore the effect of handedness on the neuroanatomical correlates of intelligence. A summary of the results for each of the main aims is given below. A summary of the main results is presented visually in Figure 10.1. The main variables (or categories) explored in this thesis in relation to handedness are brain structure, function and cognitive ability. The outcome variables which are significantly associated with handedness are given in the yellow squares (in Figure 10.1) and the lines joining the squares indicate a link between each category and outcome variable.

Aim I: Brain structure and handedness

Behavioural lateralities and parental handedness:

- A right foot preference was found significantly more often in right-handers than left-handers (79 vs. 50% respectively). No significant association was found between handedness and eye preference.
- A significant association was found between parental and offspring handedness: the odds of being left-handed are approximately 13 times greater when the father is left-handed than when the father is right-handed.

Sulcal contours:

- The interaction between handedness and hemisphere side is significant for the inferior frontal sulcus (IFS) and indicates that, while in right-handers the most common hemisphere with a discontinuous IFS is the right, in left-handers it is the left.

PO and PTR volume:

- Relative PO volume was leftward (left-greater-than-right) in right-handed males, non-asymmetrical (i.e. did not differ between the hemispheres) in right-handed females, and was rightward in left-handed males and females. Significant differences in PO asymmetry between right- and left-handers were found.
- Left hemisphere relative PO volume differed significantly between right and left-handers. No significant difference was found between the handedness groups for right hemisphere relative PO volume.
- Leftward PTR volume was found in right-handed males and females, and non-asymmetrical PTR volume was found in left-handed males and females.

White matter anisotropy:

- Greater anisotropy was found in right-handers than left-handers in the uncinate fasciculus (UF) within the limbic region and in regions of WM within the prefrontal lobe, medial and inferior frontal gyri (IFG).
- Both groups presented leftward FA asymmetry in regions of the IFG, uncinate fasciculus (UF) and arcuate fasciculus (AF).
- Rightward FA was observed in middle temporal gyrus, posterior cingulum and the genu of the corpus callosum in both handedness groups.

Language laterality and spatial laterality:

- Significantly greater leftward language laterality was found in right-handers than left-handers. No significant difference was found for spatial lateralization between the handedness groups.
- Sex was significantly associated with activation in the left and right IFG in response to the word generation task with males showing greater activation than females.
- A significant effect was found for handedness on language activation in right IFG but not left IFG: left-handers showed significantly greater activation than right-handers in the right IFG.
- Dissociated language and spatial laterality was found in 65% of subjects and associated laterality was observed in 35% of subjects suggesting that dissociated laterality is not the rule but is observed in the majority of cases.

Aim II: Handedness, brain structure and cognitive functioning

Handedness, language laterality, spatial laterality and executive function:

- Left-handers showed significantly lower working memory score than right-handers.
- Rightward language lateralization was associated with a reduction in working memory score.
- When language and spatial lateralization were dissociated between the hemispheres a significant increase in verbal comprehension and perceptual organisation performance was found.

Fluid and crystallised intelligence, GM volume and handedness

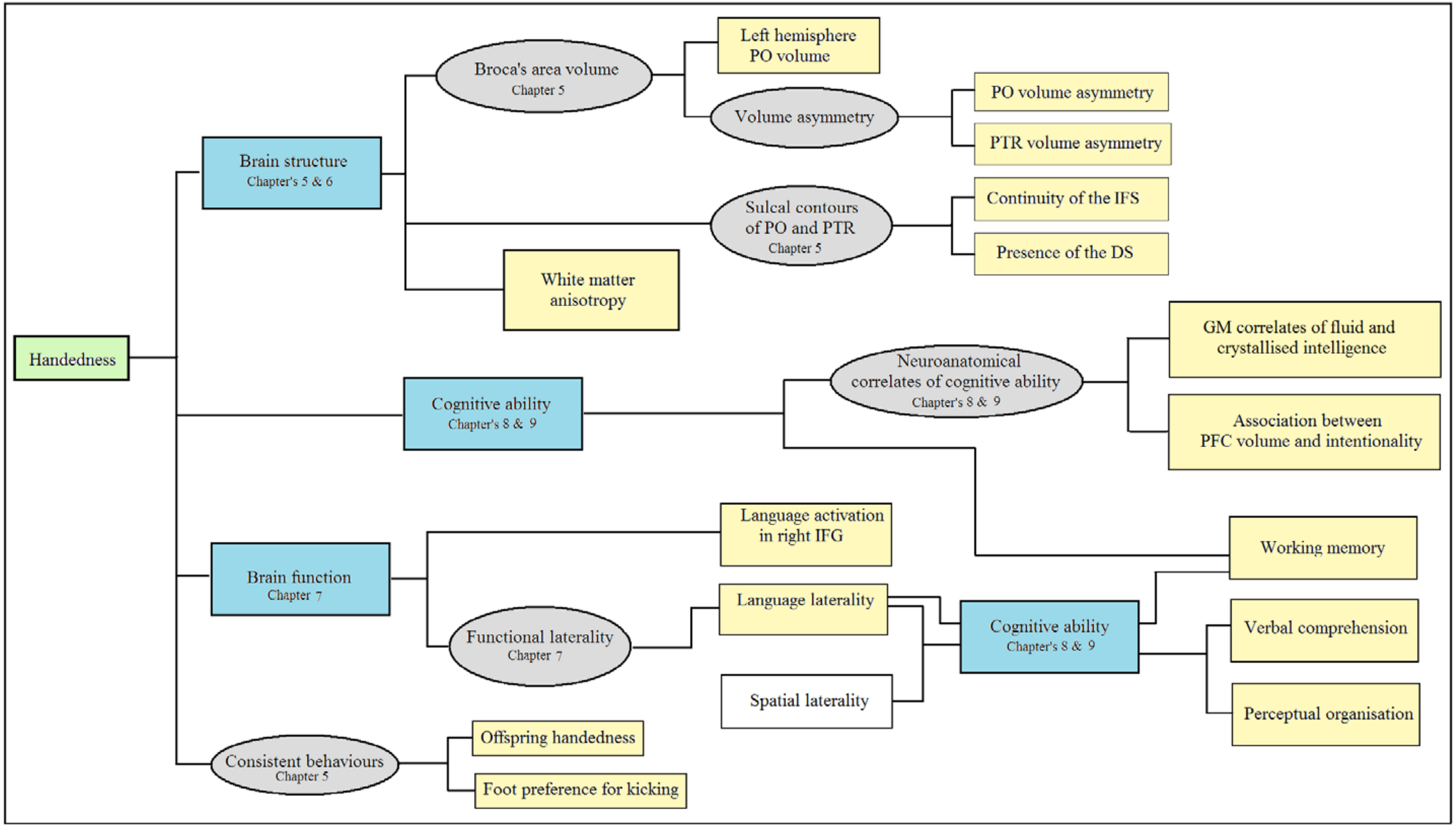
- Fluid intelligence was correlated with GM volume primarily in lateral and inferior frontal lobe (BA8, BA9, BA11 and BA47), inferior temporal gyrus (BA37), posterior cingulate cortex (BA31) and lingual gyrus (BA18) within the occipital lobe.
- Correlations were found between crystallised intelligence and GM volume in medial-superior frontal gyrus (including BA6, BA8 and BA9) and cuneus (BA7).
- Results showed significant differences in the GM correlates of fluid intelligence between the handedness groups in left hemisphere inferior (BA20) and superior (BA22) temporal gyrus.
- Significant differences in the GM correlates of crystallised intelligence was found between the handedness groups in bilateral superior temporal gyrus (BA38) and left middle frontal gyrus (BA8 and BA11) and right precuneus (BA7).

Handedness, prefrontal volume and intentionality

- In right-handers there was a significant correlation between intentionality and orbital PFC volume (6.96cm^3 volume increment per intentionality level). In left-handers there was a significant correlation between intentionality and dorsal PFC volume (6.28cm^3 volume increment per intentionality level).
- Direct comparisons showed a statistically significant difference in this association between handedness groups.

- An association was found between intentionality and short-term memory in left-handers but not right-handers.

Figure 10.1. A visual summary of the main significant results obtained in this thesis. The figure shows the effect that handedness has on brain structure, function and cognitive ability (blue squares) which are the main broad categories explored in this thesis in relation to handedness. Sub-categories are shown in grey ovals. For instance, volume asymmetry is one sub-category of Broca's area volume and Broca's area volume is one sub-category of brain structure. Behavioural laterality is classed as a sub-category as it is not considered part of one of the main categories explored in this thesis. Yellow squares represent the main significant outcomes. Lines represent associations between the categories, sub-categories and significant outcomes. For instance, handedness has an effect on the neuroanatomical correlates of cognitive ability as well as having a direct relationship with working memory score. Additionally, handedness has an effect on language laterality but not spatial laterality (hence the square is not coloured), however the association between language laterality and spatial laterality is associated with verbal comprehension and perceptual organisation (thus spatial laterality is included in the figure), whereas language laterality by itself is directly associated with working memory score. As such the lines can be used to trace a route between handedness and each of the outcomes. The chapter's where each category, sub-category and outcome can be found is shown. PO=pars opercularis, PTR=pars triangularis, IFG=inferior frontal gyrus, IFS=inferior frontal sulcus, DS=diagonal sulcus, PFC=prefrontal cortex.


Handedness
Brain structure
Chapter's 5 & 6
Broca's area volume
Chapter 5
Left hemisphere PO volume
Volume asymmetry
PO volume asymmetry
PTR volume asymmetry
Sulcal contours of PO and PTR
Chapter 5
Continuity of the IFS
Presence of the DS
White matter anisotropy
Cognitive ability
Chapter's 8 & 9
Neuroanatomical correlates of cognitive ability
Chapter's 8 & 9
GM correlates of fluid and crystallised intelligence
Association between PFC volume and intentionality
Brain function
Chapter 7
Language activation in right IFG
Working memory
Functional laterality
Chapter 7
Language laterality
Spatial laterality
Cognitive ability
Chapter's 8 & 9
Verbal comprehension
Perceptual organisation
Consistent behaviours
Chapter 5
Offspring handedness
Foot preference for kicking

10.2 METHODOLOGY AND LIMITATIONS

Observer-based vs. VBM-type methods for volume estimates

Stereological volume estimates of the PO, PTR, PFC and hemispheres were obtained from T_1-weighted MR images to investigate: (i) the effect of handedness and sex on PO and PTR volume and volume asymmetry (Chapter 5) and (ii) the effect of handedness on the association between intentionality and PFC volume (Chapter 9). VBM was performed on the T_1-weighted MR images to investigate the association between cognitive ability and GM volume in left- and right-handers (Chapter 8).

Manual-based methods, such as stereological methods, where the structure of interest is identified and analysed by an expert in brain anatomy, are generally regarded as the *gold standard*. Stereological methods have been used to obtain anatomical measurements of the PO, PTR and PFC (Cowell *et al*., 2007; Foundas *et al*., 1996, 1998, 2001; Howard *et al*., 2003; Keller *et al*., 2007; Knaus *et al*., 2006, 2007; Tomaiuolo *et al*., 1999). It has the advantage of detecting subtle asymmetries in brain regions that are morphologically variable between hemispheres and individuals. Manual techniques require experienced raters with detailed knowledge of neuroanatomy resulting in volumes which can be confidently ascribed to the ROI. On the other hand, manual techniques have practical drawbacks including increased labour intensity which results in reduced time efficiency, particularly when dealing with large samples of subjects (Ashburner and Friston, 2000). They also require the researcher to determine a priori ROIs limiting any analysis to those specific regions. This is in contrast to VBM which allows the investigator to detect differences in GM and WM volume across the whole brain at the voxel level.

Previous research has applied the principles of stereology in healthy (e.g., Howard *et al*., 2003; Mackay *et al*., 1998; Roberts *et al*., 2000; Sheline *et al*., 1996) and clinical populations (e.g., Keller *et al*., 2002; MacKay *et al*., 2000) to measure regional brain volumes on MR images. Moreover, point counting, in combination with the Cavalieri method, has been shown to have excellent inter- and intra-rater reliability (Cowell *et al*., 2007; Doherty *et al*., 2000; Howard *et al*., 2003; Mackay *et al*., 1998, 2000; Keller *et al*., 2002, 2007). Keller *et al* (2007) for instance, demonstrated reliability in the repeatability of measurements of the PO, PTR and planum temporale using stereological methods. This method of volume estimation is generally believed to be both more efficient and more precise than manual tracing of transect areas (Gundersen and Osterby, 1981). Inter-rater analysis was performed on PO, PTR and PFC volume estimates showing good inter- and intra-rater reliability (see Section 4.4.2 for study and results).

In contrast to manual techniques which are dependent on pre-defined ROIs, VBM-type methods are approaches to quantifying group differences in cortical morphology that do not require pre-defined ROIs and require less observer interaction when calculating brain volumes. VBM studies which do not rely on sulcal contours for anatomical specificity may distort directional asymmetry of homologous regions of cortex through spatial normalisation of images to stereotaxic space (Hammers *et al*., 2007). VBM is a powerful tool for identifying differences in brain morphology between two distinct subject groups but VBM may not be sensitive enough to detect subtle morphological differences between similar groups of subjects, or to detect subtle atrophy in areas where there is a lot of variation. Using both methodological techniques will help provide confirmatory evidence of regional volume differences between two groups of subjects.

Data analysis of diffusion weighted images

Diffusion-weighted images were obtained to investigate the effect of handedness on WM anisotropy and anisotropy asymmetry (Chapter 6). Diffusion tensor imaging measures water movement on the micron scale and yields information about the WM fibres that pass within a voxel. In WM, water molecules encounter many aligned structures including protein filaments, cell membranes and myelin, as well as a dense array of various kinds of glial cells, including oligodendrocytes that are unique to WM (Beaulieu, 2002; Shimony *et al*., 1999). The microscopic information is averaged over the voxel volume (Mori and Zhang, 2006). Thus changes in diffusion anisotropy do not necessarily result from changes in cellular level structures such as myelin and axons; it could be due to the reorganisation of axons at macroscopic levels (Mori and Zhang, 2006). Additionally in areas of tissue partial volume (where WM/GM or WM/CSF reside in the same voxel) or of WM partial volume (where two fibre systems cross the same voxel, often in different orientations) the DTI model will fail (Jansons and Alexander, 2003; Papadakis *et al*., 1999; Tuch *et al*., 2002). Indeed, areas of WM where two or more fibre systems pass within the same voxel will appear hypointense and will interpreted as low anisotropy (Assaf and Pasternak, 2008).

Calculation of the laterality index

Functional MR images were obtained to explore language and spatial processing in left- and right-handed individuals (Chapter 7). Laterality indices were computed for both language and spatial tasks within ROIs using a bootstrapping approach (see Wilke and Lidzba, 2007; Wilke and Schmidhorst, 2006). While the bootstrapping approach used in the studies presented in Chapter 7, can be seen to circumvent a number of problems associated with the classical LI calculation approach (see Wilke and Schmidhorst, 2006), there are a number of inherent problems with the principles of calculating a LI. Firstly, a LI represents the extent to which activation occurs in a ROI in one hemisphere compared to the corresponding ROI in the opposite hemisphere for a particular task. This represents a comparison of activation between two hemispheres within the same individual. When comparing individuals the LI does not take into account the absolute degree of activation of one hemisphere in one individual compared to the same hemisphere in another individual. Thus a greater degree of activation may be observed in both hemispheres in one individual compared to that in another individual and yet they may present the same LI value. Understanding hemispheric dominance and degree of activation may be equally important when understanding their biological and behavioural relevance. Whether a hemisphere is simply dominant or not may not always provide the most biologically meaningful interpretation. The advantages of the bootstrapping approach used in this thesis to calculate LIs are given in Section 4.5.5.

Neuropsychological assessment

A battery of neuropsychological tests was administered to participants, which included sub-tests from the Wechsler Adult Intelligence Scale – version III (WAIS-III), an imposing memory task (IMT) and the Edinburgh Handedness Inventory (EHI). The WAIS-III was used to assess metacognitive EFs specifically: working memory, verbal comprehension and perceptual organisation (see Section 4.2.2). The WAIS-III is a standardised task for assessing metacognitive EFs and has been used repeatedly in cognitive neuroscience to explore the neuroanatomical correlates of intelligence (e.g. Frangou *et al*., 2004; Haier *et al*., 2004; Lee *et al*., 2005; Schmidthorst *et al*., 2005; Shaw *et al*., 2006; Wilke *et al*., 2003). According to Wechsler, intelligence is influenced by personality traits and other non-intellectual components, such as, anxiety, persistence and goal awareness (Lichtenberger *et al*., 2002). The implication here is that despite assigning an individual a score for each sub-test it is important to consider the possibility that this score is susceptible to environmental and internally generated components.

In this thesis, intentionality was assessed using a 'false belief task' called the Imposing Memory Task (IMT) (Powell *et al*., 2010; Stiller and Dunbar, 2007). An intentional capacity is perhaps most clearly demonstrated in 'false belief' tasks (the belief that something is true when it is not), because this requires an appreciation of the thoughts and beliefs of another based on understanding that person's perspective and a distinction between own and other beliefs (Sommer *et al*., 2007; Van Overwalle, 2009). A number of ToM studies employing true and false belief stories highlight the importance of both dorsomedial PFC (Ferstl and von Cramon, 2002; Perner *et al*., 2006; Saxe and Powell, 2006; Vogeley *et al*., 2001) and orbitomedial PFC (Saxe and Kanwisher, 2003; Saxe and Powell, 2006; Vogeley *et al*., 2001; Wang *et al*., 2006) for intentionalizing ability. Verbal stories may require more cognitive or complex processing subserved by dorsomedial PFC (Amodio and Frith, 2006; Leslie, *et al*., 2004; Northoff and Bermpohl, 2004). Alternatively verbal stories, being typically richer in socially relevant context, may induce participants to infer not only action goals but also traits of the actors involved, which would involve orbital PFC. Therefore the task used may have an effect on the results found. This suggests future research may wish to consider the effect that handedness has on intentionality when other tasks are employed. Additionally, future research may wish to replicate this study using functional MR imaging to provide evidence of the functional correlates of intentionality in left- and right-handers.

The main limitation on the IMT is a lack of standardisation. It was first constructed by Stiller and Dunbar (2007), underwent a number of revisions and was used by Powell *et al* (2010) to distinguish between levels of intentionality within participants aged 18-47 years. Perhaps the main strength of the IMT relates to its construct validity. The IMT assesses both intentionality and short-term memory capacity, and are found to be distinct in right-handed individuals i.e. no correlation is found between these two variables (Powell *et al.*, 2010) indicating that the task can be reliably used to assess intentionality competence.

10.3 INTERPRETATION

Overall the results indicate that there are differences between the handedness groups in terms of brain structure and brain function including brain sulci, GM volume, WM anisotropy and language processing. Furthermore, there are differences in the neuroanatomical correlates of intelligence including intentionality, fluid and crystallised intelligence.

The novel findings in this thesis are: (i) a relationship between handedness and sex on PO volume asymmetry, (ii) an effect of handedness on the sulcal contours defining the PO and PTR, and (iii) greater anisotropy in right- than left-handers in regions throughout the frontal lobe and in regions of the temporal lobe. This thesis presents for the first time (iv) voxel-wise statistical analysis of asymmetric FA images in a large cohort composed solely of left-handers. Moreover, presented here for the first time is (v) a relationship between language and spatial laterality interaction and the cognitive variables: verbal comprehension and perceptual organisation. This thesis also contributes to the literature in this field by showing for the first time (vi) the neuroanatomical correlates of intentionality in a cohort comprised solely of left-handers, (vii) differences in the neuroanatomical correlates of intentionality between left- and right-handers, and (viii) significant differences in the GM correlates of fluid and crystallised intelligence.

Sulcal contours in the brain

The effect of handedness on sulcal contours in the brain.

In right-handers the inferior frontal sulcus (IFS) is discontinuous more often in the right than the left hemisphere (62% vs. 43%), while in left-handers it is discontinuous more often in the left than the right hemisphere (65% vs. 48%) although the difference in left-handers was not significant. The present study supports that of previous studies which suggest variability in the continuity of the IFS (Keller *et al.*, 2007, 2009b; Ono *et al.*, 1990) and this can be seen in Table 10.1 which shows continuity of the IFS in the left and right-hemisphere in each study reviewed. Findings in the left hemisphere in right-handers (i.e. 43%) are similar to previous reports (ranging from 40-46%), whereas a discontinuous IFS in the left-hemisphere in left-handers (i.e. 65%) occurred more often than has previously been reported in right-handers. A greater degree of variability of discontinuous IFS is seen in the right hemisphere (see Table 10.1). Results for either handedness group however, cannot be compared directly to these previous studies as Keller *et al* (2007) used a sample of left- (n=13) and right- (n=37) handed subjects, Ono *et al* (1990) do not report the number of right-handed subjects studied in their sample of 2 post-mortem brains and Keller *et al* (2009b) do not report handedness in their sample of 30 subjects.

Variability is further reported in connection patterns between the IFS and IPCS, the incidence of ‘no connection’ between these two sulci ranging from 12% to 33% (Ono *et al.*, 1990; Keller *et al.*, 2007). The current study reports no connection in 19% left and 29% right hemispheres for right-handers and 30% left and 25% right hemispheres for left-handers, all within the range reported in previous studies.

The second significant association related to the sulcal contours was between presence of the DS and handedness. The probability of presence of the diagonal sulcus (DS) is higher in the right than in the left hemisphere for left-handers (63% vs. 28%), although not significantly so for right-handers (64% vs. 45%). Table 10.1 shows the percentage of left and right hemispheres presenting a DS which have been reported in a number of different studies. It can be seen that the DS was present almost as often in the right hemisphere in left- (63%) and right-handers (64%), a figure which is the same as that reported by Ono *et al* (1990) i.e. 64% for right-handers at least. The presence of the DS has been associated with increased PO volume (Keller *et al.*, 2007, 2009b), presumably as a result of increased intrasulcal area which the DS creates.

Table 10.1. Percentage of individuals with a discontinuous IFS and present DS in five different studies including the present study. Figures are given in percentages. RH=right-handers, LH=left-handers, nr=not reported.

	Discontinuous IFS		**Presence of DS**	
	left hemisphere	**right hemisphere**	**left hemisphere**	**right hemisphere**
Present Study n=42RH, 40LH	RH: 43% LH: 65%	RH: 62% LH: 48%	RH: 45% LH: 28%	RH: 64% LH: 63%
Keller *et al* (2009b) n=30, handedness=nr	43%	37%	nr	nr
Keller *et al* (2007) n=37RH, 13LH	46%	50%	52%	20%
Ono *et al* (1990) n=25, handedness=nr	40%	56%	72%	64%
Galaburda (1980) n=102, handedness=nr	nr	nr	26.5%	12.75%

Whilst differences in the sulcal contours defining the PO and PTR are found the functional role of the sulci is not clear. One suggestion is that the sulci increase the surface area of a region and therefore the neuronal number underlying the surface area. This would then increase the information processing capacity (IPC) of the area (see Section 2.4 for the functional interpretation of surface area). For instance, the presence of the DS in the PO is thought to increase the surface area of the region thereby increasing its IPC (Keller *et al*., 2007). In this thesis presence of the DS is similar in the right hemisphere in left- and right-handers and both handedness groups show similar right hemisphere PO volume. However a DS is present more often in the left hemisphere PO in right- than left- handers and this may explain the significantly larger left hemisphere PO volume right- than left-handers. An increase in neuronal number would then increase the IPC of the region and may explain the greater involvement of the left hemisphere is language in right-handers than left-handers.

Broca's area volume

Relative pars opercularis and pars triangularis volume

The results presented in Chapter 5 showed leftward PO volume asymmetry in right-handed males only, with no significant difference (in fact no numerical mean difference at all) between left and right PO in right-handed females. Male and female left-handers showed rightward PO volume asymmetry. Significant differences in PO asymmetry were found between left- and right-handed males and between left- and right-handed females. This supports previous studies which have shown leftward asymmetry of the PO (e.g. Foundas *et al*., 1998; Uylings *et al*., 2006). For example, in a post-mortem study Uylings *et al* (2006) found greater PO volume in the left hemisphere in all 10 subjects (5 male): asymmetry was only significant for the subgroup of males. These findings resemble the present results in right-handers however, handedness was not reported by Uylings *et al* (2006).

The findings indicating symmetry of PO volume (i.e. no signficiant difference between left and right PO volume) in right-handed females support previous studies which indicate hemispheric specialisation is less marked in females (Baxter *et al*., 2003; Gur *et al*., 2000; Jaeger *et al*., 1998; Kansaku *et al*., 2000; Rossell *et al*., 2002; Shaywitz *et al*., 1995; Vikingstad *et al*., 2000).

Significant differences in PO volume asymmetry were found between left- and right-handed males. The effect of handedness seems to be greater for males; this is supported by VBM studies on structural images (Pujol et al., 2002; Watkins et al., 2001), as well as morphology (Witelson and Kigar, 1992), morphometry (Witelson, 1989) and DTI (Hagmann et al., 2006) studies using healthy subjects. For instance, Witelson (1989) found that handedness was a factor in corpus callosum size for males but not females. Witelson and Kigar (1992) documented anatomical details of the Sylvian fissure as a measure of language lateralisation in 67 post-mortem brains (24 males), and found that these correlated with handedness in males but not females: specifically, right-handed males had longer horizontal Sylvian fissure segments in both hemispheres than males who were not consistently right-handed, while the direction and magnitude of asymmetry did not differ between these two groups. No significant difference in PO volume asymmetry was found between left- and right-handed females, which supports the above literature.

Whilst the results demonstrate significantly larger left PO volume in right-handers than left-handers, no significant difference was found for right PO volume. This suggests that the significant difference in PO asymmetry between the handedness groups is the result of smaller left PO volume as opposed to increased right PO volume. This interpretation is similar to that of Foundas *et al* (2002), who investigated asymmetry of the planum temporale in 37 right-handers and 30 left-handers and found that only the size of the left planum was significantly related to handedness: in this sample right-handers had significantly larger left planum than left-handers. The present findings also indicate that volume of the right PO is less variable than the left PO across handedness and sex groups.

Right-handed males and right-handed females had larger left-than-right relative PTR volume, whilst left-handed males and left-handed females showed no significant difference between left and right PTR. The present findings appear to be consistent with that of previous studies which show a greater degree of variability in PTR asymmetry in left-handers compared to right-handers (e.g. Foundas *et al.*, 1995, 1998). For instance, Foundas *et al* (1995) showed that 7/8 (88%) right-handers had a larger PTR on the left, with more variable asymmetry in left-handers. Additionally, Foundas *et al* (1998) found a significant leftward asymmetry of the PTR in right- and left-handers, although this asymmetry was reduced in left-handers who presented leftward asymmetry in 9 out of 16 cases, compared to 11 out of 16 cases in right-handers. Overall findings from the present study are consistent with studies reporting significant leftward volume or surface area asymmetries of the PTR, particularly in right-handed people (Foundas *et al.*, 1995, 1996, 1998, 2001).

No effect of sex was found on PTR volume asymmetry. A number of studies have reported an effect of sex on brain structure and function (for a review see Cosgrove *et al.*, 2007), however, a meta-analysis of the fMRI data from 2,151 subjects from 26 studies found no effect of sex on language lateralization (Sommer, 2010). Inconsistent findings related to the effect of sex on language lateralization suggest that the difference, if any, in the functional organisation of language and language associated cortex is small. The findings indicate that the effect of sex on brain structure is highly variable and not always consistently observed in language associated cortex.

Cytoarchitectonic and anatomical definitions of the PO and PTR

Research suggests different roles for the PTR and PO in language tasks, which are often thought to correspond with the cytoarchitectonic definitions of BA45 and BA44 respectively. Paulesu *et al* (1997) for example, demonstrated that PTR was activated with phonemic and semantic fluency tasks, whereas PO showed activation only with the phonemic fluency task. Costafreda *et al.* (2006) demonstrated in a meta-analysis that whereas semantic fluency tasks tended to activate a more ventral-anterior portion of the IFG (roughly corresponding to BA45), phonological fluency appeared to involve a more dorsal-posterior aspect (approximately BA44). In Heim *et al* (2008) semantic, syntactic and phonological fluency tasks were found to involve both BA44 and BA45, although phonological fluency was found to activate BA44 more strongly than semantic or syntactic fluency.

Additionally comparisons between studies are difficult to make when PO and PTR regions are defined with respect to cytoarchitectonic features. The cytoarchitectonic differentiation of the IFG proposed by Brodmann (1909) was based on the layering of the isocortex and the presence of particular cell types therein. According to this criterion, Broca's area is divided into a more posterior part of the IFG (i.e. BA44) from the more anterior BA45 (Amunts *et al.*, 1999). Cytoarchitectonic studies examining anterior and posterior speech regions of the IFG have reported a leftward asymmetry of area 44 and/or area 45 (Amunts *et al.*, 1999, 2003; Hayes & Lewis, 1993, 1995; Uylings *et al.*, 2006). These regions are argued to be the closest cellular sub-regions to the PO and PTR, respectively, although they do not correspond exactly (Keller *et al.*, 2007). Amunts *et al* (1999) demonstrated that borders of cytoarchitectonically defined brain areas such as BA44 or BA45 do not necessarily coincide with sulcal landmarks. Given the lack of macroscopic-microscopic correspondence, the current study uses sulco-gyral contours to define PO and PTR cortical regions. Results in the study presented in Chapter 5 concur with that reported by Keller *et al* (2007) who conclude that the sulcal contours defining the PO and PTR are naturally variable between people making a standard definition of these regions difficult, hampering cross-study comparisons.

Behavioural lateralities

Parental handedness and behavioural lateralities

Results presented in Chapter 5 showed a significant association between parental handedness and the handedness of the participant, with the odds of being left-handed 13 times greater when the father is left-handed than when the father is right-handed. The number of left-handers with a left-handed father was much greater than that seen in right-handers (36.8% vs. 4.8% respectively). The number of left-handers with a left-handed mother was also larger than that seen in right-handers (18.4% vs. 9.5% respectively), however no significant association was found between participant handedness and that of their mother. Additionally two right-handed parents were seen more often in right-handers (85.7%) than left-handers (47.4%). The findings here support previous literature which indicates that two right-handed parents produce the fewest number left-handed offspring (McManus, 1991; McKeever, 2000). However findings in this study suggest stronger paternal influences on offspring handedness which is in contrast to that reported by McManus (1991) and McKeever (2000) who report stronger maternal influences on offspring handedness. There are however, limitations to the way in which parental handedness is assessed. In this thesis participants were asked to report their parents writing hand (if known). This does not preclude the possibility that the parent writes with the left hand but performs the majority of tasks with the right hand for instance. Future research should consider assessing parental handedness using the EHI to get an indication of the degree of hand preference not just hand direction for writing.

Results showed a significant association between handedness and foot preference for kicking with 78.6% of right-handers and 50% of left-handers showing a right foot preference and 40% of left-handers and 7.1% of right-handers showing a left foot preference. Nachshon *et al* (1983) found in a sample of children consisting of approximately 80% right-handers, that 80% of subjects reported a right-foot preference which is similar to the right foot preference reported in the sample of right-handers in the present study. Gabbard (1992) investigated hand and foot preferences in children aged 3-to-5 years. The majority of the sample (i.e. 75%) reported a right-hand preference, and most of these showed concordant right-hand and foot preference (52%) and right-hand, mixed-foot preference (23%). Of the right-handers in the study 67% were concordant for foot preference. Only 19% of left-handers presented concordant hand-foot preference. Although concordance rates in the study reported by Gabbard (1992) are much lower than that observed in the present study right-handers still show a much higher concordance rate between hand and foot preference than left-handers.

No significant association was observed between hand and eye preference in Chapter 5, although marginally more right-handers than left-handers showed a right eye preference (i.e. 52.4% vs. 40% respectively). Nachshon *et al* (1983) also reported that 50% of children reported a right-eye preference which is not that dissimilar to that reported right-handers in the present study. A meta-analysis of the handedness and eye dominance literature was performed by Bourassa (1996). This was based on 54,087 individuals from 54 different populations. Results showed that in a population consisting of 9.25% left-handers and 36.53% left-eyedness, 34.43% of right-handers and 57.14% of left-handers present a left-eye preference. An overall left-eye preference was observed in 29.3% of subjects, which was higher in left- than right-handers (i.e. 37.5% vs. 21.4% respectively). These figures are lower than that reported by Bourassa (1996) however the present study is consistent in the fact that left-eyedness is reported in more left-handers than right-handers.

In the study presented in Chapter 5 consistent hand, foot and eye preference was found in 32% of participants overall: 40% of right-handers and 22.5% of left-handers. The results for right-handers are similar to that reported by Nachshon *et al* (1983) who found consistent hand, foot and eye lateralities in 37% of right-handers. However, results for consistent laterality in left-handers are much larger in the present study compared to that reported by Nachshon *et al* (1983) (i.e. 22.5% vs. 3% respectively). These results suggest that right-handers present consistent laterality more often than left-handers. This may reflect a greater degree of cerebral dominance in right-handers than left-handers, the latter of which are more likely to present weaker hemispheric dominance (e.g. Pujol *et al*., 1999). Foot preference for kicking and eye preference was established in the present study using only one question and therefore may be considered a limited assessment of foot and eye preference. An assessment of eye and foot preference using a wider array of tasks might yield different results and future studies may want to consider this.

White matter anisotropy

Arcuate Fasciculus

The AF is a WM pathway reported to be involved in language processing (e.g. Catani *et al.*, 2007; Friederici, 2009). It extends from frontal language cortex (i.e. IFG) to temporo-parietal language regions (Catani *et al.*, 2005, 2007). In the present study which uses 82 subjects (of which 40 were left-handed), a leftward asymmetry of the AF as indicated by the clear C-shaped structure extending from frontal to temporal lobes, supported the findings of Büchel *et al* (2004) who report the same C-shaped structure in two small samples totalling 9 left- and 19 right-handers. The occurrence of the AF in the right hemisphere has been debated, with some authors reporting its presence in only 40% of their 50 right-handed subjects (Catani *et al.*, 2007), and others reporting it in all (e.g. all 12 right-handed subjects in Gharabarghi *et al.*, 2009). Overall asymmetry results shown in Chapter 6 are supported by DT-tractography results which indicate structural differences in the AF between left and right hemispheres (Catani *et al.*, 2007; Glasser and Rilling, 2008; Hagmann *et al.*, 2006; Nucifora *et al.*, 2005; Parker *et al.*, 2005; Powell *et al.*, 2006; Vernooij *et al.*, 2007). The finding of leftward asymmetry of the AF does not rule out the existence of a right hemisphere AF; instead I suggest greater anisotropy of this tract in the left hemisphere. Present findings also support those of Takao *et al* (2011) who showed WM asymmetry in the AF using FA maps. They also report no effect for sex on WM asymmetry which is consistent with the findings in the present study.

A number of studies have used fMRI to explore the association between asymmetry of language-related pathways and language lateralization (Glasser and Rilling, 2008; Hagmann *et al.*, 2006; Powell *et al.*, 2006; Saur *et al.*, 2008; Vernooij *et al.*, 2007), with mixed findings. For example, Powell *et al* (2006) found that subjects with more lateralized fMRI activation presented more highly lateralized mean FA. However, Vernooij *et al* (2007) found an overall significant leftward asymmetry in relative-fibre density of the AF irrespective of handedness or functional language lateralization. These findings challenge the widely held hypothesis that structural asymmetry in language-related brain regions reflects functional language lateralization (Falzi *et al.*, 1982; Foundas *et al.*, 1995; Geschwind and Levitsky, 1968; Good *et al.*, 2001a; Josse *et al.*, 2003; Moffat *et al.*, 1998; Shapleske *et al.*, 1999; Tzourio *et al.*, 1998; Watkins *et al.*, 2001). In this thesis findings show leftward asymmetry of the AF in right- and left-handers, with a greater degree of anisotropy asymmetry underlying superior temporal gyrus in right-handers, a region which corresponds closely to the ventral portion of the AF. However no significant differences in FA asymmetry were observed between the handedness groups. Direct comparisons showed no significant difference in FA asymmetry between the handedness groups suggesting that whilst differences in anisotropy asymmetry between left- and right-handers may be observed in small regions of WM these differences are not statistically significant.

Glasser and Rilling (2008) used fMRI and DT-tractography to examine terminations of the AF in 20 healthy right-handed males. The AF was reported to be composed of two segments, one terminating in the superior temporal gyrus (STG), and the other in the medial temporal gyrus (MTG). STG terminations were strongly left lateralized and overlapped with phonological activations. MTG terminations were also strongly left lateralized, overlapping with left lateralized lexical semantic activations, and smaller right hemisphere MTG terminations overlapped with right lateralized prosodic activations. These findings are supported by functional activations in lexical-semantic, prosodic and phonological processing, which report a left lateralized lexical-semantic system (Ahmad *et al.*, 2003; Binder *et al.*, 1997, 2000; Hickok and Poeppel, 2004; Poeppel *et al.*, 2004; Price, 2000; Vandenberghe *et al.*, 1996), and right lateralized prosodic processing (Ethofer *et al.*, 2006; Meyer *et al.*, 2002; Mitchell *et al.*, 2003; Riecker *et al.*, 2002; Wildgruber *et al.*, 2005). The present study indicates leftward anisotropy along the STG, and rightward anisotropy along the MTG in both groups, which may correspond with the terminations reported by Glasser and Rilling (2008).

Uncinate Fasciculus

The UF is the major fibre tract connecting the orbital frontal cortex and limbic lobe, within the temporal lobe. There are reports of its asymmetry (Hasan *et al.*, 2009; Highley *et al.*, 2002; Kubicki *et al.*, 2002; Park *et al.*, 2004; Yu *et al.*, 2008). In a post-mortem study of 28 brains (15 males, handedness unknown) Highley *et al* (2002) report the UF to be asymmetrical, being 27% larger and containing 33% more fibres in the right than the left hemisphere. This is supported by Yu *et al* (2008) who reported in a voxel-wise study of FA images of 79 right-handers (44 males) rightward anisotropy in a region corresponding to the UF. Other studies exploring anisotropy of the diffusion tensor have found leftward anisotropy in the UF (Kubicki *et al.*, 2002; Park *et al.*, 2004). Powell *et al* (2006) used fMRI to activate frontal and temporal language regions in a sample of 10 right-handed subjects, and used DT-tractography to visualise WM pathways connecting these regions. In addition to the asymmetry seen in language-specific pathways, stronger fronto-temporal connections via the inferior fronto-occipital and UF were seen on the left, suggesting a possible role for the UF in language processing. Other studies indicate that asymmetry of the UF depends on the region considered. For instance, Park *et al* (2004) found rightward FA asymmetry in the middle and inferior portion of the UF, and leftward FA asymmetry in the superior portion in 32 healthy right-handed subjects (all males).

The study presented in Chapter 6 indicates leftward FA asymmetry in the pars orbitalis and the subinsular segment and posterior extrainsular portion of the UF in left and right-handers. The anterior extrainsular segments of the UF did not extend as far into orbital cortex in left-handers compared to that of right-handers. Although this difference is not significant here it may suggest a need to consider the UF as a regional structure in future handedness studies. Asymmetry findings in the present sample of participants are consistent with the study reported by Rodrigo *et al* (2007), who found a leftward asymmetry of the subinsular part of the UF. Whilst the functional significance of the UF is currently unknown (Catani and Mesulam, 2008; Duffau *et al.*, 2009; Parker *et al.*, 2005), it is thought to be related to emotion processing, semantic and episodic memory and language functions (Highley *et al.*, 2002; Levine *et al.*, 1998; Rodrigo *et al.*, 2007; Schmahmann *et al.*, 2008). To my knowledge this study provides for the first time asymmetry of the UF tract in a sample containing only left-handed subjects.

Influences of age and sex on white matter

The development of WM tracts provides the connectivity essential for normal cognitive function, integrating processes across segregated regions (Barkovich, 2000; Ben Bashat *et al.*, 2005; Luna and Sweeney, 2001; Paus *et al.*, 2001). WM tract development, including myelination (Ben Bashat *et al.*, 2005; Hayakawa *et al.*, 1991; Mukherjee *et al.*, 2001; Reiss *et al.*, 1996; Schmithorst *et al.*, 2002) continues well into adulthood (Lebel *et al.*, 2008). In Chapter 6 no significant effect was found for age (P>0.05, FDR) for either WM anisotropy or FA asymmetry. However, only a narrow age range was used (mean±SD = 21.4±3 years), limiting the availability of data in which to draw any solid conclusions regarding the effect of age on WM anisotropy. Using DT-MRI in subjects aged 5 to 30 years, Lebel *et al* (2008) found FA increases with age in almost all structures, rapidly in the youngest and eventually reaching a plateau. The development of the genu and inferior longitudinal fasciculus showed early rapid changes, reaching 90% of maximum FA by 11 years (Lebel *et al.*, 2008). Areas with fronto-temporal connections develop more slowly, for example, the UF showed a linear growth of FA which appeared to continue beyond 30 years (Lebel *et al*., 2008). The present study uses a tight age range (18-31 years). The strong leftward asymmetry of the UF observed in our study may be influenced by late development of the UF in the right hemisphere compared to that of the left hemisphere. It is therefore possible that the leftward asymmetry of the UF is not fixed but changes with age. The significant differences in WM anisotropy between right- and left-handers might be a function of developmental differences in WM: left-handers have been shown to lag behind right-handers developmentally. For instance, compared to right-handers, left-handers have lower height and body weight (Coren & Halpern, 1991), show pubertal delay (Coren *et al*., 1986) and more often report low birth weight (Van Strien *et al*., 1987). No study to date however, has explored WM development in left-handed individuals.

No significant effect of sex was found for WM anisotropy. The interaction between the effects sex and handedness on anatomical differences and asymmetries in the brain is unclear. Other studies report no significant effect of sex on WM volume asymmetries (Pujol *et al*., 2002) or WM anisotropy asymmetries (Takao *et al*., 2011). Takao *et al* (2011) for instance, showed WM asymmetry in the AF and report no effect for sex on WM asymmetry which is consistent with the findings in the present study. Pujol *et al* (2002) demonstrated leftward WM volume asymmetries using MRI in a sample of 50 females and 50 males all of whom were right-handed. Asymmetries were found to be greater in men than women although no significant differences were observed between the groups.

Functional laterality

The effect of handedness on language processing

Overall both handedness groups showed similar regions of activation across the brain for language which is primarily localised to left hemisphere IFG. Also for spatial processing similar regions of activation are observed in both left- and right-handers with activation localised primarily to right hemisphere parietal lobe. Direct comparisons across the whole brain for both the word generation task (language) and landmark task (spatial) reveal no significant differences in activation following correction for multiple comparisons.

A significant association was found between handedness and language lateralization, with 100% of right-handers and 80% of left-handers presenting leftward language lateralization. This is consistent with previous studies which demonstrate a higher proportion of leftward language lateralization in right-handers than left-handers (Annett and Alexander, 1996; Corballis, 2003; Deppe *et al*., 2000; Knecht *et al*., 2001; Pujol *et al*., 1999; Szaflarski *et al.,* 2002). For instance Pujol *et al.* (1999), using the word generation task and fMRI to examine only the IFG in 100 individuals balanced for handedness and sex, found leftward laterality in 76% of left-handers, rightward laterality in 10% of left-handers and bilaterality in 14% of left-handers; leftward laterality was found in 96% of right-handers. Szaflarski *et al* (2002), using a language task and fMRI in 50 non-right-handers, found laterality to be 78% leftward, 8% rightward and 14% bilateral. Flöel *et al*. (2005), using fTCD, found that in left-handers language laterality was leftward in 74% and rightward in 26% (they did not take into account bilaterality, having too few left-handers). In right-handers language laterality was shown to be leftward in 97% and rightward in 3%. Together, these studies find that the proportion of right-handers with leftward language laterality is typically 96-100%, while in left-handers the proportion of left hemispheric language laterality is 74-80%. No significant effect of sex on language laterality was found in the study presented in Chapter 7, which supports previous studies (Buckner *et al*., 1995; Frost *et al*., 1999; Knecht *et al*., 2000; Pujol *et al*., 1999; Springer *et al*., 1999; Szaflarski *et al*., 2002).

The word generation task produced similar average activation in both left and right-handers, yielding greatest activation in the left hemisphere for the majority of participants. Regions of activation included Brodmann areas 44 and 45, superior frontal gyrus, inferior occipital gyrus and cerebellum, consistent with previous studies which used this task (e.g. Badzakova-Trajkov *et al.*, 2010; Deppe *et al.*, 2000; Knecht *et al.*, 2003; Jansen *et al.*, 2004). Activation in left IFG did not significantly differ between the handedness groups however, left-handers showed significantly greater activation in right hemisphere IFG than right-handers. This suggests that differences in language laterality across the IFG observed between the handedness groups is due to greater involvement of right hemisphere IFG in left-handers. It is possible that the effect of handedness on neuronal activation in right IFG in response to the word generation task would also extend to whole hemisphere activation i.e. when language activation is assessed across the whole hemisphere. Thus the effect of handedness on language activation may not be specific to the IFG. However, it must be noted that direct comparisons for activation between left- and right-handers across the whole brain corrected for multiple comparisons showed no significant results (FDR, $P>0.05$) suggesting that the difference in activation between left- and right-handers is only small and perhaps specific to the IFG which is why direct comparisons across the whole brain were non-significant.

The results presented in Figure 7.1 showed substantial activation in the third and lateral cerebral ventricles in response to the word generation task in right-handers only. Importantly peak talairach coordinates did not fall within this region. One potential explanation for this activation is that participant movement correlated with the task in right-handers alone. Motion correction parameters were not used as regression parameters within first-level analysis and further analysis should consider including the six motion parameters as a covariate in the first-level analysis in order to clarify whether this removes activation from the ventricles.

The effect of handedness on spatial processing

The landmark task produced similar average activation in both left and right-handers, yielding greatest activation in the right hemisphere for the majority of participants. In the right hemisphere significant activations were found in the inferior and medial frontal gyrus, precuneus and inferior parietal lobule for both left- and right-handers. Although marginally more right than left-handers presented rightward hemispheric spatial lateralization (67% vs. 63%) this difference was not significant. This differs from results of two studies investigating spatial lateralization in addition to that of language using functional transcranial Doppler sonography (fTCD) (Flöel *et al*., 2001, 2005; Jansen *et al*., 2004). Jansen *et al* (2004) found, in a group of 9 right and 6 left-handers, right hemispheric spatial dominance in 80% of subjects. Flöel *et al* (2005) found right hemispheric spatial dominance in 95% of 37 right-handers and 81% of 38 left-handers. However, this discrepancy may be explained by the relatively poor spatial resolution of fTCD, which assesses changes in CBFV over the whole vascular territory of the insonated artery (the MCA) and by the small sample size involved in the first study. The MCA supplies blood to the lateral surface of the temporal and parietal lobes and part of the frontal lobes. By contrast the greater spatial resolution of fMRI allows the ROI to be restricted to the parietal cortex. Therefore findings in this thesis are not directly comparable with those studies that have established spatial lateralization using fTCD.

Nevertheless, the significant overall rightward spatial lateralization found in Chapter 7 in parietal cortex alone is in accord with the above studies (Flöel *et al*., 2005 and Jansen *et al*., 2004) as well as with other studies (Lux *et al*., 2003; Ng *et al*., 2001; Vandenberghe *et al*., 1996). Additionally, Jansen *et al* (2004) assessed spatial laterality using fTCD which assessed cerebral perfusion over the whole of the MCA and spatial laterality using fMRI in two regions of interest, a parietal and a frontal region. Concordance between fTCD and fMRI generated LI's was found in 12 out of the 15 cases assessed. The results presented in this thesis are however consistent with Badzakova-Trajkov *et al*. (2010) who showed that while handedness is associated with left-frontal lateralization for language, no association was found between handedness and parietal lateralization for spatial processing. This thesis used fMRI to establish lateralization over selected ROI's, specifically frontal cortex for language production and parietal cortex for spatial processing.

Associated and dissociated language and spatial laterality

There is still debate regarding the dissociation of language and spatial laterality between the hemispheres (Knecht *et al*., 2001, 2002; Lezak, 1995). In the study, presented in Chapter 7, language and spatial lateralization are dissociated in approximately two-thirds of all cases, with 60% of subjects showing typical lateralization for both language and spatial processing (i.e. leftward language and rightward spatial lateralization) and only 5% showing atypical lateralization for both language and spatial processing (leftward spatial and rightward language lateralization).

Reports of small numbers of subjects using lesion studies (Alexander and Annett, 1996; Osmon *et al*., 1998; Trojano *et al*., 1994) and activation studies (Flöel *et al*., 2001, 2005; Jansen *et al*., 2004) indicate that a dissociation of language and spatial function is not an invariable principle of brain organisation. For example, Flöel *et al* (2001) examined both language and spatial lateralization (using the word generation and landmark tasks, respectively) in a group of 20 subjects selected on the basis of their language lateralization: although all 10 subjects with left hemispheric language dominance presented right hemispheric spatial dominance, 4/10 subjects with right hemispheric language dominance also exhibited right hemisphere spatial dominance. These results indicate that language and spatial laterality do not always dissociate between the hemispheres.

Flöel *et al* (2005) reported a similar finding with a larger sample (n = 75), demonstrating leftward language and spatial laterality in 5 subjects and rightward language and spatial laterality in 8 subjects. This thesis reports a greater proportion of subjects (30%) with leftward language and spatial hemispheric dominance. Additionally, rightward lateralization for both language and spatial processing is found in 4 subjects, all left-handers (this equates to 5% of the total sample and 10% of the left-handed subjects). In particular, when language laterality was atypical (n=8), spatial functioning was lateralized to the same hemisphere in half (n=4). One hypothesis is that when language is lateralized to the right hemisphere, spatial functioning is randomly lateralized. However, the small number of subjects presenting atypical language laterality in this study makes this finding difficult to extrapolate.

Functional laterality and cognitive ability

Laterality, handedness and executive functioning

This thesis adds to the body of literature reporting differences between left- and right-handers in cognitive ability performance (e.g. Aggleton *et al*., 1994; Casey *et al*., 1992; Crow *et al*., 1998; Kopiez *et al*., 2006) by showing significant differences between right- and left-handers on tasks of auditory working memory (in Chapter 7), with right-handers performing significantly better than left-handers.

Increased rightward language lateralization was also associated with a decrease in working memory score. This association can be interpreted in relation to Baddeley's model of working memory (Baddeley, 1986), which decomposes verbal storage into a short-term phonological buffer refreshed by a subvocal rehearsal process (Baddeley, 2003). The task used in this study to assess working memory involved hearing and repeating an increasingly longer sequence of numbers, or mentally arranging vocally presented words and letters in a sequence and can therefore be considered a measure of auditory working memory. Given the role of the left IFG in the production of speech, the frontal speech areas likely mediate subvocal rehearsal of targets following vocal presentation, for which there is evidence from PET and fMRI studies (Awh *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1997; Jonides *et al.*, 1997; Schumacher *et al.*, 1996; Smith and Jonides, 1999; Smith *et al.*, 1996).

Results which show an association between increased working memory score and increasing leftward language laterality support the work of Nettle (2003) and Leask and Crow (2001). The fact that the advantage is in a leftward direction is presumably related to the involvement of the left hemisphere is subvocal rehearsal. Additionally the advantage to right-handers is perhaps due to them being more strongly lateralized for language than the left-handers. It is possible in this thesis that the association between laterality and cognitive ability differ between left and right-handed individuals however, the absence of right-handed subjects with right-hemispheric dominance in the present study precluded this interaction (handedness*language LI) in the model and the hypothesis could not be tested. Specifically 100% of right-handers (n=42) and 80% of left-handers (n=32) showed left-hemispheric language dominance. Moreover, when subjects are divided into subgroups of laterality i.e. left, right and bilaterality using the criteria of rightward laterality ≥ +0.2, leftward laterality ≤ -0.2 and bilaterality is anything in the range of -0.19 to +0.19 the number of individuals with rightward laterality (n=6) and bilaterality (n=3) are too small to generate any meaningful statistical analysis. Therefore I opted to maintain a laterality continuum rather than separate subjects into left, right and bilateral groups.

A link has been reported between cognitive performance and language laterality in healthy subjects (Everts *et al.*, 2009; van Ettinger-Veenstra *et al.*, 2010) and in patients with epilepsy (Everts *et al*., 2010). The present study reports a significant effect of the interaction between language laterality (within IFG) and spatial laterality (within parietal cortex) on both verbal comprehension and perceptual organisation ability: when language and spatial LIs are dissociated cognitive performance is higher (and this effect is more pronounced when language is lateralized to the right hemisphere and spatial processing is lateralized to the left hemisphere). The sample size, although relatively large, included only 8 participants with right-hemispheric language dominance, and future studies with larger numbers in this group are needed to confirm the findings.

The idea that dissociated language and spatial laterality convey advantage is consistent with the hemispheric ‘crowding’ hypothesis, which argues that when more than one cognitive function (such as language and spatial processing) is lateralized to the same hemisphere, there will be a relative deficit in cognitive ability. Usually the deficit is for non-verbal abilities following damage to the left hemisphere at an early onset, but can also occur following damage to the right hemisphere (Vargha-Khadem *et al*., 1992). Previous studies report reduced visuospatial function in children and adults with atypical language laterality (Kadis *et al*., 2009; Loring *et al*., 1999). These studies however, assumed rightward spatial laterality. The study presented in Chapter 7 is, to my knowledge, the first to demonstrate an association between spatial and language laterality and cognitive ability in a group of left- and right-handed individuals. Results indicate that hemispheric specializations for language and spatial functions interfere with one another and favour the dissociation of functions for increased cognitive ability, specifically verbal comprehension and perceptual organisation ability. Whilst any of the ‘transfer of information’, ‘cost of neural tissue’ and ‘hemispheric indecision’ hypotheses referred to above might explain why increased leftward language lateralization is association with increased working memory capacity, they do not explain why dissociated lateralities should provide a cognitive advantage for verbal comprehension and perceptual organisation, as found in this thesis.

The findings of a cognitive disadvantage when language and spatial laterality are associated is supported by Strauss *et al* (1990) who examined verbal and non-verbal cognitive abilities in a group of epileptic patients who had undergone the carotid amytal test. The onset of left hemisphere dysfunction in these patients occurred early. Those with atypical language laterality (i.e. those without left hemispheric language laterality) performed as well as those with typical speech patterns in most measures of language function. However a deficit was seen in those with atypical speech during non-verbal tasks compared to those with typical laterality for language. These results provide some support for the hemispheric crowding hypothesis by showing that associated lateralization of language and spatial functioning in the right hemisphere affects non-verbal abilities. These studies show a deficit to non-verbal abilities which supports the decreased perceptual organisation ability observed in the present study when language and spatial laterality are associated.

What this thesis suggests is that dissociation between the hemispheres is the most prevalent pattern in the population and that this pattern of brain organisation carries a cognitive advantage. Support for dissociation between the hemispheres comes from Jansen *et al* (2005) who showed that individuals with atypical right-hemispheric language dominance have more bilateral activation during spatial judgement than individuals with typical, disjunct hemispheric specialization, that is, left dominance for language and right dominance for spatial tasks. Their findings suggested that hemispheric specializations for language and spatial functions interfere to some extent and favour additional recruitment of the opposite hemispheres for spatial functions. Their study did not explore the effect of associated laterality on intellectual functioning. This thesis however shows that there is a clear advantage to verbal comprehension and organisation processing skills when there is dissociation between language and spatial lateralization in the IFG and parietal cortex respectively.

Brain volume and cognitive ability

Fluid and crystallised intelligence, GM volume and handedness

After extensive review of the functional and structural MR, PET and diffusion evidence Jung and Haier (2007) developed the parieto-frontal integration theory of intelligence (P-FIT), according to which intelligence is localised to regions of frontal, temporal, parietal and occipital lobes cortex, information being transferred between regions through efficient white matter tracts. Results obtained in this thesis indicate an important role for medial-superior frontal gyrus (including BA6, BA8 and BA9) and cuneus (BA7) in the occipital lobe crystallised intelligence. Fluid intelligence was correlated with GM volume primarily in lateral and inferior frontal lobe (BA8, BA9, BA11 and BA47), inferior temporal gyrus (BA37), posterior cingulate cortex (BA31) and lingual gyrus (BA18) within the occipital lobe. The majority of these regions (i.e. BA6, BA7, BA9, BA18, BA37 and BA47) correspond to those regions which are correlated with better performance on measures of intelligence and reasoning in the P-FIT model of intelligence proposed by Jung and Haier (2007).

Previous research has shown correlations between measures of intelligence and reasoning and GM volume within: BA6 (Shaw *et al*., 2006), BA7 (Colom *et al*., 2006; Frangou *et al*., 2004), BA8 (Colom *et al*., 2006; Gong *et al*., 2005; Shaw *et al*., 2006), BA9 (Frangou *et al*., 2004; Gong *et al*., 2005; Schmithorst *et al*., 2005), BA10 (Colom *et al*., 2006; Frangou *et al*., 2004; Haier *et al*., 2005; Shaw *et al*., 2006), BA18 (Colom *et al*., 2006; Shaw *et al*., 2006), BA37 (Haier *et al*., 2003, 2004) and BA47 (Colom *et al*., 2006; Frangou *et al*., 2004). These findings support the results shown in Chapter 8.

The fact that a large proportion of GM residing within the frontal lobe is correlated with increased intelligence score supports Duncan *et al* (2000) who proposed that the frontal lobe is the neural basis for intelligence. The results presented here differ in the sense that both crystallised and fluid intelligence are correlated with discrete regions of the frontal lobe. Duncan *et al* (1995, 2000) proposed that only fluid intelligence is correlated with frontal lobe not crystallised intelligence. Similarly Gong *et al* (2005) showed, using a VBM study, that non-verbal intelligence (i.e. fluid intelligence) is correlated with dorsomedial intelligence whilst crystallised intelligence shows no such association. The findings presented in this thesis are similar to those presented by Colom *et al* (2006) who showed a distributed neural basis to intelligence across frontal, temporal and parietal regions. Geake and Hansen (2005) also showed that BA9 residing within the frontal lobe is correlated with verbal intelligence measures. Although their study was an fMRI study the findings are similar to that presented in Chapter 8 where GM volume in BA9 correlated with increased crystallised intelligence which contains only measures of verbal comprehension.

Fluid intelligence in this thesis contains intentionality as assessed using the Imposing Memory Task (IMT) as well as sub-tests from the WAIS-III including those which assess perceptual organisation and working memory. Intentionality here is a measure of social fluid intelligence and does not include pre-learned material. This is the first time that a measure of social cognition is included as a general measure of fluid intelligence and this may affect the results obtained in this thesis.

A role for dorsolateral regions of the frontal lobe (especially BA9, BA10 and BA46) in working memory is suggested by structural (e.g. Colom *et al* 2007) and functional imaging (Hampson *et al*., 2006; Salmon *et al*., 1996) studies. Dorsolateral regions of the PFC are thought to house the central executive. Engle *et al* (1999) for instance, argue that the dorsolateral PFC and associated structures mediate the controlled processing functions of working memory. Studies have shown a role for the dorsolateral PFC in auditory working memory (Crottaz-Herbette *et al*., 2004), spatial working memory (McCarthy *et al*., 1994) and in delay tasks (Bechara *et al*., 1998), memory tasks involving visually presented sequential letters (Cohen *et al*., 1997) and tasks involving verbally presented material (Smith and Jonides, 1999).

Other studies of the neuroanatomical correlates of working memory have shown a role for both frontal and parietal regions (Paulesu *et al*., 1993). Salmon *et al* (1996) for instance showed that the left BA40 and premotor cortex (BA6) are the key regions subserving short-term verbal memory performance. Other regions of the posterior parietal cortex (PPC; BA40/BA7) and mid dorsolateral frontal cortex (MDLFC; BA46/BA9) have been implicated during letter-number sequencing (Emery *et al*., 2008) and digit backward tasks (Gerton *et al*., 2004; Sun *et al*., 2005). Both of these tasks were used in this thesis to assess working memory and involve the manipulation and monitoring of information. Champod and Petrides (2010) demonstrated a greater role for MDLFC during the monitoring of words, and intraparietal sulcus (IPS: within the PPC) during the manipulation of words, supporting the functional distinction between PPC and MDLFC during working memory tasks. Results in Chapter 8 showing correlations between increased fluid intelligence and GM volume within BA6, BA7, and BA9 are consistent with the reviewed literature. Fluid intelligence, as assessed in the present study, contained measures of working memory which might partly explain the observed associations.

Correlations between GM volume within BA18 and BA37 and increased intellectual performance (as shown in this thesis) are consistent with the P-FIT model of intelligence, which suggests that these regions contribute to the recognition, imagery and elaboration of visual input (Deary *et al.*, 2010). Many previous studies have shown associations between increased intellectual performance and BA18 (Colom *et al.*, 2006; Shaw *et al.*, 2006) and BA37 (Haier *et al.*, 2003, 2004). Superior parietal cortex, including BA7 is typically considered the next station in the chain of information processing following visual input. This region is responsible for structural symbolism, abstraction and elaboration of information (Deary *et al.*, 2010) and is correlated with fluid intelligence in this thesis. The importance of parietal cortex (particularly BA7) in intellectual functioning is supported by Lee *et al* (2006) who suggested that superior-*g* may be the result of functional facilitation of the fronto-parietal network. Following information processing in BA7 information is then passed on to frontal cortex which is responsible for decision making, planning, response inhibition and resolving goals (Colom *et al.*, 2006; Geake and Hansen, 2005; Haier *et al.*, 2004; Jung and Haier *et al.*, 2007). Frontal cortex would be involved not only in analogous thinking, which is fundamental to fluid intelligence but also verbal intelligence measures (Geake and Hansen, 2005). This supports the correlations between frontal GM volume and measures of fluid and crystallised intelligence found in this thesis.

Importantly results showed significant differences in GM correlates between fluid and crystallised intelligence in left hemisphere middle frontal gyrus (BA8 and BA11), medial temporal gyrus (BA21) and right hemisphere inferior temporal gyrus (BA37), inferior frontal gyrus (BA47), middle frontal gyrus (BA8) and precuneus (BA7). The planum temporale (BA21) is a region of cortex involved in the comprehension of verbally presented material and might be considered more important in measures of crystallised intelligence. Differences in GM correlates of BA8, BA11 and BA47 (frontal cortex) between fluid and crystallised intelligence may be the result of greater dependence of fluid intelligence on these regions (e.g. Duncan *et al.*, 1995, 2000; Gong *et al.*, 2005).

Findings also showed significant differences in the GM correlates of fluid intelligence between the handedness groups in left hemisphere inferior (BA20) and superior (BA22) temporal gyrus. Fluid intelligence is comprised of perceptual organisation, working memory and intentionality scores. Overall, both handedness groups performed equally well on measures of perceptual organisation and intentionality however, working memory scores differed significantly between the handedness groups with right-handers showing superior performance. BA22 is one region residing within Wernicke's area: suggested to be involved in syntactic auditory input (Deary *et al.*, 2010). Volume differences in this region between the handedness groups have been found. For instance, Steinmetz *et al.* (1989) found in a sample of 26 right-handers and 26 left-handers that leftward planum temporale asymmetry was on average less pronounced in left-handers. In the present study the GM correlates of fluid intelligence differ significantly between the handedness groups in left BA22, and this might contribute the difference in working memory score between the handedness groups. This conclusion however is just conjecture and further research is required to clarify this point.

The GM correlates of crystallised intelligence differs significantly between the handedness groups in superior temporal gyrus (BA38: bilaterally), left middle frontal gyrus (BA8 and BA11) and right precuneus (BA7). BA38 is located at the anterior end of the temporal lobe, corresponding with temporal pole. The role of BA38 is not entirely clear from the literature, however, Ding *et al* (2009) suggests it does have a role in processing perceptual inputs. Clearly further research is required to understand twhy significant differences in the GM correlates of fluid and crystallised intelligence are observed between the handedness groups.

Intentionality and the PFC

The literature suggests a functional distinction between dorsal and orbital regions of the PFC in social cognitive operations, with dorsal PFC supporting the widely acknowledged 'metacognitive' EFs (Ardila, 2008), such as planning (Damasio and Anderson, 1993), working memory (Goldman-Rakic, 1996), attention (Vendrell *et al.*, 1995) and delayed judgements (Curtis and D'Esposito, 2003), whilst orbital PFC supports 'emotional/motivational' EFs, coordinating cognition and emotion (Mitchell and Phillips, 2007). The finding in Chapter 9 of a significant correlation between orbital PFC volume and intentionality in right-handers is therefore consistent with previous functional imaging studies reporting an association between orbital PFC and social cognition (e.g. Lewis *et al.*, 2011; Spreng *et al.*, 2009; Völlm *et al.*, 2006). In particular the orbital PFC is shown to have an important role in social cognition, including functions, which support social cohesion such as social reward (Cohen *et al.*, 2009) and response inhibition (Elliott *et al.*, 2000). Additionally a previous study reported a positive association between orbital PFC volume and intentionality in right-handed individuals (Powell *et al*., 2010) which is confirmed in the study presented in Chapter 9 using a different cohort of right-handed subjects. This thesis sheds light for the first time on the anatomical correlates of intentionality in left-handers by demonstrating a linear relationship between intentionality and dorsal PFC volume that is specific to left-handers. It is not entirely clear why there are differences in the PFC correlates of intentionality between the handedness groups. A theoretical justification for performing this study is given in Section 2.5, however, it should be noted here that the study is exploratory in nature.

One explanation for the difference in PFC volume associated with intentionality is that the localisation of intentionality differs between the handedness groups. A change in the neuroanatomical correlates of intentionality in left-handers may occur later in development. This interpretation is similar to that proposed by Deeley *et al* (2008) who explored changes in the neural response to fearful and disgusted facial expressions in 8-50 year olds. A negative correlation was found between increasing age and neural response in the dorsomedial DM PFC and middle frontal gyri. By the time the individual reached between 20-30 years of age facial expressions were processed primarily in the limbic system. This change in neural response may be due to a reduction in attentional demands as perceptual skill increases or changes in processing the self-relevance of facial expressions during social and cognitive development. Left-handers may develop more slowly in some respects than right-handers. For instance, compared to right-handers, left-handers tend to have smaller body size in both height and weight (Coren & Halpern, 1991), show pubertal delay (Coren *et al.*, 1986) and more often report low birth weight (Van Strien *et al*., 1987). In this thesis participants were aged between 18-31 years with a mean age of 21.4 years (±3.0 years). Although the study by Deeley *et al* (2008) explored neural response and the present study explores structural correlates, a similar phenomenon may occur. The mechanism of the difference in the neuroanatomical correlates of intentionality between left- and right-handers is not yet clear.

Left- and right-handers did not show significant differences in intentionality competence suggesting that individuals may achieve similar cognitive ability scores with different brain designs. This interpretation is similar to that proposed by Haier *et al* (2005) and Narr *et al* (2007). Haier *et al* (2005) found that in males, intelligence was more strongly correlated with fronto-parietal GM volume whereas, in females, intelligence showed stronger correlations with WM volume and GM volume in Broca's area. In another study Narr *et al* (2007) found that cortical thickness in frontal regions correlates more strongly with intelligence in females, whereas temporal-occipital cortical thickness shows a stronger correlation with intelligence in males. The differences in brain volume correlates with different cognitive abilities in left- and right-handers may be related to the fact that the brains of these handedness groups are known to be organised differently, for example, right-handers show a higher degree of leftward laterality for language than left-handers (Pujol *et al*., 1999; also see Section 2.3.3 for a review of the literature). Findings suggest a need to consider differences in the neuroanatomical correlates of cognitive ability between groups known to differ in brain organisation and structure.

The association between brain structure and intelligence

Previous studies have revealed an association between brain volume and intelligence (Andreason *et al*., 1993; Flashman *et al*., 1997; Gong *et al*., 2005; Gray and Thompson, 2004; MacLullich *et al*., 2002; Toga and Thompson, 2005; for meta-analysis see McDaniel, 2005 and for a review of the literature see Jung and Haier, 2007 and Section 2.4.2). This thesis adds to these studies by showing associations between intelligence and regional GM volume which differ significantly between left- and right-handers, and by showing associations between intentionality and PFC volume which differ significantly between left- and right-handers. Although the mechanisms underlying the association between brain size and cognitive ability remains unclear, Pakkenberg and Gundersen (1997) have shown that larger brains have more neurons and it is conceivable that this increase in neuronal number benefits both cognitive capacity and cognitive complexity (through a greater number of synaptic connections). Roth and Dicke (2005) further argue that number of cortical neurons combined with a high conduction velocity of cortical fibres, which are an important parameter for information processing capacity, correlates best with intelligence.

More recent research has shown that the composition of nonneuronal/neuronal cells differ throughout the brain (e.g. Azevedo *et al*., 2009) which may be functionally relevant given the recent findings for the roles of glial cells in information processing and bidirectional communication with synapses (Araque *et al*., 1999; Iadecola and

Nedergaard, 2007; Perea *et al*., 2009). Increased GM volume cannot be assumed to reflect solely the increase in neuronal number but may be the sum of neurons and other nonneuonal cells such as glia which contribute to the surrounding neurons in terms of neurovascular regulation and integration of synaptic information. The fact that the signal of astrocytes is not based on electrical signals but rather on Ca^{2+} concentration variations in cytoplasm means that involvement of astrocytes in cognitive function cannot be investigated *in vivo* using fMRI techniques. Similarly measuring the composition of nonneuronal/neuronal cell number is not currently allowed for with modern MRI techniques. Therefore one can only infer that the increase in GM volume associated with increased cognitive function is the result of a combination of astrocytes and neurons, although the functional significance of the former in increasing cognitive capacity is unknown. The usefulness of the findings presented in this thesis regarding regional brain volume increases related to increased cognitive function is that it allows one to focus future investigations of cognitive function on focal regions of the brain. It also shows that brain structure and function differ between individual groups in a population suggesting that there is no single optimum brain design for cognitive ability.

Understanding the quantitative relationships between language and spatial lateralization and the relationship between cerebral anatomy and cognitive functioning in left- and right-handers in the normal population is of clinical relevance for three reasons. Firstly, these relationships might be useful for predicting the risk of postoperative cognitive disturbance including language, social cognition and intelligence in patients undergoing brain surgery for adult-onset disease. Secondly, such knowledge could lead to an improved understanding of the biological basis of language lateralization, which might eventually result in novel therapeutic strategies for patients with impaired language processing. Thirdly, understanding the brain's organisation within the healthy population for language and spatial processing, and its relationship with cognitive ability, will provide evidence of an optimal brain state and the possible advantages of laterality for our species and will further our understanding of the factors which have driven brain evolution. Additionally an improved understanding of the biological basis of social cognition and intelligence will further our understanding of the factors which have driven brain evolution and brain development in the two handedness groups.

10.4 SUGGESTIONS FOR FUTURE RESEARCH

This thesis shows differences in the neuroanatomical correlates of cognitive ability in left- and right-handers, specifically fluid and crystallised intelligence (Chapter 8) and intentionality (Chapter 9) as well as the effect of brain laterality on cognition (Chapter 7). Future research should also explore the effect of handedness on the neuroanatomical correlates of other cognitive domains e.g. other components of working memory or measures of intentionality. For instance, the IMT used to assess intentionality in Chapter 9 is a ‘false belief’ task involving verbal stories. Other studies, however, have used cartoons or films employing a belief reasoning task (i.e. visual representations of social situations) (e.g. Gallagher *et al*., 2000; Grèzes *et al*., 2004; Sommer *et al*., 2007). The type of task used has been shown to influence the neural correlates of intentionalizing ability (e.g. Gobbini *et al*., 2007). Future studies using tasks involving visual representations of social situations will therefore, provide further support to the findings presented in this thesis. Additionally, other measures of fluid and crystallised intelligence could be used to replicate the findings presented in this thesis, such as Cattell’s Culture Fair test of intelligence or Raven’s Progressive Matrices.

Handedness was assessed in this thesis using the EHI (see Section 4.2.1), a questionnaire designed to assess hand preference for a variety of tasks. Participants are given both a handedness score, representing their degree of handedness and a handedness classification, which in this case was binary i.e. left- or right-handed. The EHI is widely used to assess hand preference; however, handedness can also be assessed in relation to hand skill which is the ability to use one hand above the other (Annett and Manning, 1990). Future studies exploring differences in brain structure and function should consider assessing both hand preference and hand skill.

Structural differences were found between the handedness groups. Volume asymmetries of language associated cortex generally focus on differences between the sexes or handedness groups with little regard for the interaction between sex and handedness on these volume asymmetries. The study presented in Chapter 5 demonstrated a significant interaction between handedness and sex on PO volume asymmetry in the cohort of subjects examined. Future studies should consider the effect of the interaction between sex and handedness on other neuroanatomical asymmetries, particularly language associated cortex. Furthermore, the study shown in Chapter 5 found a relationship between handedness and the sulcal contours defining Broca's area. The effect of handedness on other sulco-gyral anatomy should be explored.

The study presented in Chapter 7 showed an association between language laterality, spatial laterality and measures of cognitive ability including working memory, verbal comprehension and perceptual organisation. Whilst a relatively large sample size was used in this study (n=82) the representation of language laterality across the spectrum was limited. Future studies might consider investigating the interaction between language and spatial laterality on cognitive ability with a greater number of individuals presenting right hemisphere language dominance.

It should be acknowledged here that the use of the word generation task constitutes an essential feature in the production of language; however, it is only one of the multiple dimensions of language (Benson *et al.*, 1999; Cuenod *et al.*, 1995; Hertz-Pannier *et al.*, 1997; Knecht *et al.*, 2000). There are other aspects of language which are also highly lateralized for instance findings report a left lateralized lexical-semantic system (Ahmad *et al.*, 2003; Binder *et al.*, 1997, 2000; Hickok and Poeppel, 2004; Poeppel *et al.*, 2004; Price, 2000; Vandenberghe *et al.*, 1996), and right lateralized prosodic processing system (Ethofer *et al.*, 2006; Meyer *et al.*, 2002; Mitchell *et al.*, 2003; Riecker *et al.*, 2002; Wildgruber *et al.*, 2005). Similarly there are other aspects of spatial processing which are not considered here such as spatial orientation (Lux *et al.*, 2003). In this thesis the landmark task was chosen to examine lateralization for visuospatial attention as it is frequently used in the assessment of spatial neglect and corresponds to deficits most often encountered in patients suffering from visuospatial neglect after stroke (Harvey *et al.*, 1995; Heilman and Abell, 1980; Marshall *et al.*, 1997; Mesulam, 1999). Future studies may wish to consider replicating present findings using a series of tests to discriminate other aspects of language and spatial functioning.

10.5 CONCLUSIONS

Since language dominance and handedness are not perfectly correlated, Toga and Thompson (2003) suggest that brain asymmetry, language laterality and handedness are interrelated but in a complex way, a conclusion which has received support from others (Davidson and Hugdahl, 1995; Hellige, 2001; Koff *et al.*, 1986). Findings presented in this thesis concur with this: left- and right-handers show differences in their anatomical and functional design, although the results are not always straight forward. For instance, whilst the handedness groups differ significantly in volume asymmetry of language associated cortex (i.e. PO volume within the IFG), and language laterality across the IFG, no significant difference between the handedness groups was found for WM anisotropy asymmetry underlying the language associated cortex.

This thesis sheds light for the first time on the effect of handedness on the sulco-gyral anatomy of Broca's area and highlights the interaction between handedness and sex on PO and PTR volume asymmetry (Chapter 5). Understanding how language, sex and hand preference are linked to brain structure is of concern to psychologists, neuroscientists and clinicians alike, due to the implications of these factors on the development of language, praxis, and motor control systems. Findings will also be of concern to evolutionists and biologists for understanding how the brain systems of human and non-human primates diverged in the development of oral and gestural communication.

Left- and right-handed groups have previously been found to exhibit differences in their performance on a range of cognitive ability measures. This thesis shows that left- and right-handers perform similarly on measures of verbal comprehension, perceptual organisation and intentionality, but not working memory: here right-handers perform significantly better than left-handers. These results suggest that any observed difference in intelligence or cognitive capacity between the handedness groups is likely to apply to specific abilities.

The relationships between laterality of language and spatial processing and the cognitive abilities: working memory, perceptual organisation and verbal comprehension is the first study of its kind. Increased leftward language laterality is associated with increased working memory score, and dissociated language and spatial laterality between the hemispheres is related to an increase in perceptual organisation and verbal comprehension ability. The advantage of dissociated laterality for language and spatial processing supports the hemispheric crowding hypothesis. These results suggest that the way in which the brain is organised has an effect on cognitive ability. The fact that laterality is associated with specific cognitive abilities and that left- and right-handers are known to differ in functional lateralities will be of concern to those in the area of education and developmental psychology as well as parents. What this thesis highlights is a need for further studies recruiting larger samples of individuals with rightward language laterality.

The effect of handedness on the neuroanatomical correlates of cognitive ability was explored for the first time in this thesis for fluid and crystallised intelligence (Chapter 8) and intentionality (Chapter 9). Despite obtaining almost identical intentionality scores, left- and right-handers presented different relationships between regions of the PFC volume and intentionality competence. Overall the findings suggest that intentionality is localised to different brain structures in left- and right-handers, although this does not affect intentionality performance. Similarly significant differences in the GM correlates of fluid and crystallised intelligence were found. Such differences in the GM correlates of fluid intelligence may explain the significant difference in working memory score between the handedness groups (as fluid intelligence included the component working memory). What the findings show overall is that differences in brain structure and function may underlie differences in the neuroanatomical correlates of cognitive ability in different groups within the healthy population.

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APPENDIX 1:
IMPOSING MEMORY TASK

Instructions:

This booklet gives five short stories. On the page following each story there are a number of questions about the story. For each story set, please READ the story twice, then TURN OVER the page and answer the questions.

Please answer TRUE or FALSE to each of the questions that follow each story. If the question asks for information that is not easily inferred through your reading of the story, please indicate your answer as being false, DO NOT GUESS. Please work through as quickly as possible.

DO NOT turn back to check the story once you start answering the questions for that story
……AND
DO NOT change any answer once you have answered it, go with your instinct.

Thank you for taking part in this study. If you have any further questions, please contact:

Joanne Powell
joanne.powell@liv.ac.uk
07828 910128

Some background details:

Gender (please circle): Male Female

Your D.O.B: ....

Your current age: ....

STORY 1

WHERE’S THE POST OFFICE?

Sam wanted to find a Post Office so he could buy a Tax Disc for his car. He was already late buying one, as his Tax Disc had run out the week before. Because traffic wardens regularly patrolled the street where he lived, he was worried about being caught with his car untaxed. As Sam was new to the area, he asked his colleague Henry if he could tell him where to get one. Henry told him that he thought there was a Post Office in Elm Street. When Sam got to Elm Street, he found it was closed. A notice on the door said that the Post Office had moved to new premises in Bold Street. So Sam went to Bold Street. But by the time he got there, the Post Office had already closed. Sam wondered if Henry, who was the office prankster, had deliberately sent him on a wild goose chase. When he got back to the office, he asked another colleague, Pete, whether he thought it likely that Henry had deliberately misled him. Pete thought that, since Sam had been anxious about the Tax Disc, it was unlikely that Henry would have deliberately tried to get him anxious about the Tax Disc, and it was unlikely that Henry would have deliberately tried to get him into trouble.

Story 1: Where's the Post Office

Sam left Bold Street, then went to the office and spoke to Pete **T** **F**

Pete, the man who worked at the same place as Henry, and who knew that Henry was the office prankster, was Sam's cousin **T** **F**

Henry thought that Sam knew he was a prankster **T** **F**

Henry knew Sam believed he knew where the Post Office was **T** **F**

Sam thought that Henry knew the Post Office was in Bold Street and hence that Henry must have intended to mislead Sam **T** **F**

Sam believed that Pete thought the Post Office was in Elm Street and hence that Pete must not have intended to mislead Sam **T** **F**

Sam wanted to buy a stamp **T** **F**

Pete wanted Sam to know that Henry believed that the Post Office was on Elm Street and hence did not intend to mislead him **T** **F**

The Post Office was closed and Sam's insurance had run out **T** **F**

Pete wanted Sam to know that he believed that Henry had intended not to mislead him **T** **F**

Sam needed a Tax Disc from the office **T** **F**

The Post Office was closed because it had moved to Bold St **T** **F**

Henry wanted to play a trick **T** **F**

Sam asked Henry, and did not ask Pete or the traffic wardens, about where the Post Office was in order to buy a Tax Disk **T** **F**

Sam found the Post Office closed and couldn't buy a tax disk for Pete **T** **F**

Sam thought Henry knew he wanted a Tax Disk **T** **F**

Sam who worked with Pete and Henry did not know where to buy a Tax Disk because he was new to the area **T** **F**

Henry, the man that Sam spoke to about where to buy a Tax Disk after he realized he needed to buy one soon, was a colleague of Pete's **T** **F**

The Post Office in Elm St. had a notice on the door **T** **F**

Pete suspected that Henry was playing a prank on Sam **T** **F**

STORY 2

JOHN’S PROBLEM

It was nearly the end of the day, and John thought it might be nice to go to the pub for a drink after work. At first, he wasn’t sure whom he should ask to go with him. He very much wanted to ask Sheila, whom he fancied, but he thought that she didn’t like him enough to be willing to give up her aerobics class to go drinking with him. He could, of course ask Pete, his usual drinking companion. Then he happened to see Penny. He knew that Penny was one of Sheila’s friends. She would know whether Sheila would be willing to go out for a drink with him. “Listen Penny,” he said, “I thought I might go for a drink after work. I was wondering whether you and Sheila would like to come too. Would you ask Sheila whether she would like to go for a drink with us?” Penny looked surprised. John had never asked her to go out with him before, but she knew that he was very keen on Sheila. She began to suspect that John wanted to find out whether she knew what Sheila might want to do.

Story 2: John’s Problem

John always asks Penny to go drinking with him and Pete **T** **F**

Penny thinks Pete hopes that Sheila will have a drink with him **T** **F**

Penny suspected that John wanted to know whether Penny knew if Sheila would like to go for a drink with him **T** **F**

John knew that Pete would understand not being asked for a drink, because Pete knew that John fancied Sheila **T** **F**

Sheila was surprised John asked Penny to go for a drink **T** **F**

John didn’t ask Pete or Sheila to go for a drink **T** **F**

Sheila believed that John knew she was busy so John wanted to ask Penny out alone but didn’t want Sheila to feel left out, so John instead said he wanted both women to come **T** **F**

Penny knew that John was keen on Sheila, so she suspected that John wanted to find out whether she knew what Sheila might want to do **T** **F**

Penny usually went for a drink after work **T** **F**

Pete worked with Penny and Sheila **T** **F**

Sheila, who works with John and Penny, goes to an aerobics class every day after work and doesn’t usually go drinking **T** **F**

Penny thought that Sheila wouldn’t go for a drink with him **T** **F**

John knows that Sheila likes aerobics **T** **F**

Pete, the man that John usually went drinking with after work, was not asked out because John asked Penny and Sheila instead **T** **F**

John wanted to go for a drink after work **T** **F**

John wants to go out with Jenny **T** **F**

Sheila spoke to Penny but did not speak to Pete or John about giving up her aerobics class because she knew she fancied John **T** **F**

John, who fancied Sheila but who asked Penny and Sheila out for a drink, usually went drinking with Pete, but asked the women because he is keen on Penny **T** **F**

John didn’t ask Pete or Sheila to go drinking after work **T** **F**

John thought Penny knew what Sheila wanted to do **T** **F**

STORY 3

EMMA’S DILEMMA

Emma worked in a greengrocer’s. She wanted to persuade her boss to give her an increase in wages. So she asked her friend Jenny, who was still at school, what she should say to the boss. “Tell him that the chemist near where you live want’s you to work in her shop.” Jenny suggested. “The boss won’t want to lose you, so he will give you more money” she said. So when Emma went to see her boss, that is what she told him that she would take a job at the chemist’s nearer her home if he did not pay her more. Her boss thought that Emma might be telling a lie, so he said he would think about it. Later, he went to the chemist’s shop near Emma’s house and asked the chemist whether she had offered a job to Emma. The chemist said she hadn’t offered Emma a job. The next day the boss told Emma that he wouldn’t give her an increase in wages, and she was welcome to take the job at the chemist’s instead if that was what she wanted to do.

Story 3: Emma’s Dilemma

Emma was offered a job at the bank **T** **F**

The greengrocer asked Jenny if Emma had been offered a job **T** **F**

Emma thought her boss knew the chemist hadn’t offered her a job **T** **F**
Jenny thought that Emma’s boss would believe that Emma would like to work for the chemist who wanted Emma to work for her **T** **F**

Jenny went to see the chemist about offering Emma a job **T** **F**

Emma worked at a chemist near where she lived **T** **F**
Jenny thought that Emma’s boss would think that the chemist, who allegedly wanted Emma to come and work, thought that Emma should be paid more **T** **F**

Jenny wanted Emma to get a raise **T** **F**

Jenny who was Emma’s friend and from whom Emma asked advice, was a career girl **T** **F**

Emma worked at a greengrocer, her friend Jenny who was still at school worked at the chemist, where Emma lied about wanting to work **T** **F**
The greengrocer, who was Emma’s boss who paid her a low wage, went to speak to the chemist after he realized that Emma might be lying and discovered that she was **T** **F**

The chemist knew about Emma’s story **T** **F**
Emma believed that Jenny hoped that her boss would believe Emma’s claim about the chemist wanting to offer her a job **T** **F**

Jenny asked the chemist if she had offered Emma a job **T** **F**

Jenny hoped the greengrocer believed the chemist had offered Emma a job **T** **F**
Jenny knew that Emma was unhappy with her wages so she believed that if she got Emma’s boss to think that the chemist wanted Emma to go and work there, he would believe her **T** **F**

Emma’s boss believed the chemist wanted to give her a job **T** **F**

Jenny thought Emma’s boss would believe the story **T** **F**
Emma, who worked at the greengrocer and lived near the chemist, asked Jenny, her friend who was still at school, for advice on what to do about her grades **T** **F**

Emma’s boss is the greengrocer **T** **F**

STORY 4

SIMON THINKS….

Simon was 19 years old and worked as a mechanic. His cousin, Jim, was quite a lot older, and worked as a milkman. Because Jim had to get up early in the morning, he seldom went out in the evening. As a result, Jim's social life was a bit restricted. Jim's and his best friend Edward had known each other since primary school; they had been inseparable when they were younger. Edward worked in a bank, and therefore had more opportunity to go out in the evenings. Simon knew that Jim wanted to marry Susan. Simon also knew that Jim believed that Susan wanted to marry Edward, and that Jim was concerned that Susan found Edward socially more exciting because he could take her out in the evenings. Simon thought that if he could convince Jim that Susan believed that Edward wanted to marry another girl named Betty (even though Betty did not actually want to marry Edward), Jim might be persuaded that Susan would say "Yes", if he asked her to marry him. So Simon planned to have a drink with Jim one lunch time when they were both free, and tell him this.

Story 4: Simon thinks

Simon knew that Jim thought that Simon found Edward more socially appealing, and that Susan thought Jim was boring **T** **F**

Edward went to primary school with Simon's cousin, Jim **T** **F**

Jim's cousin is 20 years old **T** **F**

Simon wants Jim to believe that Edward fancies Betty **T** **F**

Jim wants to marry Susan **T** **F**

Simon wants to take Jim out for a drink **T** **F**

Simon imagined that Betty wanted to marry Edward but that Edward really wanted to marry Susan, whom Jim would like to have married **T** **F**

Jim and Edward have been friends since school **T** **F**

Simon hoped that Jim would believe that Edward wanted to marry Betty because Simon wanted to make Jim happy by thinking he had a chance with Susan **T** **F**

Jim is Simon's cousin and often goes out with Susan **T** **F**

Edward, who was a friend of Jim's worked at a bank, and had time to go out at night, unlike Jim who worked as a milkman and couldn't socialize at night because of his hours **T** **F**

Jim believes Susan thought that Edward works as a milkman **T** **F**

Simon wanted Jim to know that Susan thought that he wanted to marry her and that she would like to marry him also **T** **F**

Simon is Jim's cousin and is a mechanic **T** **F**

Simon knows his cousin wants to marry Susan **T** **F**

Jim, who is Simon's cousin and Edward's friend, doesn't have much of a social life because he works as a milkman and doesn't get out in the evenings **T** **F**

Edward, who works in a bank and has plenty of spare time, was friends with Jim but didn't know Betty or Susan **T** **F**

Jim is older than Simon and is a banker **T** **F**

Jim thinks that Susan wants to marry Edward **T** **F**

Simon, who was Jim's brother and who worked as a mechanic, was 19 yrs old, which was a lot younger than Jim who worked as a milkman, and didn't socialize much **T** **F**

STORY 5

CLIVE and LUCY

It was Clive and Lucy's wedding anniversary; they had been married for one year. Lucy thought that Clive might have forgotten and was surprised when he took her out to a restaurant for dinner. Clive was pleased that she had been surprised. They sat at a table beside a window overlooking the harbour. There was a candle in a wine bottle on the table, and the tablecloth was a deep red in colour. The waiter came to take their orders, but Clive said he had not yet made up his mind. He continued to stare at the menu for a quite a length of time. Lucy had already made up her mind and said she wanted the monkfish and salad. After a few minutes, Lucy started to wonder why Clive was taking so long to choose what he wanted. She thought it might be because the food was very expensive. She began to feel upset because that might spoil their evening. Clive noticed that she was upset, but didn’t know why. 'I've noticed that there is only seafood on the menu. You know I don’t like seafood. I'll see if they have a vegetarian option instead' he explained. Lucy seemed relieved, but Clive still didn’t know what had upset her.

Story 5: Clive and Lucy

Lucy ordered monkfish and chips **T** **F**

Clive understood that Lucy knew that Clive regretted that Lucy was feeling angry because Clive did not know what to eat **T** **F**

The expensive restaurant that Clive booked only sold seafood **T** **F**

Clive wanted Lucy to know that Clive thought that Lucy understood that he didn’t like seafood **T** **F**

Clive booked a restaurant to celebrate their 2nd wedding anniversary **T** **F**

Clive thought Lucy was upset because he didn’t like seafood **T** **F**

When the waiter came to the table, Lucy had made up her mind and ordered the monkfish and salad; Clive had not yet decided **T** **F**

Lucy was worried that Clive believed she didn’t like the restaurant **T** **F**

The vegetarian restaurant overlooked the harbour **T** **F**

Clive wanted a vegetarian option **T** **F**

While having lunch at a seafood restaurant, Clive perused the menu for a vegetarian option while Lucy ordered the monkfish and salad **T** **F**

Lucy wanted Clive to know that Lucy thought that Clive believed the restaurant was too expensive **T** **F**

Clive thought that Lucy believed that Clive knew that Lucy thought that Clive felt that the food was too expensive **T** **F**

Lucy ordered the monkfish and salad, Clive ordered nothing **T** **F**

Lucy thought Clive was worried about the price **T** **F**

Lucy knew Clive had remembered their anniversary **T** **F**

Clive and Lucy sat at a table beside the window which overlooked the harbour; there was a candle in a wine bottle sitting on their table **T** **F**

Lucy thought the food was too rich **T** **F**

The table was beside a window and overlooked the harbour, it had a deep red tablecloth and a candle in a wine bottle **T** **F**

Clive booked a restaurant to celebrate their anniversary **T** **F**