Cerebral Lateralisation of Speech Production and Motor Skill

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Abstract

The association between praxis and language is longstanding in neuropsychology, with evidence revealing that left hemisphere lesions often lead to combined impairments in motor control and speech (Rasmussen and Milner, 1975; Goldenberg, 2013). Strong left hemisphere asymmetry for language is a robust finding at the population level (e.g. Knecht et al 2000a) and similarly the cortical activation patterns of manual praxis for skilled tasks also reveal a left hemisphere bias (Buxbaum et al, 2005; Haaland et al, 2004). As such, common neural mechanisms are thought to underlie both speech and motor skill, especially actions involving fine motor control of the hands. However, evidence for a clear causal relationship between handedness and speech laterality has proven somewhat weak and inconsistent, due to the wide variation in measurement and classification approaches used (Groen, et al, 2013). A suggestion by Flowers and Hudson (2013) is that motor and speech laterality are related where they involve a common feature of motor output, namely the co-ordination of sequences of movements or utterances to execute a plan or intention so as to achieve a goal; either limb movement or expression of an idea (e.g. Grimme, et al, 2011). The research conducted here investigates speech and motor lateralisation from the hypothesis that sequencing based tasks will be best able to elicit the predicted left hemisphere activation patterns. Five empirical chapters are presented detailing a number of studies involving healthy adults, typically developing children and adults with Developmental Coordination Disorder. The research uses an emerging technique in cognitive neuropsychology; functional Transcranial Doppler (fTCD) sonography, to explore hemispheric laterality of speech and motor skill. Measurements of the degree of activation in each of the hemispheres during language tasks, and the use of a skill-based motor task to determine handedness, are the primary indicators of lateralisation used throughout this thesis. Results from the first 3 chapters reveal that 1) atypical patterns of speech laterality are linked to greater performance differences on motor skill tasks; 2) that whilst hand preference is established early on in childhood the relative performance ability between the non-preferred and preferred hands develops linearly with age; 3) adults with developmental coordination disorder display atypical patterns of laterality of speech networks. The final 2 empirical chapters employ novel neuroimaging paradigms to investigate the mechanisms underlying the links between speech and motor sequencing. Results show that the pegboard task elicits left hemisphere dominant activation regardless of the hand used, unlike other motor tasks with similar properties. Finally a dual task paradigm demonstrates that speech production suffers greater impairments than motor skill when performed simultaneously, providing support for theories proposing a gestural origin to speech. The data are discussed in terms of the specialisation of the left hemisphere for higher order sequential processing, in the context of a lateralised speech-praxis centre model.

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Notes on Thesis Structure

This thesis has a paper-based structure. Specifically, four of the five empirical chapters (Chapters 4-7) are presented in the form of manuscripts submitted for publication. These manuscripts are at various stages of the publication/review process, and the status of each paper is summarised in Table *i*. Inevitably, there is some repetition in the 'Method' section of each paper as a consequence of this. A preface is presented at the beginning of each chapter to clarify the contribution of each manuscript to the aims and hypotheses of the thesis, and to aid integration of the papers. Some minor adjustments have also been made to the presentation of the papers to help the reader. Specifically, sub-sections of each paper have been re-numbered to provide a global numbering system for the entire thesis, and figures and tables have been presented in the appropriate positions rather than the end of each manuscript.

Table *i.* The publication status of the papers presented in this thesis.

	Journal	*Status*
Chapter 4	Laterality	Under Review
Chapter 5	Developmental Cognitive Neuroscience	Under Review
Chapter 6	Journal of Neuropsychology	Published 2016
Chapter 7	Behavioural Brain Research	In prep

Chapter 1

Cerebral lateralisation of speech and motor control: An Introduction

The cortical organisation of speech and language processes has been the subject of much research in cognitive neuroscience and neuropsychology, and yet is still incompletely understood. Historically speech production has been seen solely as a left hemisphere function, due to early evidence from patients with brain injury and their subsequent language impairments (Broca, 1861 as cited in Price, 2000). However, modern neuroimaging techniques have revealed a more intricate set of cortical networks underlying speech processing, which integrate associated sensory input and output modalities such as motor control, and result in a distributed and complex pattern of cerebral lateralisation of function. The neural relationship between speech production and motor action underlie the long established links language lateralisation research has with hand preference research, which was driven initially by accounts of patients displaying co-occurring deficits in motor control and language following focal left hemisphere lesions.

However, evidence for a clear causal relationship between handedness and speech laterality has proven inconsistent, due to the wide variation in measurement and classification approaches used. A suggestion by Flowers and Hudson (2013) is that motor and speech laterality are related where they involve a common feature of motor output, namely the co-ordination of sequences of movements or utterances to execute a plan or intention so as to achieve a goal; either limb movement or articulation of an idea (e.g. Grimme, Fuchs, Perrier and Schöner, 2011). This thesis sets out to investigate cerebral lateralisation from this perceptive, specifically exploring the hypothesis that sequencing based motor skill and speech production share common neural networks and are lateralised to the same hemisphere. The research will incorporate novel studies on a number of participant groups, including healthy adults, young children, and individuals who have developmental motor control impairments, as a means by which to investigate the properties underlying cerebral lateralisation. The research will use an emerging technique in cognitive neuropsychology; functional Transcranial Doppler (fTCD) sonography, to explore hemispheric laterality of speech and motor control. Measurements of the degree of activation in each of the hemispheres during speech tasks, and the use of a skill-based motor task to determine handedness, are the primary indicators of lateralisation used throughout this thesis. Chapter 4 presents an initial experiment that aimed to replicate the results of Flowers and Hudson (2013) in a group of healthy adults. In this experiment the relationship between motor laterality and speech representation is replicated in healthy adult participants, and demonstrates that typical cerebral lateralisation patterns are linked to improved motor skill performance. The experiment also serves as an opportunity to test the reliability and validity of the fTCD method and the speech production tasks used in subsequent chapters, by presenting data on test-retest reliability and adults' performance on a speech task designed for children.

Having demonstrated that the word generation and animation description fTCD paradigms, and electronic peg-board task, are suitable methods for the current research programme, exploration of the developmental trajectories of speech and motor laterality commences in chapter 5. This chapter describes the novel findings of an investigation into whether sequencing based motor and speech tasks mediate the variation in laterality profiles of young children, and forms the basis of a manuscript currently under review for publication in *Developmental Cognitive Neuroscience*. A large sample of typically developing children aged 3 - 10 years completed the peg board task as well as motor and language assessments, and a sub set of these children also underwent fTCD imaging to determine language lateralisation. Evidence of an increased performance difference between the hands was found in those children who had atypical language representation. Furthermore no evidence of age effects in direction of hemispheric language lateralisation or in hand dominance was found, although younger children had a greater performance difference between their hands.

Chapter 6 examines the links between speech and motor lateralisation from the novel perspective that individuals with developmental motor coordination impairments, such as Developmental Coordination Disorder (DCD), but with normal speech and language skills, may also have atypical language representation as a result of the common neural basis to speech and motor function. This paper reports the findings of an experiment with adults with DCD and healthy control participants, which is published in the *Journal of Neuropsychology*. The study required all participants to perform the word generation paradigm whilst undergoing fTCD and to then undertake the motor skill pegboard task. Results showed that the control group were significantly more left hemisphere lateralised during the speech tasks than the DCD group, despite no evidence of behavioural speech impairment in these individuals. This provides additional evidence for the hypothesis that sequencing based tasks are crucial for exploring cerebral lateralisation of speech and motor skill.

Having found evidence from a range of participant groups that performance on a motor skill task relates more closely to the profile of speech lateralisation displayed than does the handedness classification derived from self-report measures, chapters 7 and 8 set out to investigate the mechanisms behind the links between these two function. Chapter 7 investigates whether the specific components of the peg board task could be deconstructed to better understand the common properties between speech and motor control, which may underlie the results seen thus far. In Experiment 1 healthy adult participants were asked to undertake a range of motor tasks which were derived from component processes involved in the pegboard task. The performance on these tasks were then compared to the speech lateralisation indexes derived from the same participants using the word generation paradigm. Correlational analysis revealed links between speech lateralisation and only two of the 6 motor tasks; coin rotation and the pegboard. Experiment 2 then employed a novel fTCD paradigm in new participants which measured the lateralisation index of each hand whilst performing each of the two task found to link with speech scores. These results demonstrated strong left hemisphere activation patterns for the pegboard task regardless of the hand used, in contrast to clear contralateral activation for the baseline tasks.

A final empirical chapter, chapter 8, explores whether the mechanisms underlying the relationship between speech and motor control could be explored further by interrupting the effectiveness of cortical processing via a dual-task methodology. In this preliminary study participants were asked to complete the pegboard task and a word generation task separately and then simultaneously. Performance on this set of tasks was then compared to a baseline condition of single and dual task completion, consisting of a different set of motor and speech tasks with properties unrelated to each other. Results indicated that speech production performance was more severely impeded than motor performance under dual task conditions.

Several conclusions can be drawn from these studies. Most importantly, they demonstrate support for the hypothesis that motor and speech sequencing are mediated by common neural networks in the left hemisphere, and that links between handedness and language lateralisation are detectable when measured using tasks with this property. This interaction is evidenced in a developmental sample, those with motor coordination difficulties, as well as in neuro-typical adults. These novel findings have implications for our understanding of the neural basis of speech and motor control and indicate that theories proposing a manual basis to speech lateralisation may be appropriate. Chapter 9 discusses the relationship between properties of motor tasks and speech production, and considers these results in the context of a left lateralised speech-praxis centre model which could account for the relationship shown between speech and motor sequencing. It culminates in the consideration this work has for future research in this area.

Chapter 2

Literature Review

One of the most well established findings in cognitive neuropsychology is the specialised role played by each half of the brain in the production of language and movement. Over the last 150 years scientists have examined the effects of brain injury on speech and motor control, the implications of atypical development on these functions and the neural relationship underlying them. And yet, despite this focus, our understanding of how the two functions are linked neurologically and the cortical processes which underlie them is still evolving. Understanding the interaction between hemispheric speech dominance and handedness forms the central theme of this thesis and is crucial to arguments and theories surrounding the behavioural significance and neural basis of laterality. This chapter reviews the literature on hemispheric lateralisation of speech, handedness and motor control, and draws together the arguments set out in this thesis.

2.1 The Asymmetrical Brain

The left and right hemispheres of the brain, whilst intricately connected, have long been supposed to be functionally separate. For some cognitive tasks the notion that one hemisphere is more involved than the other has been borne out by research with brain injured patients and also by neuroimaging of healthy participants (Josse and Tzourio-Mazoyer, 2004). As such, the brain is considered to be asymmetrical or 'lateralised' if one hemisphere or region is structurally different from another and/or performs a different set of functions (Bisazza, Rogers and Vallortigara, 1998). Hemispheric asymmetries exist and they influence behaviour (Hellige, 1993), however, it is debated as to why this neural organisation is necessary. One advantage of hemispheric specialisation is that it avoids unnecessary duplication of valuable neural tissue, which may be especially important in complex functions requiring extensive neural circuitry, such as language. Complementary specialisation in the two hemispheres is thought to result in a gain in overall computational efficiency. Most individuals, for example, demonstrate left-hemisphere dominance for language (see Section 2.2) and right-hemispheric dominance for spatial attention (Groen, Whitehouse, Badcock and Bishop, 2011). A second advantage of lateralisation 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, where separate processing of simultaneous visual input would leading to conflicting response preparation (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”.

Another advantage of lateralisation 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). Ringo et al (1994) also 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 2.3 the speed in which information is passed from one brain region to another is an important factor for 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. 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). Since men have larger brains than women (Amunts et al., 2000; Good et al., 2001a; Gur et al., 1999) and smaller brains tend to have a relatively larger corpus callosum (Jäncke et al., 1997), less marked hemispheric lateralisation in females could be reflected in the reduced anatomical asymmetries and a larger corpus callosum (Luders et al., 2002). 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.

The concept of functional lateralisation, such as in the case of language or motor control, raises questions regarding the structural correlates of such lateralisation (Amunts, 2010). Anatomical asymmetries exist within the brain, and have been found specifically in regions of the cortex related to language processing. For example Heschl's gyrus, a structure found in the temporal region which includes the primary auditory cortex, has been shown to have greater grey and white matter asymmetry, and for this asymmetry to be linked to language lateralisation (Penhune et al., 1996; Dorsaint-Pierre, et al., 2006). In addition, the planum temporale (PT), a region found on the superior temporal plane and part of the classical Wernicke's area, has been shown to be larger in the left hemisphere than the right (Geschwind and Levitsky, 1968; Witelson and Kigar, 1992; Wada et al., 1975), even prenatally, suggesting a predisposition for left hemisphere language processing (Chi et al., 1977), although there is limited evidence that this asymmetry can predict language lateralisation (Dorsaint-Pierre, et al., 2006). More recently it has been shown that volume asymmetry in the Insula can be a predictor of hemispheric language dominance (Keller, et al., 2011). Structural differences have also been found in the neurobiology of the cortex including larger micro-anatomical cell size, greater thickness of myelin, wider micro-columns, and larger spacing of macro-columns in the left hemisphere (Hayes and Lewis, 1993; Penhune et al., 1996; Seldon, 1981; Galuske et al., 2000). Furthermore, the patterns of connectivity across brain regions also differ between the two hemispheres, with a larger volume of fibre tracts in the arcuate fasciculus in the left hemisphere (e.g., Duffau, 2006).

2.2 Cerebral lateralisation of Speech

Speech production is one of the most studied aspects of functional cortical asymmetry and hemispheric lateralisation. The traditional neural model of language production, namely that the left hemisphere is more specialised at this task than the right hemisphere, arose in the 19th century through various works by Dax (1865, as cited in McManus, 2002), Broca (1865, as cited in Price, 2000) and Wernicke (1874, as cited in McManus, 2002) who were among the first individuals to identify that patients with left frontal temporal lesions had distinct language and speech production impairments; patterns which weren't observed in patients with homologous right hemisphere lesions. The conclusions from these observations were that the left hemisphere had developed a functional specialisation for speech and language processing, which was not evident to the same degree in the right hemisphere. Some early evidence for language dominance came from split-brain patients, whose corpus callosum was sectioned to control intractable epilepsy. The seizures were decreased by disconnecting the two hemispheres. Testing of each disconnected hemisphere in split-brain patients revealed reasonable language understanding in the isolated right hemisphere, but no speech output, which remained confined to the specialised processing of the left hemisphere (Gazzaniga and Sperry, 1967; Gazzaniga, 1983). These findings still underlie the predominant view of cortical language organisation today. 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 pars opercularis (PO) in particular) are crucial for speech production (Costafreda et al., 2006; Geschwind and Galaburda, 1985; Geschwind and Levitsky, 1968; Stephan et al., 2003; Toga and Thompson, 2005).

Research using neuroimaging techniques have attempted to localise characteristics of language to regions within the dominant hemisphere. Speech 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 pars triangularis (PT) regions of the inferior frontal gyrus (IFG), also known as Broca's area (Brodmann Areas 44 and 45). Lesions to this area have effects including inability to generate word lists and difficulty with naming and articulation (Binder et al., 1997). By contrast, language comprehension, such as understanding spoken words (Price, 2000), is served primarily by the posterior temporal-parietal region, including Wernicke's area (Brodmann Areas (BA's) 39 and 40, posterior BA21, BA22, and part of BA37). Neuroimaging evidence has also extended our view of the cortical organisation of speech and language by providing data indicating that the right hemisphere has an important role to play in speech production processes. Examples of this include the utilisation of contextual cues to inform speech production and the insertion of emotive inflection into speech (e.g. Gardner, Brownell, Wapner and Michelow, 1983). 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). Furthermore evidence suggests that the right hemisphere may even be the dominant hemisphere for speech in a proportion of the population (e.g. Knecht et al 2000a; Hertz-Pannier et al 2002; Szaflaski et al 2002; Moddel et al 2009; Vingerhoets et al 2013).

Predominant neural models of speech processing suggest a differential contribution of the two hemispheres which may be task dependent. One such account is the dual stream model (Hickok and Poeppel, 2004, 2007) which proposes that a distinction should be made between the dorsal and ventral streams of language processing and production (see Figure 2.1).

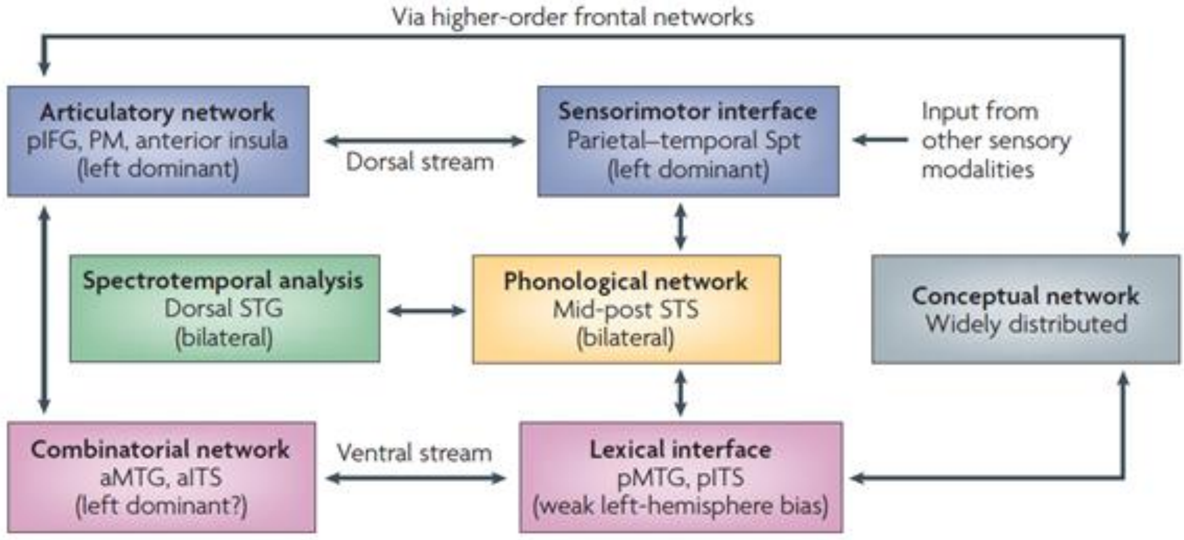


Figure 2.1 The dual-stream model of the functional anatomy of language, taken from Hickok and Poeppel, (2007). aITS, anterior inferior temporal sulcus; aMTG, anterior middle temporal gyrus; pIFG, posterior inferior frontal gyrus; pITS, posterior inferior temporal sulcus; PM, premotor cortex; pMTG, posterior middle temporal gyrus; Spt, sylvian fissure at parietal temporal junction; STG, superior temporal gyrus; STS, superior temporal sulcus

This model indicates that the specialisation of the left hemisphere can be associated with particular aspects of language production, characterised by the dorsal processing route. The dorsal stream is said to involve the posterior and dorsal-most aspect of the temporal lobe and parietal operculum, as well as the posterior frontal lobe, to convert sensory input into motor information. Conversely the ventral stream, involving structures in the superior and middle portions of the temporal lobe, processes verbal input for comprehension. Hickok and Poeppel (2007) suggest that the dorsal stream is left-lateralised, while the ventral stream is organised bilaterally, a suggestion which has recently been supported by studies using diffusion tensor imaging (Rilling et al., 2012) and fMRI (Häberling, Steinemann and Corballis, 2016). The idea that speech production processes may rely on a different set of neural structures and networks than those used for language comprehension is perhaps unsurprising, given the differing sensory processing requirements of each function. Indeed, evidence from patients with focal lesions allows the dissociation of component processes of the language system, due to specific deficits being associated with damage in particular areas (Wise and Geranmayeh, 2016). For example, lesions to Broca’s area affect the ability to produce fluent and coherent speech, as well as sometimes producing difficulties in naming and word finding. This damage, however, does not affect comprehension abilities, indicating that different brain regions or networks must be involved in that process.

The idea that networks supporting language function may be distributed across the hemispheres has important implications for the experimental paradigms used to elicit speech activation. Studies using a verbal fluency, or word generation, paradigm dominate the literature on speech lateralisation (e.g. Knecht, et al., 1998; Knecht et al. 2000a, 2000b; Bishop, Watt, and Papadatou-Pastou, 2009; Somers, et al., 2011). This paradigm requires participants to produce corresponding words when shown a letter or category stimulus, and tends to produce a clear left hemisphere activation pattern which is highly reproducible within individuals (Knecht, et al., 1998). However, paradigms which rely more upon receptive language skills, such as matching pictures and words, semantic decision making, reading or listening to spoken words, have been shown to produce increased bilateral or right hemisphere activation (e.g. Stroobant, Buij and Vingerhoets, 2009; Haag et al., 2010; Bishop et al., 2009; Badcock, Nye and Bishop, 2012; Hodgson, Benattyallah and Hodgson, 2014). These differences in lateralisation patterns are likely due to the variations in processing requirements of each task, where tasks which rely more on working memory and semantic decision making, rather than lexical retrieval and phonological processing, may produce a more distributed LI pattern. Studies which have compared the activation patterns produced by different language tasks reveal that expressive tasks tend to produce a stronger left hemisphere bias than receptive tasks (e.g. Buchinger et al., 2000; Hertz-Pannier et al., 2002). Stroobant et al (2009) compared a story listening task which required participants to subsequently answer questions on the content, with an expressive story telling task. They found that whilst 90% of individuals were left lateralised on the expressive task, the listening task only produced left hemisphere dominance in 60% of participants. The evidence suggests that productive or expressive tasks are more strongly lateralised than passive or receptive tasks; however, individual lateralisation varies between different expressive tasks also (Bishop et al., 2009).

The effect of task complexity on speech lateralisation profiles has also been explored. It has been suggested that paradigms which are more difficult may require a wider range of cognitive functions to be involved to complete the task, which in themselves may rely on more distributed neural networks and brain regions. However, Drager and Knecht (2002) varied the complexity level of the word generation paradigm by introducing word string stimuli of high and low frequency words. They found no variation in lateralisation patterns as detected by fTCD; the left hemisphere was still dominant. Badcock, Nye and Bishop (2012) argue that the effect of task difficulty on lateralisation profile is not straightforward, and that whilst additional areas of the cortex may be recruited to help with a complex task (thus reducing the lateralisation profile), it may also be the case that the specialised system becomes *more* involved in task completion, thus increasing lateralisation. They also point out that previous studies have not controlled for individual variation in rehearsal and recall strategies, which may have affected the results displayed. To overcome this Badcock, Nye and Bishop (2012) compared three speech production tasks with varying degrees of expressive and receptive features and differing levels of difficulty, as measured by the inclusion of both high and low frequency stimuli. Results showed that although increased task difficulty affected participants' accuracy levels and reaction times, these differences did not relate to physiological changes in lateralisation indices. This indicates that task complexity is independent of LI scores, which are more likely to be affected by task type.

One factor which is frequently raised in research on cerebral lateralisation of speech is whether differences occur on the basis of sex. Previous research indicates that sex differences exist generally in brain structure and function (for a review see Cosgrove et al., 2007), however, 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 lateralisation in males but no clear lateralisation 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 lateralisation in both sexes. A meta-analysis of the fMRI data from 2,151 subjects from 26 studies found no effect of sex of language lateralisation (Sommer, 2010). Using data from a sample of 3,822 subjects the effect of sex on dichotic listening tasks was also investigated (Sommer, 2010). The effect of sex was not significant with both sexes demonstrating a right ear advantage. Additionally the inclusion of non-right-handed subjects had no major influence on the sex difference in language lateralisation. Furthermore a recent study by Hudson and Hodgson (2016) indicated via fTCD, a direct measure of speech laterality, and digit ratio, a well-established method of estimating pre-natal testosterone exposure, that effects of sex difference on laterality of speech were not discernible. Inconsistent findings related to the effect of sex on language lateralisation suggest that the differences in the functional organisation of language processes, if any exist, are small.

2.2.1 Patterns of Cerebral Lateralisation through Development

Researchers have focussed on understanding whether the left hemisphere is predisposed to support speech function, and if so, whether left hemispheric dominance for language is present at birth or if it develops during childhood and early adolescence. It has been shown that left hemisphere language specialisation can be observed even in very young babies who display adult-like left-lateralised activation in perisylvian areas when listening to sentences in their native language (Dehaene-Lambertz and Houston, 1998) as well as left inferior frontal lobe (e.g., Broca’s area) activation during speech processing (Dehaene-Lambertz, Dehaene and Hertz-Pannier, 2002; Imada, et al., 2006). Furthermore studies have shown that the behavioural repertoire of infants with regards to language include abilities in categorical perception of phonemes (Eimas, Siqueland, Jusczyk and Vigorito, 1971) and early involvement of Broca’s area in verbal memory (Dehaene-Lambertz et al., 2006). This evidence supports the notion that the brain is predisposed to support speech function several months before the onset of speech production or even pre-speech babbling.

School aged children and adolescents typically show a predominant left hemisphere activation for silent word generation tasks (Norrelgen et al., 2012, Szaflarski et al., 2012 and Wood et al., 2004), silent reading (Gaillard, Balsamo, Ibrahim, Sachs and Xu, 2003) and an auditory categorisation task (Balsamo, Xu and Gaillard, 2006) in areas of the frontal and temporal gyri as well as fusiform and supplementary motor area. In addition, a number of these studies have indicated a positive correlation between left hemisphere activation and task proficiency (Balsamo et al., 2006; Wood et al., 2004). Magnetoencephalography (MEG) studies with children and adolescents aged 5–19 years have also shown a predominant left lateralisation to word generation tasks but, unlike in fMRI studies, one that increases in prominence with age between around 5–7 years and mid-late adolescence (Balsamo et al., 2006; Kadis et al., 2011; Wood et al., 2004). Typically developing children have also been shown to vary in the degree of language lateralisation compared to adults (Holland et al., 2001). In Holland et al’s (2001) study, although most subjects at all ages tested showed left hemisphere dominance for the language task, the degree of lateralisation increased with age. This study demonstrates that fMRI can reveal developmental shifts in the pattern of brain activation associated with semantic language function. The idea that strengthening of lateralisation increases with age has also been supported by a recent functional transcranial Doppler study in children aged 1-5 years (Kohler, et al., 2015). This data showed that although most children displayed the typical left hemisphere dominant pattern during speech, the variability of the response changed as a function of age, with younger children producing a more variable lateralisation index.

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 white matter (WM) anisotropy (a measure of WM integrity) as assessed with DTI techniques. The fact that language is lateralised 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.

Developmental neuropsychological research into functional localisation of speech has predominantly focussed on children with acquired language impairments (e.g. Ballantyne et al., 2008; Liegeois and Morgan, 2012). Evidence shows that children's brains have a greater propensity towards cortical plasticity; the ability of the brain to re-wire and establish new connections following injury (e.g. Duffau, 2006), and studies have shown that children with brain injuries affecting speech and language have better and faster recovery than adults with the same pathologies (Beharelle et al. 2010). Furthermore it has been shown that children exhibit superior capacity to transhemispherically compensate for impaired language functions compared to older children and adults (Lohmann et al 2004; Ballantyne et al., 2008). This therefore suggests that there are fundamental differences between the way in which the developing brain processes and produces speech and language. Evidence from neurodevelopmental disorders indicates the profile of cerebral lateralisation changes when development does not follow a typical pattern. Stuttering is a motor speech disorder which has also been associated with bilateral language lateralisation (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). Furthermore atypical lateralisation for language has been shown in disorders such as Dyslexia (Illingworth and Bishop, 2009) and Specific Language Impairment (SLI; Whitehouse and Bishop, 2008) where higher proportions of these groups display reduced left hemisphere bias during speech than typically developing controls. It is thus suggested that atypical hemispheric speech activation could be representative of an immature, or impaired, neural speech network (Bishop, 2013).

2.3 Handedness

The most obvious behavioural asymmetry displayed in humans is hand dominance; the fact that in most people one hand is preferred over the other for skilled work and fine motor control (Papadatou-Pastou, 2011). Handedness reflects an asymmetry of cortical processing and neurological organisation, as opposed to an asymmetry of the hands themselves (Corballis, 2010). Traditionally, handedness was considered a uniquely human trait, however, recent ecological work has shown that other species in fact also display hand preferences (see Corballis, 2003 for review), although the population level bias to the right hand side is considerably marked in humans (around 90%). Multiple factors are thought to affect the determination of 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, 1975). 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, however, genetic models linking handedness and cerebral asymmetry for language are discussed in section 2.4.2.

Human hand preference emerges very early in an infant’s life, where genetics and environmental influences are believed to play a key role in development (Scharoun and

Bryden, 2014). Some evidence suggests hand preference in adulthood can be predicted from lateralised motor behaviour observed in early gestation (for review see Scharoun and Bryden, 2014), for example through ultrasound observation of thumb sucking preference behaviours (Hepper, et al.1991), and grasp reflex strength measured in neonatal infants (Tan and Tan, 1999). Researchers have also studied infant postural preferences with a view that these behaviours in fact guide the development of handedness (e.g. Coryell and Michel, 1978; Michel, 1981). These observational studies showed strong correlations between hand preference in infancy for reaching (Marschik et al, 2008) and grasping objects (Michel et al., 2002, 2006) and hand-use distributions amongst adults. Research has also indicated that hand preference can be reliably detected from 6-months onwards (see Butterworth and Hopkins, 1993, for review of handedness in infants). Evidence from cross-sectional (Hawn and Harris, 1983; Peters, 1983; Morange and Bloch, 1996) and longitudinal studies (Coryell and Michel, 1978; Ramsay et al., 1979; Carlson and Harris, 1985; Ramsay, 1985; Michel and Harkins, 1986; McCormick and Maurer, 1988) indicate that some degree of hand preference can be observed at the point at which the infant is developing grasping skills. Although these findings indicate that hand preference can be observed very early in life, there is also evidence which suggests that handedness is a highly malleable trait (Corbetta et al, 2006). Different patterns of hand preference development have been observed in young children, including frequent shifting from right to left hand use during fine motor tasks (e.g. Corbetta et al., 2006; Michel et al., 2006). Studies measuring hand preference from early childhood to adolescence (i.e., ages 3–12) provide no general consensus regarding the age at which adult-like handedness is actually attained (Scharoun and Bryden, 2014). Some researchers (Archer et al., 1988; Longoni and Orsini, 1988; McManus et al., 1988) suggest that *direction* of hand preference is fixed at age 3, further explaining that degree increases between the ages of 3-7. Based on this idea, an individual’s hand preference cannot be reliably assessed until at least 4 years of age (McManus, 2002), although some studies have noted that children 3–4 years of age do not reliably select a preferred hand when performing unimanual tasks, and that it is not until the age of 6 that a clear preference can be observed (e.g., Bryden et al., 2000a, b). The equivocal findings here may be due to the different ways of quantifying hand preference and performance abilities in the research (Scharoun and Bryden, 2014).

2.3.1 Measurement and Classification

An important factor for the effective examination of the development of hand preference is the exact definition of handedness itself. There are various elements that make up motor skill, such as grip strength, dexterity, sequencing ability and co-ordination, all of which can be revealed in different functional tasks (Bishop, 1990). However, most studies allude to handedness as a unitary phenomenon and seek to measure and classify across a simple dichotomy of right versus left. 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 (Annett, 2002). 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). A common issue arises from the fact that handedness is actually classified differently between studies, with particular variation when it comes to classifying ambiguous or mixed handedness. These can either be treated as distinct categories or as a continuum of handedness as determined by a laterality quotient (see Annett, 1985, for review). Laterality quotients are used to provide a standardised measurement of handedness direction from responses on a handedness inventory or performance task. However, their use as a way of quantifying inventory responses has been criticised for disguising the variance in hand usage across different tasks (because responses are simply converted to a numerical value); indeed, such nuances may actually be very informative when it comes to assessing and classifying an individual's hand preference (Annett, 2002).

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, 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 the dextral direction, the so-called 'right-shift' (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., 1979).

Alongside classification, another crucial issue with research into handedness is how it is measured between studies. Some studies define hand preference simply on the basis of writing hand (Stellman, Wynder, DeRose, and Muscat, 1997; Perelle and Ehrman, 2005), as this skill is largely specific to one hand in the majority of people, and remains poorly executed in the non-preferred hand even after considerable training

(Perelle and Ehrman, 2005). Furthermore, Perelle and Ehrman (1994) found that only 0.9% of individuals considered themselves to be ambidextrous for writing, meaning that the majority of people will be easily categorised as either right or left handed using this approach. However, writing is a skill which has been subject to cultural and societal influence in terms of the hand individuals have been taught to use; normally the right hand. This results in people over a certain age (as this practice was common up until the mid-20th century) and from different cultures showing a right hand bias that does not necessarily reflect the actual manual skill or dexterity of their hands.

Other approaches to hand preference measurement include the use of self-report questionnaires or inventories that examine hand preference for everyday tasks, such as throwing, striking a match, using scissors (e.g. Annett, 1970; Oldfield, 1971). One of the most well-established of these is the Edinburgh Handedness Inventory (EHI: Oldfield, 1971) which 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. Other self-report tools have been developed such as Annett's hand preference questionnaire (Dragovic and Hammond, 2007), or the Waterloo Handedness questionnaire (Steenhuis and Bryden, 1989). Inventories are the most commonly used indicators of hand preference, however, results are highly malleable and open to variations in interpretation of hand dominance. There is no consensus in the field about how to classify inventory responses, and specifically on how many separate classifications or groups to use, which leads to an unsatisfactory situation where arbitrary cut-offs are used to distinguish groupings (McManus, Van Horn and Bryden, 2016). Preference measures have also been criticised over reliability (McMeekan and Lishman, 1975) and validity (Williams, 1991), with the suggestion that respondents may either avoid extreme responses to the inventory items, or, select solely extreme responses, thus confounding the measurements (Beaton and Moseley, 1984).

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, 1972), Tapley-Bryden's dot-filling task (Tapley and Bryden, 1985), and the Wathand Box (Bryden et al., 2000a). Such techniques are based on the premise that manual action and dexterity is best understood in the context of a task which requires the use of such skills. Performance measures are able to detect subtle differences in the performance of each hand, and place handedness on a continuum based on relative skill. Such measures of hand skill are preferred as the J-shaped distribution which results from handedness questionnaires is unlikely to reflect the underlying continuous distribution of handedness scores (Tapley and Bryden, 1985). Steenhuis and Bryden (1989) characterised manual activities as either those that were "skilled" (e.g. writing, throwing darts) or those that were "unskilled" (e.g. picking up large objects, petting a cat or dog). They reported differences in handedness distribution between skilled and unskilled activities, with weaker hand preference scores associated with less skilled behaviours. In a later study by the same authors (Steenhuis and Bryden, 1999) it was demonstrated that stronger hand performances are dependent on the difficulty level of the task being measured. Participants completed a battery of tasks including self-report hand preference measures and skill-based tasks which varied in complexity. Results showed that although self-reported hand preference scores correlated well with performance scores (in other words, people can accurately report which hand is their dominant hand), the extent to which the non-preferred hand was used varied between participants. Left handers used their non-preferred hand more frequently than did right handers, and their relative skill differences were smaller. Similarly the non-preferred hand of right handers (i.e. the left hand) was only rarely used in skilled, complex tasks (Bryden, 2015). This conclusion is supported by recent findings that increasing the task difficulty in a performance measure, such as using a grooved pegboard where pegs only fit the holes when placed in a specific orientation, increases the performance advantages of the preferred hand (Bryden and Roy, 1999; Bryden, Roy, Rohr and Eglio, 2007).

Bishop, Ross, Daniels and Bright (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. However, there was a difference between the groups on an experimental measure of preference rather than performance. Participants performed a novel reaching task which significantly distinguished the predominant right handers from the other groups, due to their variation in choosing the left hand when reaching on the ipsilateral side of space. This finding provides support for the idea that hand preference measurements need to be based on empirical data. Taken together these results indicate that classifying handedness on a simple dichotomy of right versus left does not provide a comprehensive view of behaviour across task and skill conditions.

2.4 Associations between Speech Laterality and Handedness

Research on the association between handedness and language lateralisation spans at least the last four decades and is thought to comprise over 10,000 studies (Sommer, 2010). Crucially for research into hemispheric asymmetry and lateralisation of function, Broca himself also made the observation that there was a neurological connection between speech production and motor control, due to the common presence of contralateral hemiplegia in the aphasic patients he reviewed. Broca's rule proposes that hemispheric specialisation for speech and language correlates with handedness and motor control, and more specifically that right handed people (the majority of the population) would be left hemisphere dominant for speech (see McManus, 2002, for detail on Broca's work). The general consensus to emerge from these studies is a difference in language lateralisation between left- and right-handers (e.g. Annett and 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, 1975; 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 lateralisation 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).

A series of seminal papers from Knecht et al., (2000a; 2000b), using functional Transcranial Doppler (fTCD) ultrasonography, drew interesting observations on the natural distribution of language dominance across the hemispheres in healthy right and left handed subjects. Their studies indicated that atypical right-hemispheric language dominance increased linearly with the degree of left-handedness from 4% in strong right-handers to 15% in ambidextrous individuals and to 27% in strong left-handers. While these results clearly show a relation between handedness and language dominance, they also illustrate that 73% of strong left-handers show typical left-hemispheric language dominance, just as most right-handers do. This work was critical in demonstrating that functional localisation of language processes is not automatically assigned to the left hemisphere, as some people display right hemisphere dominant speech networks. This work also suggested that hand dominance and speech lateralisation can be seen as independent biases, whose lateralisation profiles may not be solely reliant on one another.

To investigate this idea further several studies have compared handedness measures and language lateralisation profiles. Badzakova-Trajkov et al. (2010) used fMRI to measure brain activation during word generation in a sample of 155 adults and correlated it with the handedness LQ (laterality quotient) obtained from a 12-item questionnaire. The correlation coefficient for the correlation between the laterality index for frontal activation asymmetries during word generation and the handedness LQ was $r = 0.357$. The coefficient was significant at the $p < 0.001$ level, indicating that individuals with stronger right-handedness were also more likely to show a strong leftward bias for speech activation. However, the coefficient of determination r^2 for this correlation coefficient is 0.127, indicating that roughly 13% of the variance in the handedness data could be explained by the language lateralisation data (Ocklenburg, Beste, Arning, Peterburs and Güntürkün, 2014). More recently Somers et al (2015) also examined whether hand preference was related to direction of hemispheric language dominance as measured by the EHI and fTCD. They concluded that degree of hand-preference does not predict the degree of language lateralisation, but their data showed that increasing strength of left-handedness was associated with increased variation in directionality of cerebral dominance. These studies appear to undermine the functional relationship between speech and handedness, however, it is important to note that in each case handedness measurements were done via self-report questionnaire. As discussed in section 2.3, these methods are potentially less likely to detect the underlying component processes of motor sequencing and skill that may relate to speech processing.

A similar study by Groen et al (2013) compared three different handedness tasks with a direct measure of speech lateralisation in children aged 6-16 years. Two of the tasks were skill-based; a peg board task and a reaching task (see Bishop et al., 1996) and the third was a shortened version of the EHI. Correlational analysis showed that it was in fact the reaching task and the shortened handedness inventory that significantly reflected speech lateralisation indices, and not the peg moving task. This is initially surprising given the neurophysiological and neuropsychological evidence indicating a link between skilled manual tasks and language. However, closer inspection of the results reveals that the correlations with speech scores only existed at the level of hand preference groupings, and that when the scores in each task were converted into laterality quotients the relationship with speech indices disappeared. Performance on the pegboard is measuring hand skill, rather than preference, and so is not equally comparable to the other measures used. In addition the authors themselves point out that none of the measures were able to explain the variance in speech lateralisation by more than 16%, leading to their conclusion that motor performance and language networks are relatively independent of one another. It would appear that weak connections between hand preference and speech lateralisation exist when measured as factors in a preference continuum, however, what is not yet understood is how direct measures of relative hand skill (regardless of an individual's hand preference) relate to direct measures of speech lateralisation. McManus et al. (2016) argue that measurements of performance rather than preference should be relied upon as indicators of cerebral lateralisation, because such tasks tap into the mechanisms thought to be common to both functions.

2.4.1 Neuropsychological Evidence Linking Speech and Handedness

Even though in the healthy brain the associations between speech and handedness are variable and task dependent, there are clear links between the two functions in the neuropsychological literature. After focal left sided brain injury aphasia and apraxia often co-occur (e.g. Vingerhoets et al. 2013), suggesting that the region affected by the lesion must be sub-serving both functions. Patients with apraxia experience difficulties in manual action including gestural ability and tool use, both real and pantomimed, as well as with communicative gestures. Evidence suggests that the incidence and severity of apraxia is reduced in left handed patients, for example Kimura, (1983b) found that the frequency of apraxia in left handed patients was 9% compared to an incidence of 30% in right handed patients with left hemisphere damage. Furthermore a study of defective hand gestures and imitations in apraxic patients showed that left handers were defective in approximately 35% of cases, compared to 66% in right handed patients (Goldenberg, 2013). This data suggests that patients whose hemispheric dominance is more bilaterally dispersed experience milder impairments. However, there is criticism of these figure as they fail to adjust for the incidence of impairments in right handed patients with right sided damage (Goldenberg, 2013).

The distribution of hand preference in individuals with neurodevelopmental disorders has been found to deviate from the general population (Geshwind and Behan, 1982). Left handedness has been more highly associated with language and motor disorders including Dyslexia (Galaburda, et al., 1985) and Autism (Cornish and McManus, 1996) and Developmental Coordination Disorder (DCD; Goez and Zelnik, 2008). Early suggestions were that developmental disorders occurred because of faulty cerebral lateralisation which was also reflected in the handedness distribution amongst those individuals. However, despite these early theories a comprehensive review of studies of handedness in SLI and dyslexia concluded that there was no association with either hand preference or hand skill (Bishop, 1990). Indeed, as mentioned above, atypical cerebral lateralisation is not indicative of reduced language ability, and left handedness is not a prerequisite for neurodevelopmental disorders (Bishop, 2013).

A means of addressing the variability in evidence for the association between handedness and hemispheric language dominance is to examine the predictive power of handedness measures to detect lateralisation scores. Flowers and Hudson (2013) used this approach in the assessment of motor and language laterality in a group of epilepsy patients undergoing the Wada procedure for establishing hemispheric speech dominance prior to surgery. In this study patients were given a peg board task and a handedness inventory based upon the shortened EHI, and these handedness results were compared with the eventual classification of speech dominance derived from the Wada results. The data showed that patients whose between-hand difference on the pegboard task was small or inconsistent were likely to have ambiguous or atypical speech representation (speech apparently partly located in both sides or in the side opposite to that controlling the dominant hand). Those with a consistently large between-hand difference on the motor task all showed clear unilateral speech representation in the hemisphere controlling the better hand (Flowers and Hudson 2013). This is important evidence for arguments supporting an association between cerebral laterality and handedness, and crucially it is derived from a skill-based performance measurement of handedness, rather than a preference categorisation.

2.4.2 Genetic Considerations

The idea that language lateralisation and handedness are related is captured by the genetic models put forward by Annett (1972; 2002) and McManus (1985; 2002) which seek to explain the dominant pattern of left hemisphere bias and right handedness at the population level. Both theories suggest that genetic expression affects the hemispheric lateralisation of language and motor control (Corballis, 2010). For example, Annett's right shift (RS) theory suggests that individual differences in cerebral organisation 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.

Attempts to localise and identify candidate genes driving cerebral lateralisation and handedness have had mixed results. 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 criticised (Crow et al., 2009) leaving the genetic debate in the air (Francks, 2009). A recent meta-analysis of handedness genome-wide association studies (McManus et al., 2013) estimated the number of genetic loci involved in determining handedness to be at least 40, but possibly up to 100, thus also providing evidence against single gene accounts of handedness. Heritability estimates for handedness are in the range of 0.23 to 0.45 (Medland, et al., 2002; Annett, 1985; McManus and Bryden, 1992; 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; McKeever, 2000; McManus, 1991; Risch and Pringle, 1985). 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). However, these studies are confounded once again by the variability in classification and measurement of handedness, making it very difficult to infer causal patterns of heritability.

Research into genetic determinants of language dominance have produced several candidate genes (Bishop 2013). One of the best studied is FOXP2 which has been causally linked to individuals with severe childhood apraxia of speech. Watkins et al. (2002) showed that a mutation in FOXP2 in some members of the KE family had resulted in severe deficits in articulation and speech production. Further studies showed that these mutations were also linked to an absence of Broca’s area activation during speech, as well as to atypical hemispheric speech lateralisation (Liegeois, et al, 2004). However, the role of FOXP2 as an indicator of speech lateralisation is not proven, indeed it is likely that is it not the primary source of lateralisation determination (Corballis, 2010) as its influence on the brain has been shown to occur bi-laterally (Vargha-Khadem, et al., 2005). Furthermore affected members of the KE family show no deficits in motor control and appear to have typical handedness distributions. Other genes which have been considered to play a role in language include CNTNAP2 (Folia, et al., 2011; Kos et al., 2012), DCDC2 (Darki, et al, 2012), DYX1C1 (Darki, et al, 2012) and KIAA0319 (Darki, et al, 2012; Pinel et al., 2012), however, inconsistencies between studies cast doubt on the robustness of the results (Bishop, 2013). Although evidence suggests genetic variants are involved in determination of hemispheric dominance to some degree, it is likely that the picture is more complex than being dependent on just one or two genes.

2.5 Neurophysiological Links between Language and Movement

There is converging evidence from neuropsychology and neurophysiology that cortical networks which support language function are related to those which support motor control. This includes the following strands of evidence 1. Common brain mechanisms are activated by both language and motor function; 2. Motor action (especially fine motor skills and hand usage in complex tasks) is located in areas known to be involved in language; 3. Speech production also activates areas known to be typically involved in motor tasks (e.g. cerebellum, pre-motor area, motor cortex); 4. Patterns of breakdown and recovery of language functions are closely linked (Iversen and Thelen, 1999; Vingerhoets et al., 2013).

The specialised role of the left hemisphere for controlling performance of skilled complex tasks, such as those underlying praxis and speech, has been suggested through the early work of Steenhuis and Bryden (1989). This theory is supported by evidence that larger performance differences were found favouring the preferred hand (usually the right) for complex highly skilled manual tasks compared to simple tasks (e.g. Flowers, 1975; Bryden, Mayer and Roy, 2011). Evidence suggests sequencing and motor timing are common mechanisms that are supported by a network distributed in key regions of the left hemisphere. Broca’s area has been observed to be associated with various non-language motor functions such as planning, recognition and imitation of actions (Nishitani and Hari, 2000; Binkofski and Buccino, 2004) as well as with syntactic operations required for the hierarchical representation of sequential behaviour (Ocklenburg, et al, 2014). The contribution of each hemisphere to motor control is also modulated by movement complexity. Whereas a simple movement such as unimanual finger tapping is organised by a local neural circuit, more complex actions such as those involving a sequence of finger movements engage distributed (often bilateral) networks (Haaland, et al, 2004). Indeed, patients with left hemisphere parietal lesions are likely to show impairments in producing skilled actions with either hand, whereas comparable right hemisphere lesions produce deficits that are largely restricted to the contralateral hand (Wyke, 1971).

A significant factor linking speech and motor control neurologically is the association in overlapping cortical regions that are activated during tasks thought to be functionally independent. Neuroimaging studies of speech production have shown that during speech activation is evident in motor control regions as well as in classic speech production areas. The premotor cortex is known to become active not only during motor tasks but also during action observation and listening to common action-related sounds (Gallese et al., 1996; Kohler et al., 2002). Spoken and written words can also activate the motor system (Sahin et al, 2009) and this activation can even be specific to semantic word types (Pulvermuller, Hummel, and Härle, 2001; Hauk and Pulvermuller, 2004; Shtyrov, Hauk and Pulvermuller, 2004). Words related to actions involving different body parts, such as pick and kick, activate motor and premotor cortex in a somatotopic fashion so that, for example, the reading of leg-related words ‘makes the motor humunculus move its feet’ (de Lafuente and Romo, 2004). This demonstrates category specific links between the core language areas and motor representations in the processing of action words. Furthermore there is evidence that manual action with the hands, in the form of communicative gestures, may be beneficial in aphasia recovery (Rose et al., 2013), again indicating a crucial link between these two systems.

One dominant hypothesis emphasises functional connections between the cortical hand motor area and language circuit (Hauk, Johnsrude and Pulvermüller, 2004; Pulvermüller, Hauk, Nikulin, and Ilmoniemi, 2005) may have been essential for the evolution of language from manual gestures rather than vocal calls (Corballis, 2003), which is supported by the robust use of gestures that typically accompany speech (Iverson and Goldin-Meadow, 1998). People gesture as they speak, and these actions tend to be more frequent with the dominant hand (Kimura, 1973). Evidence from sign language users shows that although both hands are involved in the signing action, one hand tends to be dominant (Corballis, 2003). In addition, evidence for the role of gestures in early language acquisition demonstrates that there is a close link between motor and speech developmental trajectories, with gestural ability at 18 months being shown to predict language ability at 4 years (e.g. Alcock and Krawczyk, 2010). There is some consensus that language may have evolved from manual gestures rather than from indistinct vocalisations (e.g. Arbib, 2005; Corballis, 2003; Pollock and de Waal, 2007; Tomasello, 2008). Supporting evidence for the idea that gesture forms the neural basis of language comes from the observation of the firing patterns of a group of cells in the brain known as 'mirror neurons' (Rizzolatti and Craighero, 2004). These cells, identified in macaque monkeys, were shown to activate when the monkey performed a manual action, but also crucially when the monkey *observed* a manual action being performed. This finding led to the conclusions that motor simulation provides the basis for understanding the actions of others, a necessary component of gestural communication (Rogalsky, et al, 2013). What was important about the discovery of mirror neurons, however, was that these cells seemed to cluster specifically in area F5 of the macaque brain, an area which is deemed to be the homologue of Broca's region in the human brain.

Neuropsychological evidence suggests a causal link between damage to the mirror neuron system and subsequent impairments in speech and motor control, such as those seen in aphasia and apraxia. Evidence shows that gesture recognition is impaired in apraxic patients and that damage to Broca's Area is correlated with poor gesture recognition (Pazzaglia et al., 2008). However, the validity of the mirror neuron theory has been questioned (e.g. Hickok, 2014) by evidence showing that damage to motor speech mechanisms in aphasia does not impair speech recognition (Hickok et al, 2011) and that sign language comprehension is not impaired in deaf individuals despite damage to the mirror system (Rogalsky et al, 2013).

2.5.1 Neurobiology of Sequential Processing

It has been suggested the crucial component underlying the relationship between language lateralisation and handedness is the extent to which each of these functions relies on sequential processing, for example through motor phrases or speech utterances (Kimura, 1993). Speech production is a highly complex motor act involving the coordination and synchronisation of multiple neural and muscular networks. During speech a number of component processes occur to support the retrieval of the phonological code which underlies the lexical representation of word forms (Tremblay, Deschamps and Gracco, 2016). This code consists of segmental information, such as syllables and phonemes, and suprasegmental information, such as emphasis, or stress. This process of retrieval of phonologically encoded material is associated with the preparation of speech motor action, which involves the activation and translation of phonological representations into multiple domain-general mechanisms, such as response selection, response sequencing and movement initiation. These so called 'supra-motor' functions are not specific to speech but underlie all action preparation. Such models of speech motor planning posit that speech builds on common action control and motor sequencing mechanisms which support many different cognitive processes (Freund, Jeannerod, Hallett and Leiguarda, 2005; Tremblay, Deschamps and Gracco, 2016) and therefore suggest that the neural organisation of speech production is likely to overlap with motor control regions.

Studies have examined each component process of the speech motor control system and have made considerable progress identifying the associated neural substrates. Response selection processes involve a bilateral network of supporting motor areas, predominately the pre-SMA, which have been shown to activate more strongly during execution of specific stimulus responses tasks requiring selection of appropriate responses from a range of alternatives (Crosson et al, 2001). Speech motor response sequencing, the act of organising segmental information into words and sentences prior to vocalisation, relies more heavily on the motor areas. Indeed interruption of these regions via Transcranial Magnetic Stimulation (TMS) has been shown to disrupt sequencing performing on a finger tapping task and impair performance on oral-motor gestures (Tremblay and Gracco, 2009), which demonstrate the complementary cortical organisation of motor and language networks. Finally the response initiation component of speech production is perhaps the least well documented, although early studies show a clear role for the cerebellum and basal ganglia in translating motor planning into action (Tremblay, Deschamps and Gracco, 2016). Indeed, deficits in cerebellar-parietal networks have been identified in children who have neurodevelopmental motor impairments such as Developmental Coordination Disorder (DCD) (Zwicker et al, 2011), supporting the suggestion that response initiation involves these regions.

2.6 Summary and Research Questions

It has been demonstrated in the literature reviewed above that the evidence supporting a direct relationship between speech laterality and handedness is variable, mainly due to the differences in measurement and classification used in such research. However, as has been discussed, neurophysiological evidence demonstrates links in the neural processing components of praxis and speech, and neuro-computational models have suggested that the specialisation of left hemisphere regions for speech production is crucially mediated by the sequential processing of auditory stimuli and complex motor output. This is complemented by handedness and praxis research examining left hemispheric processing specificity for tasks which are complex and highly skilled, demonstrated through behavioural impairments in patients with left sided lesions. This combined experimental evidence is built upon theories that suggest an evolutionary trajectory for gesture as the basis of speech, which in itself is supported by research on sign language abilities in the deaf, and separately the motor and language milestones commonly interlinked in both typical and atypical development.

To that end it seems likely that tasks which tap into the sequential processing capacity of the left hemisphere may be useful in determining the extent to which speech and motor laterality overlap. Flowers and Hudson (2013) demonstrate the potential for skilled sequential motor tasks to predict the hemispheric lateralisation profile of individuals. However, this evidence resulted from neurological populations (e.g. epilepsy patients) rather than neuro-typical participants, and so may be indicative of a difference in brain functioning due to atypical development in these patients rather than due to similarities in the underlying neurological processing of the two functions. Therefore the first section of this thesis seeks to examine the relationship between speech lateralisation and hand skill in healthy adults, to determine whether sequencing based motor ability can predict direction of speech laterality. This study also enables the confirmation of fTCD as a reliable measure of laterality by testing the test-retest variability in speech laterality scores. The hypotheses in this study are that healthy participants will show a similar pattern of speech and motor laterality correlation to the Epilepsy patients tested previously, whereby those with smaller differences in performance between their hands will be more likely to show atypical speech profiles.

Secondly, the developmental profile of laterality has been looked at in detail for language development and handedness as separate functions, however, there have not been large scale investigations of the common developmental trajectory between these two functions (see section 2.2 and 2.3 above). It is still unclear whether theories suggesting motor action as the basis of speech production would mean that there are differences in the profile of hand skill and speech lateralisation as a function of age, or whether these two modalities develop independently, despite a possible common underlying brain network. It is expected that language laterality would predominate to the left at the group level, but there is still conflicting data over the variability of LI scores in younger children and also whether handedness as assessed by sequencing based skilled manual tasks relates to profiles of speech lateralisation. This study hypothesises that younger children will show more variability in both their speech laterality and their motor skills than older children, representing an immature level of hemispheric specialisation for complex sequencing behaviours.

A novel question regarding the development of motor control and speech processes arises from previous research showing atypical speech lateralisation and handedness profiles in individuals with neurodevelopmental disorders. It has been shown that individuals with language and reading disorders such as Dyslexia (Illingworth and Bishop, 2009) and SLI (Whitehouse and Bishop, 2008) have atypical speech representations, but it has not been investigated whether individuals with neurodevelopmental disorders affecting motor coordination also have atypical cortical organisation for language. If it is accepted that speech production and fine motor coordination share common neural networks then it could be predicted that a disorder affecting one of these linked functions may also affect the neurological representations of the other function, even in the absence of behavioural deficits. What has not yet been explored is whether neurodevelopmental disorders affecting the motor system also impact upon the organisation of associated speech and language networks. This question will be addressed experimentally in chapter 6 of this thesis in a group of adults with DCD, where it is hypothesised that the DCD group will show more atypicality in their speech profiles than control participants.

Finally the literature above suggests that relatively little is known about how the various component processes and mechanisms inherent within the motor tasks deployed to measure lateralisation impact upon the profile of laterality observed. Many studies rely on preference based handedness measures and indirect measurements of speech lateralisation (e.g. dichotic listening) to draw conclusions about the relative associations between motor and speech laterality. Chapters 7 and 8 will focus on revealing the sequencing based mechanisms underlying motor skill and speech. Here it is hypothesised that tasks with high levels of sequential processing will show close associations with speech lateralisation indices, and will be more affected by overloading the lateralised system when requiring dual-focus on competing tasks.

Chapter 3

General Methods

The accepted ‘gold standard’ assessment of cerebral lateralisation is the intracarotid sodium amobarbital procedure, also known as the Wada test (Wada and Rasmussen, 1960), whereby patients being prepared for neurosurgery to treat intractable epilepsy are given a sodium amobarbital injection to anaesthetise each hemisphere in turn. Language lateralisation direction is determined by the arresting of speech function following administration of the anaesthetic to one of the hemispheres. This procedure is complex, expensive to administer and can be distressing for the patients. In addition, the clinical risks are high; intracarotid catheterisation carries a morbidity risk as high as 5% (Rausch et al., 1993), with ‘lesser’ complications, such as stroke or cardiac failure, even more common. As such, the search for suitable alternatives to assessing language lateralisation are ongoing. There have been a range of methods used to study cerebral lateralisation in non-clinical samples, including behavioural techniques such as dichotic listening and visual half field paradigms, as well as neuroimaging approaches such as functional magnetic resonance imaging (fMRI), Positron Emission Tomography (PET) and Electroencephalogram (EEG). Each of these methods has been shown to have the ability to detect patterns of hemispheric lateralisation, although each has its disadvantages in terms of reliability, complexity and accessibility. This chapter will focus on functional Transcranial Doppler (fTCD) sonography, an emerging imaging method in cognitive neuropsychology/clinical neuroscience for detection and measurement of cerebral blood flow, and the approach used in this thesis to measure activation across the hemispheres.

FTCD has a number of distinct advantages for use in cognitive neuroscience research, primarily the ease with which special populations can be assessed (e.g. patients or children). This suitability stems from the fact that fTCD is non-invasive, does not involve ionising radiation, is relatively robust to movement artefacts, especially compared to techniques like fMRI, and does not involve isolating the participant in a noisy scanner, which can be intimating for such groups. Furthermore fTCD equipment is portable, and so testing can be done in participants' homes or other places where they feel at ease and it is relatively inexpensive and straightforward to operate. It also has the benefit of being inclusive for those with medical conditions or others who may normally be excluded from fMRI experiments (e.g. pregnant women, or those with non-MRI compatible medical devices).

This chapter will give some background to the technique and briefly evaluate the reliability and compatibility this approach has with some of the other techniques listed above, however, an in-depth review of each alternative approach and its comparability with fTCD is beyond the scope and purpose of the chapter. Finally this section will also cover the other methodologies used in this thesis, namely the electronic pegboard and handedness questionnaire and the verbal fluency paradigm used to elicit speech activation.

3.1 Functional Transcranial Doppler Ultrasound

Functional transcranial Doppler (fTCD) sonography is a non-invasive neuroimaging technique suitable for the real-time evaluation of intracranial cerebral circulation. It makes use of ultrasound technology to measure the velocity of blood flowing in the cerebral arteries. Christian Johann Doppler, a mathematician, physician, and astronomer, first described the Doppler principle in 1843 (as cited in Kassab, et al, 2007). Its use in neurology was first reported in 1982 (Aaslid, Markwalder and Nornes, 1982) and since then its convenience and the growing range of applications in research and clinical settings have made it a useful tool to evaluate cerebral activation. FTCD can be used as a direct measure of cognitive activity in a given region of the cortex, based upon the principle that increased energy to a particular part of the brain will be required when that area is involved in the control or coordination of actions being executed at any given moment. This principle of associating brain related metabolic and vascular changes to cognitive or behavioural activity underlies many neuroimaging techniques used in psychology and cognitive neuroscience.

3.1.1 Basic Cerebral Hemodynamics and the Doppler Principle

The brain is metabolically dependent on a continuous supply of oxygen and glucose, which is delivered by the blood stream at a rate of approximately 750ml/min^{-1} which amounts to 15% of cardiac output (Alexandrov, 2011). To ensure this high demand is met, the cortex is supplied with blood via two main arterial branches, the intra-carotid and the basilar. These branches are connected by a circular arterial structure known as the Circle of Willis. The Circle of Willis ensures that blood is supplied to all areas of the brain, and crucially that oxygenated blood is delivered quickly when metabolic demand increases. One of the largest arteries supplying the cortex is the middle cerebral artery (MCA) which extends bilaterally from the intra-carotid arteries and supplies much of the temporal lobe, as well as areas of the parietal lobe and frontal cortex. The brain’s effective cerebral autoregulation systems mean that resting cerebral blood flow (CBF) is relatively stable despite changes in body position, cardiac output (i.e. heart rate) and arterial blood pressure (Alexandrov, 2011), however, focal changes in CBF correlate with metabolic demands, in that neural activity within specific regions leads to increased energy consumption. This mechanism is known as ‘metabolic coupling’ and is characterised by the neuro-vascular related changes in regional CBF (rCBF) in response to the activity of the underlying cortex, resulting from specific cognitive functions. Such vascular activity causes changes to the resting profile of the blood flow, which can then be detected and measured via fTCD.

The frequencies of sound waves change if they are reflected by moving objects. When a sound source moves towards an observer, the observed wavelength decreases and the frequency increases. When a sound source moves away from an observer, the observed wavelength increases and the frequency decreases. This effect, where there is a change in frequency and wavelength, is called the Doppler Effect. A classic example of the effect in practice is the change in pitch of an ambulance siren as it approaches an observer, passes them and then moves further away. Transcranial Doppler instruments analyse blood flow by having the sound source and the observer at the same location (i.e. the transducer probe). The ultrasound signal crosses the intact adult skull at points known as “windows” and is reflected by the blood cells of all vessels flowing in its path. An ultrasound signal is used to insonate the vessels through the temporal bone window (using approx. 2MHz signal). This signal is reflected and backscattered from moving objects (e.g. blood cells) with a positive or negative frequency shift. The frequency shift is also called Doppler shift or Doppler signal. The faster the blood cells are moving the higher the Doppler shift.

The cardiac cycle represents sequential electrical and mechanical events, namely systole and diastole, which occur within a single heart beat and as a result of the heart filling with blood and then pumping it out. Changes due to diastolic pressure (when heart is filling) and systolic pressure (when heart is pumping) affect the flow profile of blood in a vessel. As such the blood flow velocity (BFV) in the cerebral arteries is not constant but exhibits areas of higher and lower velocities relative to each stage of the cardiac cycle and the properties of the artery itself. This flow profile is best represented by a parabolic curve, where the blood flow at the centre of the artery will be faster than that at the sides (Deppe, Ringelstein and Knecht, 2004). During cognitive tasks when rCBF increases due to increased metabolic activity, blood flow characteristics change more dramatically and the flow profile increases in speed and volume due to reductions in arterial resistance. These changes can be detected by fTCD insonation via the Doppler Effect. However, in its simplest form the Doppler Effect assumes that the signal received back to the probe will have been emitted from only one ‘object’. This is, in fact, not the case when insonating a blood vessel, as there are multiple particles and cells all moving at different speeds. Therefore, in order to accurately calculate the mean BFV changes to make this technique useful for experimental paradigms, the incorrect assumption that velocities of all reflected particles are constant needs to be overcome. This is done by applying complex algebraic principles to calculate the relative signal intensities of each reflected ultrasound particle (Deppe, Ringelstein and Knecht, 2004). By applying a Fast Fourier Transformation (FFT) analysis to the received signal these hemodynamic events are translated into a spectra, or waveform, meaning that the signal can be visualised and subjected to further analysis (Stroobant and Vingerhoets, 2000). The spectra represents the flow velocity displayed on the vertical scale, time on the horizontal scale and signal intensity (amplitude) is displayed as the brightness of the waveform, where brighter colours represent stronger intensity. A line is drawn electronically along the visual FFT display which tracks the velocity of each cardiac cycle. This is known as the envelope curve, and to enable accurate measurements this curve should fit snugly against each peak to denote the maximum velocity for each part of the cardiac cycle; systolic and diastolic velocities are each denoted, as well as enddiastolic velocity. The envelope curve is crucial in determining the mean BFV values subsequently used in lateralisation index calculations. The most universally accepted type of mean velocity measurement (BFVmean) is a stepped, time-averaged, area-averaged mean velocity value derived by placing a line on the horizontal axis of the envelope curve so that the area above the line, V1, is equal to the area below the line, V2 (see Fig. 3.1) (Stroobant and Vingerhoets, 2000). This measurement of mean BFV has been shown to have a higher correlation with actual perfusion than does the systolic or diastolic mean velocities (Saver and Feldmann, 1993) and is therefore most commonly used calculating average velocities over a certain time period in which a cognitive task is performed.

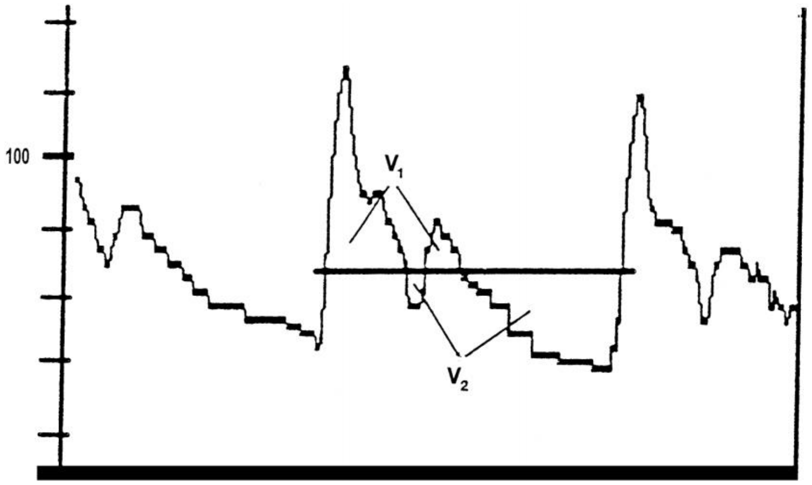


Figure 3.1. Time-averaged (mean) BFV, denoted by the horizontal line. The areas above (V1) and below (V2) this line are equal (image taken from Stroobant and Vingerhoets, 2000).

3.1.2 Examination Technique and Equipment

Ultrasound examination of a vessel by means of TCD is referred to as insonation. The TCD probe is placed over different “acoustic windows” that are specific areas of skull where there is a lack of boney covering or the cranial bone is thin. The *transtemporal* (temporal) window is used to insonate the middle cerebral artery (MCA), the anterior cerebral artery (ACA), the posterior cerebral artery (PCA), and the terminal portion of the internal carotid artery (TICA), before its bifurcation (Kassab, et al, 2007). Participants are fitted with a headset which sits comfortably around the head and can be adjusted at various point to ensure a snug fit. Mounted on this headset are two probes, which are secured either side of the head just in front of the ear (see figure 3.2), these are the devices used to insonate the MCA.

Accurate positioning of the probe is a crucial factor in the successful detection of the MCA, and indeed the angle at which the MCA will be detected varies between individuals depending on their skull contours. The direction in which the transducer probe points, the depth of the sample volume, and the direction of the flow all contribute to correct identification of each cerebral artery (Alexandrov, 2011). Due to the variation between individuals in the insonation angle required to detect the MCA it is necessary to factor this in to the analysis and interpretation of the received Doppler signal in order to make comparisons between subjects. It is generally assumed that the angle of insonation will be less than 90°, however, an exact measurement of the angle is not possible because the arteries wind and branch out (Deppe, Ringelstein and Knecht, 2004). To overcome this the TCD monitoring equipment calculates the estimated error introduced by variances in insonation angle, which is then factored into the pre-processing of the raw data.

In this thesis fTCD recording was done via the commercially available system DWL Doppler-Box^{TM}X (manufacturer, DWL Compumedics Germany GmbH). A 2-MHz transducer probe attached to an adjustable headset was positioned over each temporal acoustic window bilaterally. Ultrasound transmission gel was applied to the transducer and the participant's head just superior to the zygomatic arch. PsychoPy Software (Pierce,

2007) installed on a Dell PC with a 19-inch Digital monitor controlled the experiments and sent marker pulses to the Doppler system to denote the onset of a trial.

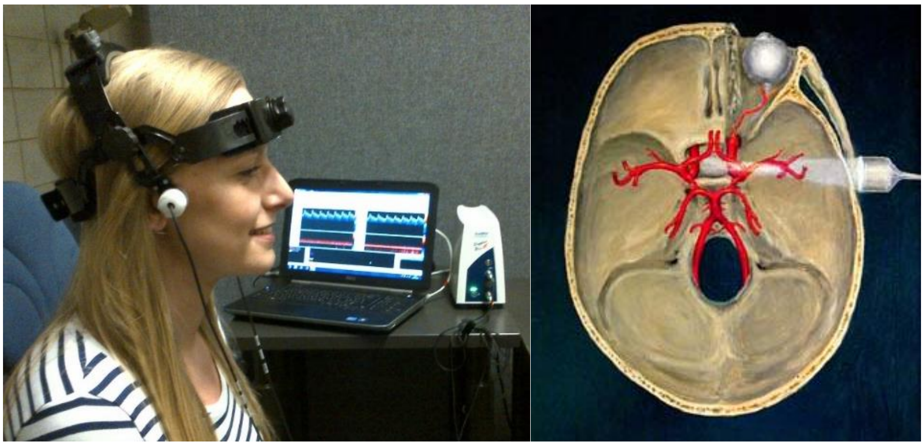


Figure 3.2 Images of fTCD headset in situ and artistic impression of MCA insonation

3.1.3 Data Processing and Analysis

In order for the raw Doppler signal to be analysed efficiently and for appropriate measurements of any changes in rBFV, it is important to remove statistical noise created by spontaneous blood flow oscillations, and artefacts in the data, caused by subject specific variations during the recording (e.g. excess movement, coughing or manual interference with the probes). To enable this analysis a series of processing stages were developed by Deppe et al (1997), known as the AVERAGE technique, to be applied to the raw data. The AVERAGE technique makes a number of assumptions about the data in terms of its normality and ‘cleanliness’, meaning that several pre-processing stages have to be carried out before the derivation of mean LI values can occur. This thesis used a Matlab based software package, dopOSCCI, (Badcock, Holt, Holden and Bishop, 2012), to analyse the fTCD data collected for each study. DopOSCCI makes use of the stages outlined in the AVERAGE technique but extends them by providing a user-friendly interface to enable greater exploration and refining of the raw data. The dopOSCCI analysis process is summarised next, with reference to the AVERAGE technique where appropriate, as the basis of the accepted approach to fTCD analysis.

The raw data is subjected to various stages of pre-processing before the mean LI values can be compared. Firstly the data is downsampled from a recorded rate of ~100Hz per second, to ~25 Hz per second, representing a ¼ sample selection rate. This reduction is satisfactory for BFV calculations which in themselves represent approximately a 3-5 s processing delay (Aaslid, 1987; Rosengarten, Osthaus and Kaps, 2002), furthermore it makes the analysis more manageable for the software and thus it can proceed at a more timely rate (Badcock et al, 2012). Following this, the raw data must be normalised to ensure that the signal coming from the left and right probes is equivalent and not unduly influenced by variances in other factors such as perfusion rate or insonation angle. Standardisation is achieved by normalising the data to a mean of 100 using the equation (100 × data)/mean (data), where data refers to the selected blood flow velocities values (Badcock et al, 2012). This formula accommodates the adjustment of average signal levels on an epoch by epoch basis, whilst still retaining the relative variance between the left and right recordings for each trial. DopOSCCI allows for individual epoch normalisation in order to exclude trials where the signal is corrupted from the overall analysis; these trials can be excluded at the outset, usually due to excessive participant movement, however, sometimes subtle and gradual ‘drift’ in probe positioning can only be detected during the analysis, thus requiring removal at that stage. This general loss or reduction in signal sometimes occurs, especially over longer recording sessions, where the ultrasound gel begins to dry out or manual adjustments to the probes are required by the experimenter. The epoch normalisation function in the software allows for the removal of any such variations, which thus avoids the LI output values being biased prior to the averaging process.

Data pre-processing in dopOSSCI also contains steps to detect artefacts in the data (for example due to probe angle) and to integrate individual heart cycle variations. These stages involve calculations designed to deal with this variation by taking an average of the activity within a single heart cycle (see Figure 3.1 above). Following this the epochs are then considered for inclusion in the final analysis based upon the variability of the signal from the left and right probes, both to the baseline condition and to each other. For the studies in this thesis the activation separation function was used, which detects whether epochs fall outside of specified higher and lower limits of acceptable variability – epoch values less than or greater than 30% of mean activation were rejected in the case of these experiments. Baseline correction calculations are then applied to the data to ensure that spontaneous disruptions to cerebral blood flow velocity (such as variances in breathing rates and arousal state) are controlled for in the LI calculations. This is performed on an epoch by epoch basis and is achieved by subtracting averaged activation during the baseline period from all other data in the epoch (Deppe et al, 1997; Deppe et al, 2004). Finally the Goodness of Recording function was enabled, which is a data quality indicator (based on root mean square; Badcock, et al., 2012) that allows for estimates of variability in the baseline measurement, which then enables removal of data that fails to meet acceptable criterion. Knecht et al (2001) define this criterion as left or right signal variation greater than 2% of mean baseline activity.

Data in each of the studies reported in this thesis was recorded at a constant sample volume (pulse length) rate of 8 mm, meaning that each TCD pulse projected to 8 mm of artery. The smaller the sample volume, the more accurately the flow volume can be recorded since the sample volume will not contain any overlaid Doppler shift signals. The power/amplitude of the emitted signal always remained within acceptable limits in terms of not exceeding the advised Thermal Cranial Index scale threshold of 1.7. This is the default setting to ensure the temperature of tissue at the ultrasound site does not exceed, or remains below, required levels. Finally, to aid sensitivity of signal detection for each participant during set up of the equipment, individual adjustments of depth (how far into the artery the reflected signal is coming from) and gain (amplitude of the received signal) settings were made. Depth measurements always remained within ranges 40 – 55 mm, and gain was never increased beyond 45%, to avoid excessive 'noise' in the recording. Any participants for whom a clear signal could not be detected even with adjustments within these parameters, did not continue with the experiment. These parameters are well within accepted ranges, and were kept strict to ensure that statistical noise was kept under tight control. Any artefacts or unacceptable trials which subsequently occurred were then removed at analysis stage, as described above.

3.2 Assessment of Reliability and Validity of fTCD

FTCD has been compared to other imaging techniques on a number of occasions to determine its efficacy as a measurement of cerebral lateralisation. Because fTCD integrates and averages repeated activations within the whole territory of the insonated artery, which in the case of language is the middle cerebral artery (MCA) (van der Zwan et al., 1993), it provides a reliable measure of hemispheric language lateralisation (Knecht et al., 1996, 1998, 2000a, b; Deppe et al., 1997). 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., 1998) indicating that large cohorts can be scanned for language dominance using fTCD, which will provide consistent results to that of fMRI. Table 3.1 provides a summary of some of the validation studies that have been done with fTCD and other measurements of cerebral lateralisation, and indicates the efficacy of fTCD as a very viable alternative to these methods.

Table 3.1. Studies directly comparing fTCD with other methodologies. (RH = Right Handed; LH = Left Handed) *individuals not reported

Authors	Methods	Task	Sample size	Handedness	Hemispheric Laterality Classification (%)	Correlation of fMRI/Wada with fTCD
Knecht et al (1998)	fTCD/Wada	Language – word generation	19 (12 male)	6 LH, 13 RH	Left: 73.3; Right: 20; Bilateral: 6.7	$r = 0.92$, $p < 0.0001$
Rihs et al (1999)	fTCD/Wada	Language – word generation	11 (4 male)	Not reported	Left: 72.2; Bilateral: 27.3	$r = 0.75$, $p = 0.008$
Schmidt et al (1999)	fTCD/fMRI	Visuospatial	14 (8 male)	14 RH	Right sided dominance at group level*	$r_s = 0.54$, $p = 0.02$
Deppe et al (2000)	fTCD/fMRI	Language – word generation	13 (7 male)	4 LH, 9 RH	RH: Left: 67; Right: 33 LH: Left: 25; Right: 75	$r = 0.95$, $p < 0.0001$
Knake et al (2003)	fTCD/Wada	Language – word generation	11 (5 male)	11 RH	Left: 81.8; Right: 9.1; Bilateral: 9.1	$r = 0.776$, $p < 0.005$
Knecht et al (2003)	fTCD/fMRI	Language – word generation	14 (7 male)	5 LH, 9 RH	RH: Left: 67; Right: 33 LH: Left: 20; Right 80	Not reported, described as 'High'
Jansen et al (2004)	fTCD/fMRI	Visuospatial-Landmark task	15 (7 male)	6 LH, 9 RH	Left: 67; Right: 33	$r = 0.89$, $p < 0.005$
Somers et al (2011)	fTCD/fMRI	Language – word generation	22 (14 male)	12 LH, 10 RH	Left: 73; Right: 27	$r_s = 0.75$, $p < 0.001$

3.3 Experimental Tasks

3.3.1 Word Generation Task

The word generation task is based on the Controlled Word Association Test of verbal fluency (Lezak, 1995), and requires participants to produce words in response to a given stimulus letter under time constraints. Word generation can be either overt or covert, as both techniques activate similar cortical regions involved in speech production and produce similar LI scores (Gutierrez-Sigut, Payne and MacSweeney, 2015). The word generation task assesses an individual’s ability in phonological fluency and lexical retrieval. The task has been used routinely previously to establish language lateralisation (Deppe et al., 2000; Flöel et al., 2001, 2005; Knecht et al., 1998, 2001, 2003; Pujol et al., 1999) and is particularly successful in eliciting 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, 2005; Gaillard et al., 2003; Hertz-Pannier et al., 1997; Knecht et al., 1998, 2001, 2002, 2003; Lust, Geuze, Groothuis and Bouma, 2011; Pujol et al., 1999; Rosch, Bishop and Badcock, 2012).

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’s area) and BA9. Knecht et al (2003) found in their study of 14 subjects that word generation led 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 (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.

3.3.2 Pegboard Task

The studies presented in this thesis make use of an electronic peg moving task to determine hand skill. This task is similar to the pegboard described by Annett (1970) and involves a rectangular board with two rows of equally spaced holes and a set of corresponding pegs (see Figure 3.3). The participant is required to move the pegs from one row to the other in sequence, as fast as possible. The pegboard taps into a number of skills underlying motor proficiency, such as motor sequencing, hand-eye coordination, timing, dexterity and grip. It has been used as a measure in the assessment of clinical populations with motor impairments since the 1950s, but become widely used to understand handedness during a series of studies by Annett and colleagues in the 1970s and 1980s (Annett, 1970; Annett, Annett, Hudson and Turner, 1979). Annett (1985) documents standardised norms for their version of the pegboard based on extensive testing of children and adults. The pegboard has been shown to provide a consistent and reliable measure of hand performance, with high test-retest reliability of between-hand differences (Annett, Hudson and Turner, 1974) and practice effects shown within sessions, but not between sessions (Flowers, 1975). In addition, although various versions of the pegboard have been used to measure handedness analysis by Annett, Annett, Hudson and Turner, (1979), demonstrated that variation in the degree of hole or row separation did not affect relative hand performance on the task. This finding has since been validated by McManus, Van Horn and Bryden (2016). This makes it an ideal tool for assessing motor skill, and crucially for making judgements of relative between-hand skill.

The pegboard used in this thesis was constructed to have an electronic timing system for monitoring of peg placement, to increase precision and accuracy of performance measurements. The pegboard consisted of a 280 × 100 × 20mm board with two rows of 20 holes (7mm diameter) drilled 13mm apart along the length. The distance between the two lines of holes was 70mm. The Fitts’ (1954) Index of Difficulty (Id) measurement for this board was Id = 7.6, making it unlikely that the task can be performed by pre-programmed aimed movements, and must involve some “online” movement control where handedness differences are most consistently found (Annett, Annett, Hudson, & Turner, 1979; Flowers and Hudson, 2013). In the construction of the pegboard, a pair of contacts was placed on opposite sides of each hole. These were made from brass wire, thin enough not to noticeably resist the passage of the pegs, and bent in such a way as to be pushed apart with the passage of the peg. Cloaked standard electrical fuses (6mm diameter × 24mm long) were used as pegs, the metal caps of which allowed conduction between the wire contacts when the pegs were inserted in the holes. When the pegs were pushed fully home the wires were in contact with the insulating shaft of the fuse, so conduction no longer occurred (see Appendix 1). The arrangement acted like a passing-contact switch. All the 'switches' for each row of holes were wired in parallel, by soldering the wires to strips of printed circuit board placed each side of the row. One strip was connected to the common pin of the PC's Parallel Port, the other to an input pin. Each of the two rows was connected to a different input pin. A computer program, written in Visual Basic, continuously monitored the state of the Parallel Port input pins, and was thus able to record the times at which pegs were removed from or inserted into the holes.

Participants were instructed to move the pegs in sequence as fast as possible. They were required to use the following pattern of trials as per Flowers and Hudson (2013); 1. Preferred hand out; 2. Non-preferred hand out; 3. Non-preferred hand in; 4. Preferred hand in; 5. Preferred hand out; 6. Non-preferred hand out, where 'out' refers to the movement of the pegs from the row nearest the body to the row of holes furthest from the body, and 'in' refers to the opposite direction, moving the outer pegs in towards the body. The standard pegboard task usually only involves 4 trials, two with each hand, however, it should be noted that in the procedure used here trials 1 and 2 and the same as 5 and 6 to allow for accurate measurement of practice effects, which are to be expected across multiple trials, and with thus ensure the task is being executed properly (Flowers and Hudson, 2013; Flowers, 1975). Participants' scores are then derived from calculations of the mean time taken to complete each trial, resulting in a mean movement time for the preferred hand and for the non-preferred hand. These mean scores are then subtracted from one another to obtain a between-hand difference time. This difference can then be converted in to a laterality quotient (LQ) to standardise results across individuals. The LQ is calculated as follows:

(Left hand mean – Right hand mean) / (Left hand mean + Right hand mean) * 100

Figure 3.3. Image of the electronic pegboard used in this thesis

3.3.3 Handedness Questionnaire

Some of the chapters in this thesis measure hand preference of participants via a questionnaire in order to obtain preference which can then be compared to pegboard motor skill data. The questionnaire used here (see appendix 2) was devised by Flowers and Hudson (2013) and was an amalgamation of several existing questionnaires (Annett, 1970a; Oldfield, 1969). The questionnaire was created to provide a shortened version of the aforementioned inventories, as previous research has suggested that key questions on such measurements are most predictive of overall scores of hand preference (e.g. Williams, 1991). It recorded the preferred hand used for 14 unimanual (e.g. hold a toothbrush) and 7 bimanual (e.g. unscrew lid of a jar) actions. The questionnaire allowed for classification of handedness either on a categorical variable or as a laterality quotient based upon number of responses in each column.

Chapter 4

Preface

Although the relationship between language lateralisation and handedness has long been a tenet of neuropsychological investigations, exactly how the two behaviours are related is seldom examined. In a recent study of epilepsy patients who underwent Wada testing it was reported that those with clear speech laterality could be discriminated from those with atypical speech representation by their performance on a pegboard test (Flowers and Hudson, 2013). It is suggested that motor and speech laterality involve a common aspect of motor sequencing and a measure of the former will indicate the representation of the latter. Therefore this study was designed to see if the same motor task could reliably indicate speech laterality in healthy controls using a direct measurement of speech lateralisation. As a crucial element of this thesis is the reliable use of fTCD to measure cerebral lateralisation, this chapter also reports the test-retest reliability for this group of participants. Also included is the correlation between activation patterns seen between the word generation paradigm and the animation description paradigm in order to ensure comparability between these results and those reported in future chapters, where the animation description paradigm is used as the speech activating task.

Motor laterality as an indicator of speech laterality

Since Broca's seminal description of language lateralisation almost one and a half centuries ago, a wealth of research using an array of methods; such as dichotic listening (Bryden, 1988), Wada tests (Strauss and Wada, 1988), imaging (Benson et al., 1999), and lesion studies (Basser, 1962) have examined the concept of hemispheric dominance. An important factor underlying many studies concerns the relationship between speech representation and handedness. It is widely reported that for the vast majority of right-handed individuals the left hemisphere is dominant for speech production (Wada and Rasmussen, 1960), however, there is a natural variance of hemispheric language dominance within the population (Clarke and Zangwill, 1965). The left hemisphere is dominant for speech production the majority of left-handers as well (Knecht et al, 2000b), although there is a higher incidence of right hemisphere dominance and bilateral speech representation than that found in right-handers (Rasmussen and Milner, 1975), however, it is unclear what determines the variation between individuals.

Fundamental to drawing conclusions about the relationship between speech lateralisation and handedness is how the latter is defined and measured. It is debatable how one should actually classify handedness, in particular whether ambiguous or mixed handedness should be treated as separate categories or put on a continuum and expressed as a laterality quotient (see Annett, 1985, for review). Handedness itself is assessed in various ways. Some studies define hand preference simply on the basis of writing hand (Stellman, Wynder, DeRose, and Muscat, 1997). Others, more commonly, deploy self-report questionnaires that examine hand preference for everyday tasks: such as throwing, striking a match, using scissors etc (e.g. Annett, 1970; Oldfield, 1971). Preference measures, however, have been criticised over reliability (McMeekan and Lishman, 1975) and validity (Williams, 1991). Moreover, it is concerning that most studies allude to handedness as a unitary phenomenon. Although it has long been argued that hand proficiency is multidimensional (Barnsley and Rabinovitch, 1970), involving independent factors, such as, hand stability, grip strength, finger dexterity, aiming and tapping, that may involve independent neural mappings (Steenhuis and Bryden, 1989), the precise components of handedness and motor laterality that are related to speech production are rarely examined.

A suggestion by Flowers and Hudson (2013) is that motor and speech laterality are related where they involve a common feature of motor output, namely the co-ordination of sequences of movements or utterances to execute a plan or intention so as to achieve a goal, either limb movement or expression of an idea (Grimme, Fuchs, Perrier and Schöner, 2011). It was argued that there must be some central control function in one hemisphere that organises the co-ordination and timing of both limbs, and that it would then be natural for this mechanism to control speech output too. If so, a motor skill task that relied upon coordinated sequential movements would be a good indicator of hand skill and could therefore also indicate the pattern of hemisperic speech dominance as well. From previous work (Annett, 1970; Annett, Annett, Hudson, and Turner, 1979) it was suggested that pegboard scores provide such a measure of motor laterality, independent of the effects of practice. This could then be correlated to measures of speech lateralisation.

To test this hypothesis Flowers and Hudson (2013) used a pegboard measure of relative hand skill to indicate motor laterality in a group of neurological patients who underwent Wada testing, which gives a clear indication of speech laterality. Their results supported the hypothesis. They found that patients whose between-hand difference on the pegboard task was small or inconsistent were likely to have ambiguous or atypical speech representation (speech apparently partly located in both sides or in the side opposite to that controlling the dominant hand). Those with a consistently large between-hand difference on the motor task all showed clear unilateral speech representation in the hemisphere controlling the better hand. The between-hand effect was, as before, found to be independent of practice and of the direction of movement.

This study was designed to replicate these findings in a group of normal participants, using functional Transcranial Doppler ultrasonography (fTCD) to determine speech laterality, correlating this with hand preference and pegboard measures of motor laterality as in the previous study. FTCD constitutes a reliable, valid and economical technique for the assessment of language lateralisation. Indeed, bilateral insonation of the middle cerebral artery (MCA) during speech production has produced asymmetrical changes in cerebral blood flow velocity (CBFV) that concur robustly with Wada outcomes (Knecht et al., 1998). Using fTCD allows the testing of the effect in a neurologically normal group using a non-invasive procedure, and also enables inclusion of a greater sample size overall, especially of left- and ambilateral-handers (Annett 1967; Flowers 1975) where the relationship is of greatest interest since it is often uncertain. This study also provided an opportunity to measure the reliability of the fTCD method as well as the comparability of the speech production paradigms used in this thesis.

4. 1 Method and Materials

4.1.1 Participants

Forty-one adults participated in the study. There were 13 males aged between 18 and 53 years (mean age = 24.08, SD age = 8.98) and 28 females aged between 17 and 59 years (mean age = 25.50, SD age = 9.76). Based on self-report, 28 participants considered themselves to be right-handed and 13 left-handed. No participants had been diagnosed with a neurological disorder nor were any taking medications known to affect the central nervous system (CNS) or circulatory system. None had impairments in speech, language or reading ability. All had normal or corrected to normal vision and gave informed consent prior to participating in the study. Participants were recruited through adverts placed in the University of Lincoln and were paid £6.00 for helping with the research. The investigation was approved by the ethics committee of the School of Psychology, University of Lincoln.

4.1.2 Motor Laterality

Hand usage was measured by a 21-item handedness questionnaire. Motor skill was assessed with an electronically timed pegboard task.

Handedness questionnaire: The questionnaire used was as described by Flowers and Hudson (2013, see section 3.3.3). In short, respondents are required to indicate their preferred hand for executing 14 unimanual (e.g. hold a toothbrush) and 7 bimanual tasks (e.g. unscrew the lid of a jar). To remain consistent with the Flowers and Hudson (2013) approach to categorical classification of hand preference participants were classified as left or right-handed if stating consistent hand preference for 90% of the tasks. Scores < 90% were classified on the basis of predominant left or right responses as either left or right ambilateral. However, in addition to this categorical approach, a continuous preference score was also created from the questionnaire responses in the form of a handedness quotient where positive numbers indicate right handedness and negative numbers left handedness. This was done via the following formula:

$$\text{Handedness quotient} = (PH - NPH) / (PH + NPH) * 100$$

This calculation was used to overcome the issues associated with a categorical approach to handedness classification which relies on arbitrary cut-off values to distinguish groups, and is an approach generally thought to be more robust at representing subtle difference between respondents (Bishop et al, 1996).

Electronic pegboard: To improve the accuracy of recording peg movement times an electronic version of the task was constructed *(see section 3.3.2 and Appendix 1 of this thesis for a full description of the pegboard properties and function)*. At the start of the task, 20 pegs were placed in the holes along one of the rows. The pegboard was placed on a table, lateral and central to the participant. The task required moving the pegs one at a time, from holes along one row to holes positioned adjacently, in as short a time as possible. There were six trials in total, on each trial participants were required to work across from the side of the board corresponding to the hand being used. Across trials, pegs were moved away from the body (Out) or towards the body (In); with either the participants' preferred hand (PH) or non-preferred hand (NPH) in the following order: 1. PH Out, 2. NPH Out, 3. NPH In, 4. PH In. 5. PH Out, 6. NPH Out.

4.1.3 Speech Laterality

Language lateralisation was determined by measuring hemispheric changes in CBFV with fTCD during a word generation task. For the purposes of the planned set of studies for this thesis, these participants also performed a second speech production task, aimed at children, in order to provide confirmation that this second task reliably activated left hemisphere speech areas. Furthermore, these participants were invited back to the lab 1 – 6 months later to perform the word generation task for a second time in order to assess test-retest reliability of the task. Although these additional tests pertain more to confirming the reliability of speech lateralisation measurement in the thesis as a whole, these two additional sets of results will be reported in this chapter.

Word generation paradigm: Word generation (WG) has been validated in numerous neuroimaging studies as an effective paradigm to elicit speech lateralisation (Benson et al., 1999). Within fTCD it has been used extensively by Knecht and colleagues (Knecht et al., 1998; Knecht et al., 1996) and is widely considered to be a reliable paradigm for determining language dominance in this technique. In brief, participants were seated in front of a computer screen with the fTCD headset fitted. Each trial began with a 5 s period in which participants were prompted to clear their mind (see Figure 1). A letter was then presented in the centre of the computer screen for 15 s, during which time participants were required to silently generate as many words as possible that began with the letter displayed. (At the onset of the trial a 500 ms epoch marker was simultaneously sent to the Doppler). Following the generation phase, to ensure task compliance, participants were requested to report the words aloud within a 5 s period. The trial concluded with a 35 s period of relaxation to allow CBFV to return to baseline before the onset of the next trial. The WG paradigm consisted of 23 trials in total. Letter presentation was randomised and no letter was presented more than once to any given participant. The letters 'Q', 'X' and 'Y' were excluded from the task.

Figure 4.1. Schematic representation of a single trial on the word generation task

Animation Description Paradigm: Animation Description was developed from the desire to test pre-literate children on speech production tasks (Bishop, Watt and Papadatou-Pastou, 2009), in order to answer questions about the developmental trajectory of hemispheric language lateralisation. The paradigm, described in detail by Bishop, Badcock and Holt, 2010), requires participants to watch a 12 second cartoon in silence, and then to report what they had seen in the clip at the onset of a question mark ‘speak’ prompt. This ‘speak’ phase lasts for 10 s, which is then followed by a rest phase for 8 s to allow the CBFV signal to return to baseline. The baseline period is taken from the ‘watch’ phase of the paradigm. Each trial lasts 30 s and there are a total of 20 animation clips displayed, in a random order generated by a python based computer script.

Figure 4.2. Schematic representation of a single trial on the animation description task

4.1.4 FTCD Apparatus and Analysis

The technique of insonation and identification of the MCA has been clearly detailed by Ringelstein, Kahlscheuer, Niggemeyer and Otis (1990). Relative changes in CBFV within the left and right MCAs were assessed using bilateral fTCD monitoring from a commercially available system (DWL Doppler-Box^{TM}X: manufacturer, DWL Compumedics Germany GmbH). A 2-MHz transducer probe attached to an adjustable headset was positioned over each temporal acoustic window bilaterally. Ultrasound transmission gel was applied to the transducer and the participant’s head just superior to the zygomatic arch. PsychoPy Software (Pierce, 2007) installed on a Dell PC with a 19-inch Digital monitor controlled the word generation experiment and sent marker pulses to the Doppler system to denote the onset of a trial

FTCD analysis: The raw fTCD output signals were analysed off-line with a MATLAB (Mathworks Inc., Sherborn, MA, USA) based software package called dopOSCCI (see Badcock, Holt, Holden and Bishop, 2012 for a detailed description).

dopOSCCI makes a number of computations in order to summarise the fTCD data and advance the validity of measuring hemispheric differences in CBFV. First, the numbers of samples were reduced by downsampling the data from ~ 100 Hz to 25 Hz. Second, variations in cardiac cycle which may contaminate task-related signals were corrected using a cardiac cycle integration technique (Deppe, Knecht, Henningsen and Ringelstein, 1997). Third, data contaminated by movement or 'drift' were removed prior to normalisation. Normalised epochs were subsequently screened and excluded as measurement artefacts if activation values exceeded the acceptable range (± 40% mean CBFV). Fourth, to control for physiological process that can influence CBFV (e.g. breathing rate; arousal), the mean activation of the baseline period was subtracted from each individual epoch. Deviations in left versus right activity were therefore baseline corrected and reflect relative changes in CBFV. A laterality index (LI) was derived for each participant based on the difference between left and right sided activity within a 2 sec window, when compared to a baseline rest period of 10s. The activation window was centralised to the time point at which the left-right deviation was greatest within the period of interest (POI). In the word generation paradigm the POI ranged from 3 – 13 s following presentation of the stimulus letter. For the animation description task the POI ranged from 12 – 22 s following onset of the trial.

The primary focus was to make comparisons between participants with typical left hemisphere speech laterality (typically lateralised) and those with atypical or ambiguous speech representation (atypically lateralised). Speech laterality was assumed to be typical in all cases in which the LI deviated by > 2 SE from 0 (Knecht et al., 2001). Left-hemisphere or right-hemisphere speech dominance was indicated by positive or negative indices respectively. Cases where LI value did not significantly differ from 0 were categorised as having low lateralisation or bilateral speech representation and thus classified as atypical. Moreover, cases in which speech was lateralised in the opposite hemisphere to that controlling their dominant hand were also classified as atypical (Flowers and Hudson, 2013).

4.2 Results

4.2.1 Handedness

The categorical classification of handedness from the questionnaire resulted in a distribution consisting of 19 (46.4%) right-handers, 6 (14.6%) left-handers, 8 (19.5%) right-ambilaterals and 8 (19.5%) left-ambilaterals, see Table 4.1.

Handedness quotient scores showed a range of left and right handedness with 13 participants indicating a bias towards left handedness and 28 indicating a bias towards right handedness. Twelve participants had quotients at +100% denoting extreme right handedness and only 1 participant had a quotient of -100%, denoting extreme left handedness. Pearson correlations between the handedness quotient and the 6 pegboard trials failed to detect any significant correlations between direction of handedness and pegboard performance.

Table 4.1. Pegboard performance for preferred (PH) and non-preferred hands (NPH) by categorical handedness classification across the whole sample

		Mean (SD) peg-placing movement times (secs)					
Group (n = 41)	**n**	**1st PH out**	**2nd NPH out**	**3rd NPH in**	**4th PH in**	**5th PH out**	**6th NPH out**
Right-handed	19	24.03	25.16	24.28	22.75	22.18	24.52
		(3.06)	(3.43)	(2.02)	(2.89)	(3.27)	(2.63)
Right-ambilateral	8	25.54	27.45	26.53	24.86	22.64	25.23
		(4.46)	(6.69)	(5.28)	(3.38)	(2.88)	(3.06)
Left-handed	6	23.38	24.53	24.49	21.63	21.62	23.63
		(2.25)	(2.62)	(3.40)	(1.67)	(1.06)	(2.76)
Left-ambilateral	8	23.55	23.63	24.37	23.31	22.38	24.07
		(3.14)	(1.86)	4.41)	(1.83)	(2.04)	(2.31)
P		0.569	0.279	0.486	0.154	0.920	0.704

4.2.2 Pegboard task

Movement times on the pegboard task for the whole sample are displayed in Table 4.1. An ANOVA treating handedness (left, left-ambilateral, right, right-ambilateral) as a between-subjects factor and pegboard trials (trials 1-6) as a within-subjects factor failed to reveal a main effect of handedness (F (3, 37) = 1.043, p > 0.385). A main effect of trial (F (1, 37) = 10.169, p < 0.003), indicated that times for the preferred hand (PH) were faster than for the non-preferred hand (NPH) on trials 3/4 and 5/6. A slight practice effect was observed for the PH (trial 1 vs. trial 5) whereas times for the NPH remained consistent across the test session. No differences were found between inward and outward movement times (PH trials 1/5 vs. 4; NPH trials 2/6 vs. 3). The interaction between hand preference and pegboard trial was not significant (F (3, 37) = 1.081, p > 0.369). Times for the PH were therefore faster than the NPH regardless of direction and handedness, and independent of practice effects.

Table 4.2. Distribution of handedness scores, laterality classification and index for typically and atypically lateralised cases.

	Laterality classification	**Atypical speech**	**Typical speech**
n		15	23
Sex: M:F		4:11	8:15
Age: mean (SD)		22.80 (6.09)	24.91 (10.77)
Questionnaire score (max = 21): mean (SD)	Right	8.64 (8.86)	15.96 (6.40)
	Left	11.29 (8.18)	3.58 (6.43)
	Either	1.14 (1.79)	1.45 (2.08)
Handedness Quotient: mean (SE)		-66.2 (14.1)	79.9 (4.3)
LI: mean (SE)		1.39 (0.69)	2.48 (0.57)

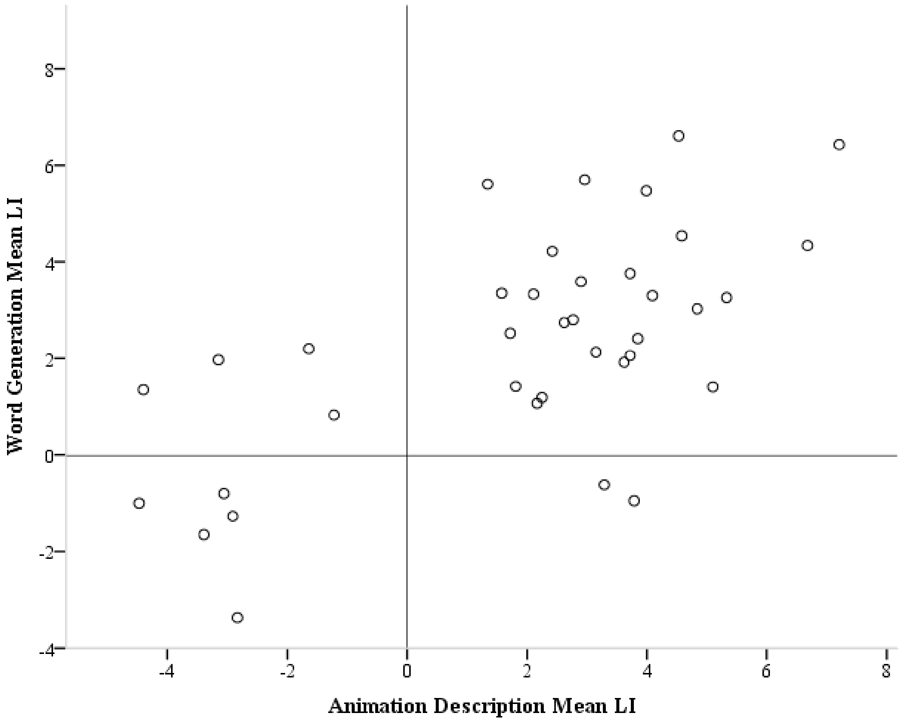
4.2.3 Speech lateralisation

Three data sets were unusable due to these cases having less than 16 acceptable epochs. In the remaining 38 participants (63% female; 37% male) the LI from the word generation task ranged from 6.61 to -6.78, mean = 2.09 (SE = 0.44). In order to validate the animation description paradigm for subsequent use in testing developmental populations (see chapter 5), 37 adults in this study also performed this task. The LI from the animation description task ranged from 7.21 to -4.4, mean = 2.32 (SE = 0.47) and a Pearson correlation showed that this task produced a reliably similar LI value to the scores from the word generation paradigm ($r(37) = 0.64$, $p < 0.001$; see Figure 4.3a).

The categorisation of speech representation based upon word generation task LIs resulted in 23 clearly lateralised (20 left, 3 right, LI mean = 2.48) and 15 atypical cases (LI mean = 1.39). Spearman's Rho showed there was no correlation between LI and scores for either left ($r = 0.156$, $p = 0.350$) or right responses ($r = 0.001$, $p = 0.997$) on the handedness questionnaire. The distribution of the sample is presented in Table 4.2.

In order to test the reliability of the fTCD setup for the measurement speech lateralisation all 38 participants were invited back between 1 and 6 months later to perform the word generation task again. Repeated test scores were performed by 34 participants (35% male) over a mean time interval of 76 days (SD = 42.5, re-test interval range 21 - 176 days) and showed a high correlation between LI scores at Time^1 and Time^2 ($r(34) = 0.71$, $p < 0.001$; see Figure 4.3b).

a)



b)

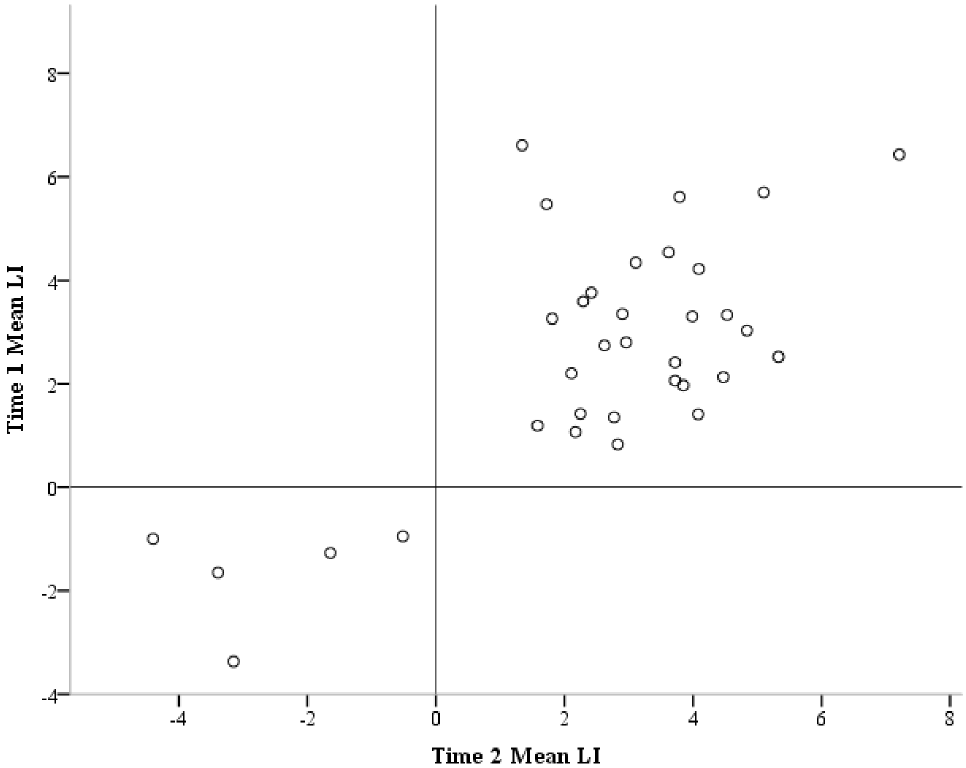


Figure 4.3. a) Plot of the correlation between mean LI scores on the two speech production tasks; **b)** Plot of test re-test correlation between mean LI scores at times 1 and 2. Negative values indicate right hemisphere activation and positive values indicate left hemisphere

4.2.4 Speech Laterality and Motor Skill

It was hypothesised that individuals who are clearly lateralised and have speech representation in the same hemisphere that controls the dominant hand, will have greater between-hand differences in speed on the pegboard task than those with atypical speech lateralisation. To test this prediction, the time differences between corresponding PH and NPH outward trials were calculated and entered into an ANOVA that treated pegboard trial as a within-subjects factor (trial 1 vs. 2, 5 vs. 6) and speech representation as a between- subjects factor (atypical vs typical). A main effect of group [F (1, 36) = 5.338, p < .027)], confirmed that the difference in times between the PH and NPH were significantly smaller in the atypical group. Neither the main effect of trial comparison [F (1,36) = 2.439, p > 0.127] nor the interaction of these effects were significant [F (1,36) = 1.077, p > 0.306], thus indicating that the relative difference in hand speed is independent of practice. Notably, between-hand comparisons of corresponding trials with related t-tests, revealed a significant advantage for the PH over the NPH on all three trial pairings in participants allocated to the lateralised group (all p's < 0.02). In contrast, between-hand difference in speed for participants with atypical speech representation did not differ as function of hand preference (all p's > 0.05). Table 4.3 displays the mean peg-placing movement times on paired trials for both groups. Further analyses of these values confirmed that the average between-hand time for the atypical group was markedly less than the lateralised group (0.842 s vs. 2.08 s). Moreover these data show that all those with atypical speech representation have an average between-hand difference in skill ≤ 3.4 s. Cases (~30%) with average between-hand movement times > 3.4 s clearly have speech representation in the hemisphere that has control over the PH.

Table 4.3. Pegboard performance as a function of laterality classification for preferred (PH) and non-preferred hands (NPH).

	Mean (SD) peg-placing movement times (secs)								
	1st PH out	2nd NPH out	P	3rd NPH in	4th PH in	P	5th PH out	6th NPH out	P
Typical Lateralisation	24.41 (3.86)	26.01 (4.83)	.014	25.17 (3.42)	23.64 (3.10)	.020	22.16 (2.69)	25.17 (2.47)	.001
Atypical Lateralisation	23.48 (2.27)	23.97 (2.22)	.310	24.04 (3.90)	22.37 (2.34)	.071	22.43 (3.01)	23.19 (2.26)	.325

A stepwise binary logistic regression model was then used to test whether pegboard performance could actually predict speech laterality. Group (atypical or typical) was entered as the dependent variable and the between-hand difference in time (NPH – PH) as the independent predictor. The model showed that between-hand differences on the last two pegboard trials is a significant albeit moderate indicator of speech representation, R2 = 0.17 (Nagelkerke) [χ^2 (1) = 5.24, Exp β = 1.321] (95% CI = 1.012 – 1.726, $p < 0.022$).

4.3 Discussion

That there is a relationship between handedness and speech lateralisation has long been accepted by researchers and clinicians with an interest in the functional organisation of the human brain. Exactly how handedness might be related to speech representation, however, is rarely examined. This study was based on the viewpoint that both behaviours involve a common feature of motor output sequencing and timing (Ojemann, 1984) and that pegboard performance constitutes a valid measure of this mechanism (Flowers and

Hudson, 2013). It was designed to replicate in a normal population the relationship found in the previous study with neurological patients, and did so.

For the whole sample, regardless of handedness, peg moving times were faster with the preferred than the non-preferred hand. A small practice effect was observed between trials one and five, but the relative asymmetry in hand skill remained stable across trials, which suggests that practice is not a confounding factor and that the test is a reliable measure of motor laterality (Annett, 1970). Moreover, the between-hand pegboard scores reliably discriminated between participants who were typically lateralised from those with atypical speech representation. At the group level, participants with clear unilateral speech representation demonstrated markedly faster peg moving times with the contralateral hand than the ipsilateral hand. In contrast, there was no significant difference in the between-hand movement times of those with atypical speech representation. The results thus concur quite closely with the previous findings, and confirm that the effect generalises to neurotypical individuals and is reliable across converging methodologies.

Categorising individuals as either left or right handed, or indeed ambilateral, on the basis of self-report questionnaire responses failed to effectively discriminate between typically lateralised and atypically lateralised groups. Almost 40% of those with clearly lateralised speech on fTCD were categorised as ambilateral, whereas almost one quarter of strong right-handers demonstrated atypical speech representation. Thus, measures of hand usage that indicate manual preference across different tasks do not mandatorily predict laterality effects. These findings suggest that if one aims to derive conclusions regarding speech representation on the basis of motor laterality, it is not hand preference per se that is pivotal but the between-hands difference in sequencing skill. Specifically, all participants with an average between-hand difference in peg movement times of more than 3.4 s showed clear speech laterality in the hemisphere controlling the proficient hand. In contrast, not a single atypical case had a between-hand asymmetry greater than 3.4 s. It is important to note, however, that many participants who were clearly lateralised also had narrow asymmetry scores. Thus, a small between-hand difference in skill does not confirm atypical speech representation; it merely indicates the possibility (actually ~ 50%). Albeit, asymmetrical scores greater than 3.4 s imply that atypical speech production is highly unlikely.

This chapter proposes that speech and motor laterality both involve a common aspect of motor sequencing, to the extent that a measure of the latter informs the likely representation of the former. Converging evidence suggests that these operations are indeed sub served by common neural mechanisms. For example, it has been shown that first, brain regions typically associated with movement are also activated by language tasks (Petersen, Fox, Posner, Mintun and Raichle, 1989); second, increased activation in Broca's area is observed during the execution of sequenced hand movements (Erhard et al., 1996); and third, aphasics (Pedelty, 1987) and children with specific language impairments (Hill, 1998) frequently display co-occurring motor deficits. These striking neuropsychological parallels between speech production and hand skill may indicate a common 'grammar' of movement (Grimme et al. 2011). In individuals with clear speech representation this mechanism is likely to be co-lateralised (see also Vingerhoets et al. 2011). By extension, however, the present findings suggest individuals with ambiguous motor laterality, for example patients with dyspraxia or developmental coordination disorder who may demonstrate reduced asymmetry in hand skill are likely to have an increased chance of atypical speech representation. This hypothesis is investigated in Chapter 6. Moreover, the coordinated action of hand and mouth is the cornerstone of the gestural theory of language origins (for review see Corballis, 2003). Iverson and Thelen (1999) posit that gesture and speech form a tightly coupled motor system sharing functional and structural brain mechanisms involved in communicative language. This speech-gesture system is argued to be present from birth and synchronous in typical (Bates, Benigni, Bretherton, Camaioni and Volterra, 1979) and atypical development (Thal and Tobias, 1992). Furthermore, encouraging communicative gestures facilitates both speech acquisition (Goodwyn and Acredolo, 1998) and recovery (Pashek, 1997). If gesture production is viewed as a motor sequencing task, and the association between speech and motor laterality postulated here is accurate, one might expect variations in gesture laterality to reflect variations in speech representation.

In the past, testing hypotheses relating to speech lateralisation has relied on studies of patients with aphasia arising from neurological impairment (Basser, 1962) or pharmacological intervention (Strauss and Wada, 1988), where there is the potential for functional reorganisation of language areas. The use of fMRI circumvents these caveats but can be expensive, sensitive to movement artefact and not suitable for certain clinical conditions. The use of fTCD as an imaging technique is an appropriate choice given that it is free of the above limitations. The WG paradigm used here is the most widely adopted method for language lateralisation in fTCD investigations, and the technique has been shown to concur reliably with both fMRI (Deppe et al., 2000) and Wada test outcomes (Knecht et al., 1998). Indeed, the data presented here demonstrates the good test-retest reliability of fTCD by showing a high correlation between LI scores over the two testing periods. Notwithstanding these advantages, however, WG is not a process-pure measure but involves a number of components, including; visual analysis, lexical retrieval, covert production and short-term verbal memory. Variation in the deployment of these processes and how participants engage with the instructions of the task is possible (Badcock, Nye and Bishop, 2012). Although this is not a caveat per se, future research may examine the generality of the findings reported here by deploying alternative fTCD tasks.

In summary, although hand preference and speech representation are assumed to be related the basis for this relationship is not clear. It is argued that handedness and speech involve a common aspect of motor output sequencing that is measurable by pegboard performance. Across studies, participants with atypical speech representation have been shown to have small between-hand differences in skill; in contrast those who have demonstrated a clear between-hand difference consistently have speech represented in the contralateral hemisphere. This pattern, which has now been observed in neurological and neurotypical samples, is relevant to evolutionary theories of handedness and language development, and we advocate that a measure of relative hand skill is included in clinical and experimental investigations of motor and language lateralisation.

Chapter 5

Preface

Commonly displayed functional asymmetries such as hand dominance and hemispheric speech lateralisation are well researched in adults. However, there is debate about when such functions become lateralised in the typically developing brain. Following on from the links found between motor skill and speech laterality in chapter 4, this chapter presents a study exploring the same question in a developmental population. This study examined whether patterns of speech laterality and hand dominance were related and whether they varied with age in typically developing children. 153 children aged 3-10 years performed an electronic peg moving task to determine hand dominance; a subset of 38 of these children also underwent functional Transcranial Doppler (fTCD) imaging to derive a lateralisation index (LI) for hemispheric activation during speech. There was no main effect of age in the speech laterality scores, however, younger children showed a greater difference in performance between their hands on the motor task. Furthermore, this between-hand performance difference significantly interacted with direction of speech laterality, with a smaller between-hand difference relating to increased left hemisphere activation. This data shows that both handedness and speech lateralisation appear relatively determined by age 3, but that atypical cerebral lateralisation is linked to greater performance differences in hand skill, irrespective of age. Results are discussed in terms of the common neural systems underpinning handedness and speech lateralisation.

Investigating speech and motor laterality during development

Functional asymmetries in hand skill and hemispheric speech lateralisation are well researched in adults. However, there is debate about when such functions become lateralised in the typically developing brain. The majority of adults demonstrate a typical pattern of right handedness and left hemispheric dominance for speech production (e.g. Knecht et al 2000), but evidence for the neural development of motor skill and speech is more varied. Studies of language lateralisation in children show that speech is clearly lateralised to the left hemisphere at around 6 or 7 years of age (Groen, Whitehouse, Badcock and Bishop, 2012; Gaillard et al., 2003) and evidence from neuroimaging of pre-verbal infants demonstrates an early left hemisphere dominance for processing of speech sounds (Dehaene-Lambertz, Dehaene and Hertz-Pannier, 2002). However, it has also been suggested that younger children exhibit more bi-lateral activation during speech production compared to adults (e.g. Holland et al., 2001). Similarly, research has suggested hand preference in adulthood may be predicted from lateralised motor behaviour in early gestation, comparing ultrasound observation of thumb sucking (Hepper et al., 1991), and neonate palmar grasp reflex strength (Tan and Tan, 1999). However, varying observations of hand preference in early childhood reveal that no general consensus exists for when adult-like handedness occurs. Some studies indicate that direction of hand preference is attained by age 3 (e.g. Archer et al, 1988; McManus, et al., 1988), with others reporting shifting hand usage and increased variability on manual tasks up until age 6, suggesting this is a more likely reflection of later handedness (Bryden, Pryde and Roy, 2000).

There is evidence that task proficiency is related to increased laterality (Groen et al., 2012; Sheehan and Mills, 2008), suggesting that very young children, who are not yet competent in either speech or motor control, may display more varied patterns of hemispheric lateralisation for these functions. Current thinking proposes that whilst the direction of cerebral lateralisation for language and motor functions may be genetically predisposed, it is in fact a complex interaction of environmental and genetic factors which mediate the individual profile of cerebral lateralisation during development (e.g. Bishop, 2013). Therefore it is crucial to understand the extent to which an individual’s laterality profile changes through development. If lateralisation shifts with age and task proficiency then it suggests that the underlying functional and structural neural architecture may also be changing and shifting in this period and is therefore potentially vulnerable to factors affecting this developmental trajectory.

Few studies have examined speech lateralisation in children below age 6, predominantly due to methodological difficulties in measuring language performance in pre-verbal children. Speech paradigms designed for adults tend not to produce a reliable enough stream of speech in children, either due to task difficulty, the requirement for literacy or complex instructions not easily understood, especially by very young children. However, notable recent exceptions have been able to demonstrate that typically developing 4-year-old children show predominantly left hemisphere lateralised speech (Bishop et al, 2014), and that no age effects in overall laterality profile could be found in preschool children aged between 1-5 years (Kohler, et al., 2015). That study did, however, find an effect of age in variability of the lateralisation measurement, which become more reliable with age. An emerging methodology known as functional transcranial Doppler (fTCD) ultrasound has been shown to be effective in overcoming the issue of problematic measurement in children, as it is non-invasive and can be performed in relative comfort, unlike other neuro-imaging techniques. Furthermore, specific speech production paradigms have been developed which allow assessment of lateralisation in pre-literate children (Bishop, Badcock and Holt, 2010; Stroobant, Van Boxstael and

Vingerhoets, 2011), and which have been validated against standard word generation paradigms used in adult language lateralisation research (e.g. Bishop et al 2009).

Research into the use of handedness as an indirect measure for speech laterality has formerly proved weak and inconclusive (Groen, Whitehouse, Badcock and Bishop, 2013), predominately due to the variability of methodologies, and hand preference and skill definitions being highly dependent on the measurement and classification used (Groen et al 2013). However, speech and motor control are said to share a common developmental trajectory (Iversen, 2010), sub served by overlapping neural pathways predominantly situated in the left hemisphere (see Binkofski and Buccino, 2004). Converging evidence underlines the relationship between language and motor function. For example, it has been shown that brain regions typically associated with movement (pre-motor cortex, supplementary motor area and cerebellum) are also activated by language tasks (e.g. Tremblay and Gracco, 2009; Petersen, Fox, Posner, Mintun and Raichle, 1989) and that classic speech production areas (i.e. Broca’s area/ Brodmann areas 44 and 45) show increased activation during the execution of sequenced hand movements (Erhard et al., 1996). In addition, individuals with aphasia (Pedelty, 1987) and children with specific language impairments (Hill, 2001) frequently display co-occurring motor deficits.

Flowers and Hudson (2013) propose that motor and speech laterality are related where they involve a common feature of motor output, namely the co-ordination of sequences of movements or utterances to execute a plan or intention so as to achieve a goal, either limb movement or expression of an idea (Grimme, Fuchs, Perrier and Schöner, 2011). This rationale has demonstrated that measures of performance based hand skill are better at revealing the underlying commonalities between the two functions, and thus are more effective at informing on their neurological relationship (Flowers and

Hudson, 2013; Groen, et al, 2013). The present study investigated the speech and motor lateralisation profiles of children aged 3-10 years to determine whether the two functions develop in parallel and, specifically, whether younger children would show more variable laterality across these functions. It focussed on a direct measure of language lateralisation (fTCD) and a handedness task (electronic pegboard) which relies on the same concept of motor sequencing suggested to underlie speech and motor action.

5.1 Method and Materials

5.1.1 Participants

Participants were 153 children aged between 3yrs and 10yrs (74 males; mean age = 5.9yrs, SD age = 2.02yrs). All children were reported by parental report to be typically developing. Parents were asked to report any reading, language or motor impairments or concerns, as well as any developmental disorders such as Autism or ADHD; any children with such conditions were excluded. All participating children had normal, or corrected to normal, vision and none had a history of neurological injury or disease or were on medication known to affect the central nervous system, or cardiovascular system. All participants were British and had English as a first and only language; 4 of the 153 children tested were of African ethnicity, and the remaining 149 children were Caucasian. Participants were recruited through local schools, parent/toddler groups and via the University of Lincoln's science outreach events. The investigation was approved by the ethics committee of the School of Psychology, University of Lincoln. Parental consent was obtained in writing at least 48 hours prior to the testing session following acknowledge receipt of detailed study information sheets and briefing on the study via phone/email contact. Children were also required to assent to participation at the time of testing. Failure on behalf of the child to assent super ceded the parental consent, such that those children did not continue with the study. During testing participants were accompanied by a female experimenter sitting beside them to ensure they were happy to continue. Children were free to withdraw at any time without prejudice, and this right was clearly explained to them and they were asked to practise saying they wanted to stop. In addition, silence, lack of response, changes in demeanour and eye contact, were all taken as signs from the child of disinclination to continue, thus triggering the cessation of testing. Only one instance occurred of a child asking to withdraw before the testing had started.

5.1.2 Behavioural Assessments

Participants completed a series of assessments to ascertain their levels of motor and language abilities.

Handedness Assessment: All participants underwent assessments of their hand preference via completion of 5 manual tasks selected as reliable indicators of manual preference. The tasks were selected from a group of manual actions usually found on handedness questionnaires (e.g Flowers and Hudson, 2013; Annett, 2002). This approach was taken due to the range of ages in the sample, where it was considered a standard handedness inventory would be inappropriate due to the literacy skills required to complete such a questionnaire. The 5 manual tasks were as follows: 1. Underarm throw of a soft ball to the experimenter; 2. Eat with a spoon from a bowl of imaginary cereal; 3. Sharpen a pencil; 4. Unscrew a lid from a jar; 5. Draw a circle with a pencil.

Each task was performed 3 times by the child and the hand used was recorded. The circle drawing task always went last, as research has shown the act of writing can influence subsequent hand use (Annett, 2002). The tasks were not demonstrated by the experimenter, only described verbally, to avoid direct copying. The amount of items performed with each hand was calculated into a laterality quotient using the following formula [(L-R)/(L+R)]*100, where positive values indicate right hand preference and negative values left handedness.

Motor Assessment: A sub set of 65 participants completed the Movement Assessment Battery of Children 2nd Edition (MABC-2; Henderson, Sugden and Barnett, 2007). This test battery assesses a range of gross and fine motor skills, including balance, dexterity and hand-eye coordination, and provides a standardised score of motor development. These scores can then be measured against sets of normalised performance scores which determine whether a child is typically developing in motor skills for their age. The MABC-2 was included to ensure all children met the criteria of having typical motor development for their age.

Vocabulary Assessment: In addition to the motor assessments 83 of the participants also completed the British Picture Vocabulary Scale (BPVS; Dunn and Dunn, 2009) to assess language ability. The BPVS requires children to select which picture out of four possible options best fits the word read aloud by the experimenter. This test was selected as it has normalised data for children aged 3 and above, and because it does not require reading and literacy skills to complete, both factors which suited our sample of participants. The BPVS produces a raw score, which, following conversion to a standardised score, can then be compared to normalised scores by age.

5.2 Experimental Procedure

5.2.1 Motor Skill Assessment

To give a more accurate measure of hand skill and motor dexterity, all the participants carried out an electronic, 4 trial version of the peg moving task described by Flowers and Hudson (2013). The dimensions of the board and peg movement procedure were identical, however, to improve timing accuracy the board was constructed to allow detection of peg lifting and placing via an electrical circuit in the board. This was connected to the PC's Parallel Port, where a Visual Basic programme continuously monitored and recorded the times at which pegs were removed from or inserted into the holes. Pegs were moved either away from the body, that is, from the near row of holes to the far one ('Out' condition) or in reverse direction toward the body ('In' condition) on successive trials, which were ordered as follows: 1. Preferred Hand Out; 2. Non-Preferred Hand Out; 3. Non-Preferred Hand In; 4. Preferred Hand In. Scores on this task were also used to confirm hand preference as measured by the 5 item task.

5.2.2 Speech Laterality

Thirty eight of the children (22 males; mean age = 6.5yrs, SD age = 1.92yrs) underwent functional transcranial Doppler (fTCD) imaging to determine their language lateralisation profile. Language lateralisation was determined by measuring hemispheric changes in cerebral blood flow volume (CBFV) with fTCD during an animation description task. The Animation description (AD) task was developed as an effective neuroimaging paradigm to elicit speech lateralisation in pre-literate children (Bishop, Watt and Papadatou-Pastou, 2009). To date the paradigm has been used specifically within fTCD and it has been validated against the standard word generation paradigm used in adult participants to determine speech laterality. The paradigm is described in detail by Bishop et al. (2010). In brief, participants were seated in front of a computer screen with the fTCD headset fitted. Each trial consisted of a watch phase, a report phase and rest phase. Initially a silent animation was presented in the centre of a computer screen for 12 s, during this time participants were required to sit silently and watch; the 'watch' phase. At the onset of the trial a 500 ms epoch marker was simultaneously sent to the Doppler. Participants were then required to describe aloud details of the cartoon for 10 s; the ‘report’ phase. The trial concluded with the ‘rest’ phase, which was an 8 s period of relaxation to allow CBFV to return to baseline before the onset of the next trial. The AD paradigm consisted of 20 trials in total, each lasting 30 seconds. Animation presentation was randomised and none were presented more than once to any given participant. The ‘watch’ phase also served as the pre-speaking baseline period, following previous research showing no evidence of lateralised activation while participants passively watched these video clips (Bishop, Watt and Papadatou-Pastou, 2009). The responses to each animation were audio recorded to enable subsequent analysis of fluency.

5.3 Data Analysis

5.3.1 Pegboard Performance

Performance on the electronic Pegboard task was measured by the speed with which the rows of pegs were completed. Mean movement times were calculated for the preferred and non-preferred hands, and a measurement of between-hand performance difference was calculated by subtracting the non-preferred hand mean time from the preferred hand mean time. To allow for more reliable comparison between individuals the between-hand difference measurement was transposed into an adapted version of the laterality quotient score, as described by Annett (2002). In this study the quotient score was derived to indicate the degree of relative hand skill on this task, rather than handedness direction, and was calculated by the following formula: [(Non preferred hand mean score – preferred hand mean score)/(Non preferred hand mean score + preferred hand mean score)]*100. Hand preference was used as opposed to right vs left as the hypothesis concerns the relative performance differences between the hands, and not the direction of preference per se (Flowers and Hudson, 2013).

5.3.2 FTCD

Relative changes in CBFV within the left and right Middle Cerebral Arteries (MCAs) were assessed using bilateral fTCD monitoring from a commercially available system (DWL Doppler-Box^{TM}X: manufacturer, DWL Compumedics Germany GmbH). A 2-MHz transducer probe attached to an adjustable headset was positioned over each temporal acoustic window bilaterally. PsychoPy Software (Pierce, 2007) controlled the animation description experiment and sent marker pulses to the Doppler system to denote the onset of a trial. Data were analysed off-line with a MATLAB (Mathworks Inc., Sherborn, MA, USA) based software package called dopOSCCI (see Badcock, Holt, Holden and Bishop, 2012 for a detailed description). DopOSCCI makes a number of computations in order to summarize the fTCD data and advance the validity of measuring hemispheric differences in CBFV. First, the numbers of samples were reduced by downsampling the data from ~ 100 Hz to 25 Hz. Second, variations in cardiac cycle which may contaminate task-related signals were corrected using a cardiac cycle integration technique (Deppe, Knecht, Henningsen and Ringelstein, 1997). Third, data contaminated by movement or ‘drift’ were removed prior to normalisation. Normalised epochs were subsequently screened and excluded as measurement artefacts if activation values exceeded the acceptable range (± 40% mean CBFV). Fourth, to control for physiological processes that can influence CBFV (e.g. breathing rate; arousal), the mean activation of the baseline period was subtracted from each individual epoch. Deviations in left versus right activity were therefore baseline corrected and reflect relative changes in CBFV. A laterality index (LI) was derived for each participant based on the difference between left and right sided activity within a 2 sec window, when compared to a baseline rest period of 10s. The activation window was centralised to the time point at which the left-right deviation was greatest within the period of interest (POI). In the present paradigm the POI was taken from the ‘report’ phase of the paradigm and ranged from 12

– 22s following onset of the trial (Bishop, Watt and Papadatou-Pastou, 2009).

Speech laterality was assumed to be clear in all cases in which the LI deviated by > 2 SE from 0 (Knecht et al., 2001; Hudson and Hodgson, 2016). Left-hemisphere or right-hemisphere speech dominance was indicated by positive or negative indices respectively. Cases with an LI < 2 SE from 0 were categorised as having bilateral speech representation. Individuals were categorised as having Typical speech representation if they displayed a clear LI score which was positive, alternatively individuals with a unclear LI score, or a clear LI score which was negative were categorised as having Atypical speech representation. Participants required a minimum of 10 acceptable trials (i.e. 50%) to be included in the analysis; all 38 participants reached this threshold.

5.4 Results

5.4.1 Behavioural Assessments

Participants were grouped by age into four categories: 3-4yrs; 5-6yrs; 7-8yrs; 9-10yrs. Table 1 shows the performance of the participants in each age group on the behavioural tests. An ANOVA with age group as the independent variable and BPVS standardised score, MABC-2 standardised score and Handedness Quotient as dependent variables showed that there were no significant differences between the age groups on any of the measures [BPVS: F (3,79) = .38, P = .766; MABC-2: F (3,61) = 1.11, P = .35; Handedness Quotient: F (3,140) = .923, P = .432], meaning that participants were similarly matched for motor and vocabulary ability; furthermore all participants fell within normal ranges for their age on these measures. Participants did not differ significantly on handedness quotients as derived from the 5-item task measure; there were 26 participants with a handedness quotient at or below zero, denoting left-handedness.

Table 5.1. Mean (M) and Standard Deviation (SD) performance scores on the behavioural assessments. There were no significant differences between these scores across the age groups.

	3-4 years		5-6 years		7-8 years		9-10 years	
	n	*m*	*n*	*m*	*n*	*m*	*n*	*m*
BPVS (standardised)	24	100.5 (13.54)	26	97.96 (13.1)	26	96.38 (13.8)	7	98.8 (14.5)
MABC-2 (standardised)	16	8.81 (1.72)	19	7.84 (1.7)	22	8.59 (1.9)	8	8.01 (1.5)
Handedness Quotient	42	4.96 (5.97)	43	4.56 (5.63)	42	4.42 (4.47)	17	2.4 (4.71)

5.4.2 Motor Skill Task

Data from 5 of the original 153 participants was incomplete, due to too few trials performed or failure to complete the task at all, meaning that adequate data was available for a total of 148 children. The excluded children were aged as follows: 2 x 3yrs, 1 x 4yrs, 1 x 5yrs and 1 x 8 yrs.

Firstly, paired samples t-tests were used to determine differences in preferred and non-preferred hand performance on the pegboard across all participants irrespective of age; a significant difference was found, where the mean preferred hand (PH) movement times were lower, thus indicating faster performance, than non-preferred hand (NPH) movement times, *t* (147) = -14.49, p< 0.001 (PH mean time = 38.94s, SD = 11.1; NPH mean time = 44.13s, SD = 13.4, *d* = .42). T-tests revealed practice effects within the pegboard task, with later trials being performed significantly faster than earlier trials, *t* (147) = 4.76, p< 0.001 (Trial 1 mean time = 41.91s, SD = 14.3; Trial 4 mean time = 38.52s, SD = 11.9, *d = .25*). There was also a significant effect of direction change on mean NPH times, *t* (147) = -3.04, p< 0.01 (Trial 2 mean time = 42.62s, SD = 13.06; Trial 3 mean time = 44.68s, SD = 14.0, *d = .15*), whereby the trials that required participants to move the pegs towards their body, as opposed to away from them, resulted in slower times specifically for the NPH. The PH was unaffected by this direction change.

There were significant correlations in pegboard performance across age groups with younger children displaying longer movement times than older children for both their preferred ($r(148) = -.78$, $p < .001$) and non-preferred hands ($r(148) = -.79$, $p < .001$). Movement times reduced linearly with increasing age.

Differences in mean performance between the hands (as determined by the Laterality Quotient score, see 2.4.1) were assessed across the age groups. This revealed that younger children displayed significantly greater between-hand differences, ($F(3, 147) = 2.78$, $P < .05$, $\eta_p^2 = .55$) demonstrated by larger laterality quotients, reflecting a stronger hand skill in the preferred hand on the peg board task, see Figure 5.1.

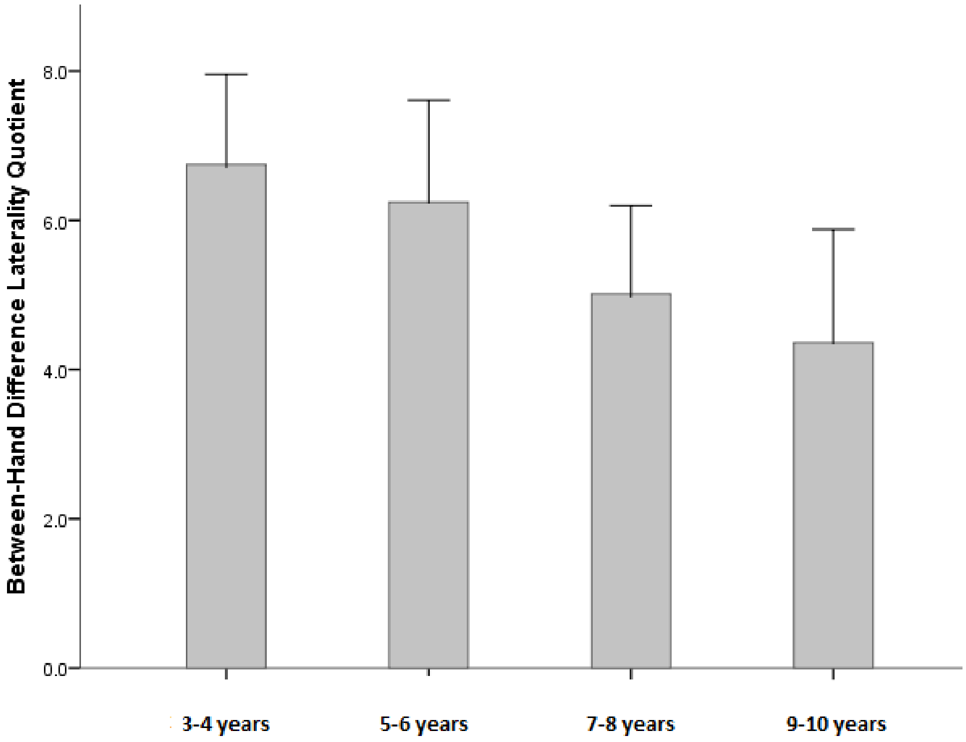


Figure 5.1. Laterality quotients, derived from the between-hand difference in pegboard performance, across age group. Higher quotient scores reflect stronger preferred hand performance.

5.4.3 Speech Lateralisation

As expected, across the whole sample there was an overall bias towards activation in the left hemisphere during speech production, with the combined mean LI = 1.17. Comparison of LI scores across age groups showed no significant differences between the groups (F(3, 37) = 1.78, P = .17), meaning that left hemisphere activation was predominant across all ages of participants. There were no significant interactions between behavioural assessment scores and speech LI scores, demonstrating that lateralisation profiles were not mediated by vocabulary or motor ability.

To ensure high reliability within the LI scores derived from the AD task, split half reliability estimates were calculated from Pearson correlations of the odd and even epochs for each individual. For the group as a whole correlations indicate a high level of internal consistency between the readings ($r = .62$, $p = .001$), meaning that the fTCD measurements were reliable.

Finally, a suggestion from research into neurodevelopmental disorders affecting speech and motor control indicate that atypical hemispheric speech activation could be representative of an immature, or impaired, neural speech network (e.g. Bishop, 2013). To examine whether atypical speech representation was reflected in the motor performance scores, the data was divided into two groups to represent; 1. Typical left hemisphere activation profiles and 2. Atypical activation profiles, denoted by right hemisphere or bi-lateral activation. Thirteen children were classed as having atypical lateralisation and 25 with typical. Figure 5.2 shows that atypically lateralised children had significantly greater performance differences between their hands (r(38) = -.359, p < .03; mean hand skill laterality quotient score = 8.51, SD = 1.81), whilst those with typical left hemisphere speech laterality demonstrated a much more similar performance ability between their hands (mean hand skill laterality quotient score = 4.77 , SD = .63). This difference was irrespective of age or participant handedness.

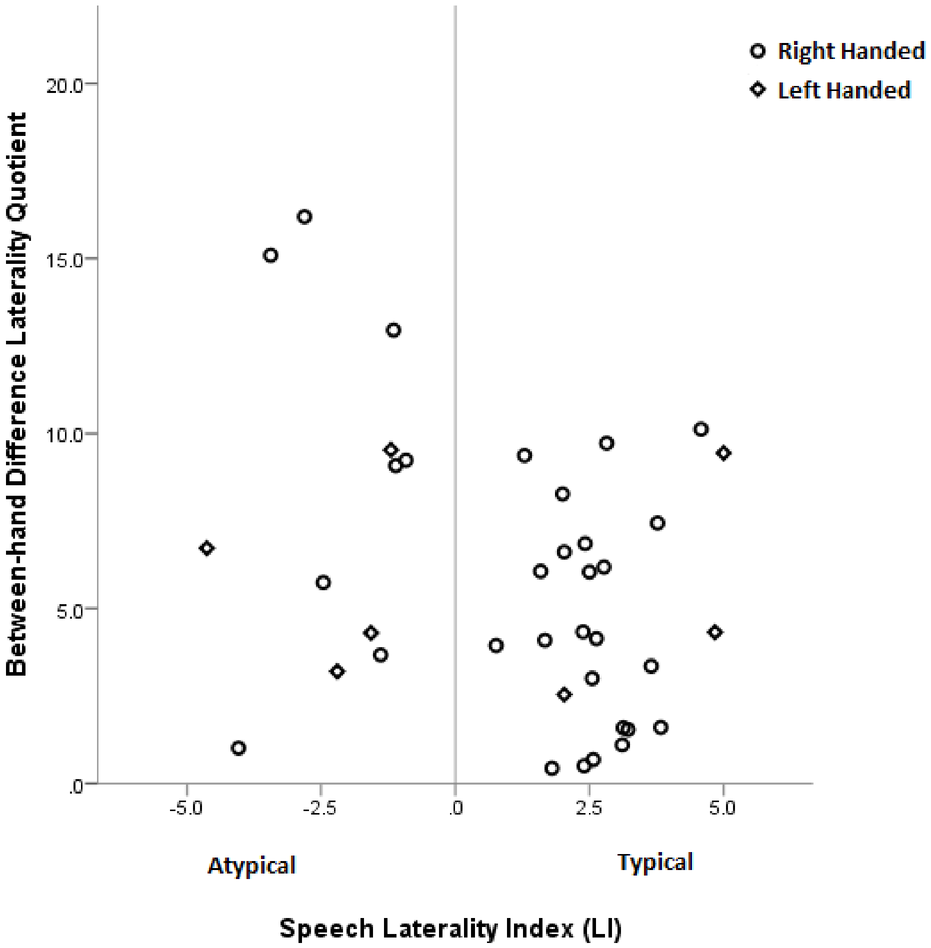


Figure 5.2. Scatterplot of the between-hand difference laterality quotient scores across two classifications of speech laterality; typical and atypical. Higher hand laterality quotients reflect greater discrepancy in performance between the dominant and the non-dominant hands.

As with the adult data from the previous chapter, here a stepwise binary logistic regression model was also used to assess whether pegboard performance was an accurate predictor of speech laterality. Group (typical or atypical) was entered as the dependent variable and the independent predictor was the time difference (in seconds) between the non-preferred hand mean time and the preferred hand mean time across the pegboard trials. The model showed that between hand difference on the mean pegboard performance scores is a significant indicator of speech lateralisation, $R2 = 0.16$ (Nagelkerke) [$\chi 2$ (1) = 4.61, Exp $\beta = 1.171$] (95% CI = 1.003 – 1.386, $p < 0.05$).

5.5 Discussion

The aim of this study was to assess the speech and motor lateralisation profiles of children aged 3-10 years to determine whether the two functions developed in parallel and whether younger children would demonstrate more variable laterality. Results showed that mean speech lateralisation scores showed a significant leftwards bias across all ages tested, giving clear indication that speech lateralisation is strongly represented in the left hemisphere at least by 3 years of age. This is in line with other recent neuroimaging data showing that even very young children display the expected pattern of left hemisphere language dominance (Bishop, 2014; Kohler et al., 2015). The data also revealed that hand preference was similarly well established by age 3, with all the children in this study showing a clear hand dominance effect on the 5-item preference score and the motor skill task. This provides confirmatory evidence, from a large sample, in line with previous research suggesting that direction of handedness is established early on in motor development (for review see Scharoun and Bryden, 2014).

Motor performance, however, was affected by age, with younger children showing a stronger performance preference for their dominant hand on the pegboard task, a difference which narrowed during development. This finding is relatively rare, but has been observed previously in studies also using a pegboard paradigm (e.g. Kilshaw and Annett, 1983; Roy et al, 2003), and represents the developmental trajectory of bi-manual proficiency. It also demonstrates that a skill-based performance measure is more sensitive to assessing handedness development, than inventories based preference tools. The motor skill data also indicates that the performance differences younger children display are mediated by the proficiency, or lack thereof, of the non-preferred hand (NPH). This is confirmed within our testing by the finding that children showed significantly longer latencies for pegboard trials requiring a change in direction when moving the NPH. This is something not seen in previous adult pegboard data (e.g. Flowers and Hudson, 2013), but is in accordance with previous evidence that children find it easier to perform away-from body manual actions, rather than those towards the body (e.g. Boessenkool, Nijhof and Erkelens, 1999). Evidence shows that specialist areas of the left hemisphere play a greater role in the control of complex, fine motor tasks for control of both the right and left hand. This ipsilateral control network for the left hand is in contrast to the typical contralateral cortico-motor control networks which govern motor actions (Serrien, Ivry and Swinnen, 2006; Haaland, et al. 2004). Therefore the finding that NPH proficiency underlies this difference in pegboard performance suggests that it is specifically the development of ipsilateral pathway, from left hemisphere to left hand, which is key to understanding the neural profile of motor skill development. This finding is in line with recent work showing that adults with developmental motor coordination impairments, such as Developmental Coordination Disorder, perform more poorly on fine motor tasks with their non-dominant hand (Debrabant, et al, 2013; Hodgson and Hudson, 2016) and that apraxic patients with left hemisphere damage show deficits performing heterogeneous motor sequences. Taken together these findings indicate that the ipsilateral pathway controlling the non-dominant hand from the language dominant hemisphere (typically the left), may take longer to develop to functional maturity, and that individuals with deficits in motor coordination are actually displaying performance of an immature ipsilateral control pathway.

A further key finding from this data was the correlation between direction of hemispheric speech representation and extent of performance difference between the hands, a finding which was independent of age or hand preference. Individuals who display atypical speech lateralisation show greater performance differences between their hands on the motor skill task. These results support the theory that action involving fine motor sequencing and speech production engage a common cognitive-motor neural network, largely supported by the left hemisphere's specialism for sequential response ordering for the left and right hand, and that these networks develop in parallel for the dominant hand/hemisphere mapping (Serrien and Sovijarvi-Spape, 2015; Kotz and Schwartze, 2016). Furthermore, this data suggest that the performance of non-dominant hand throughout development, and particularly whether this performance difference reduces with age, may be key to identifying those with atypical speech lateralisation, who are therefore potentially more likely to have difficulties with motor/language tasks. Although, it should be stressed that atypical lateralisation does not necessitate language/motor deficits, in fact little evidence exists to support this (Bishop, 2013), but rather that those who do have developmental difficulties may be detected through simple motor skill tasks. Causality cannot be inferred from this data, but the finding that atypical speech representation is linked to hand skill is in line with evidence from neurodevelopmental disorders showing atypical patterns of speech laterality in individuals with developmental motor coordination impairments (Hodgson and Hudson, 2016), indicating shifting functional organisation in speech networks as a result of impaired motor pathways.

One point of interest arising from the comparison between this data and the adult data reported in chapter 4 is that there is a difference in the direction of the interaction of between-hand pegboard performance and speech laterality. In this data children with a larger between-hand difference were more likely to have atypical speech lateralisation, whereas in the adult data atypical speech was better predicted by a smaller between-hand performance difference. One explanation for this distinction is that the comparison does not take into account actual between-hand movement time in seconds. When accounting for this total time it can be seen that the majority of children have a difference of greater than 3.4secs, which was the threshold for delineating atypical speech lateralisation in the adult data (see p84, section 4.2.4). Therefore it appears that atypical speech can be predicted from between-hand movement scores that sit at either end of a normal distribution of performance, with children showing the largest differences at over 10secs and adults with the smallest differences at under 3.4secs, revealing atypical speech processing.

One unexpected outcome from this study was that performance on the behavioural assessments of vocabulary and motor ability did not correlate with pegboard performance or speech laterality. It has been shown previously that there are links between task proficiency and degree of lateralisation (Groen et al, 2012), but our data did not replicate this. A possible explanation for that failure is that the types of behavioural assessment we used (BPVS and MABC-2) lacked sensitivity to the particular functions we were assessing. The BPVS does not contain tasks or performance measurements related to sequencing or motor response timing, and so could easily be argued not to tap into the type of phonological processing. Furthermore, the test battery does not require a verbal response to be made, but merely provides a score of vocabulary ability based upon recognition only, nevertheless due to the age ranges in our sample, it was necessary to use an assessment tool which did not rely on literacy ability. Future work should investigate the component processes involved in speech production and measure relative lateralisation profiles across development. The lack of sensitivity in the MABC-2 was more surprising, as this test battery does indeed contain several tasks directly related to sequencing, motor timing and co-ordination, all components thought to form the basis of the speech-motor system (Kotz and Schwartze, 2016). However, the scoring system employed by this battery makes it difficult to detect subtle and nuanced motor deficits as results are drawn from sub-sections of grouped tests, where some may have been performed well but others less well, resulting in an average score indicating typical development, but not an in-depth profile of differing aspects of motor development. However, as with the BPVS, the MABC-2 was useful in confirming typicality of our sample, although future work relating speech and motor ability should focus on a range of behavioural proficiency measures.

In conclusion these data suggest that lateralisation of language and motor control is a process which begins very early in development, before the child is proficient at manual coordination or speech. Evidence from early lateralisation of auditory processing (Dehaene-Lambertz, Dehaene and Hertz-Pannier, 2002) may indicate the start of this hemispheric specialisation seen in later childhood; perhaps most critical is the period in which speech sound and motor output mappings are beginning to be formed and rehearsed. The specialisation of the left hemisphere for control of response sequences and timing integration also accounts for the patterns observed between speech laterality and motor performance (Serrien and Sovijarvi-Spape, 2015). Future work needs to focus on isolating the common components of the speech and motor tasks which may be driving this relationship and will also look at the performance of individuals with motor impairments.

Chapter 6

Preface

The previous chapters have demonstrated that links between speech lateralisation and handedness can be revealed when using a motor task which relies on sequencing. The patterns of speech activation can be reliably measured with fCTD in adults and in children. The results shown so far indicate that the motor and speech systems are closely linked as suggested by several strands of evidence (see literature review) and that the typical development of these systems happens in parallel. What is less clear, however, is what happens to the functional relationship between handedness and speech lateralisation when development does not follow a typical path? The data shown in chapters 4 and 5 would suggest that where one of these functions is impaired then the other function may also be altered neurologically. Interestingly, although the literature is clear about there being developmental similarities in the patterns of motor and speech development (e.g. Iverson, 2010) there are very few studies which actually examine motor and speech *disorders* simultaneously, especially in relation to their neural substrates. It was also particularly apparent that the question of comorbidities was predominantly addressed from the perspective of neurodevelopmental disorders primarily affecting language and reading skills (e.g. Hill, 2001; Redle et al. 2014) rather than those with a primary motor disorders. This study sought to address that gap by assessing a group of adults with Developmental Coordination Disorder (DCD), sometimes referred to as Dyspraxia, to see if their motor impairments had resulted in atypical developmental of speech networks.

Atypical speech lateralisation in adults with Developmental Coordination Disorder

The relationship between motor control and speech production has long been a focus of neuropsychological research, with theories suggesting a complementary developmental trajectory between the two functions (Iverson, 2010). The majority of neuro-typical adults display a common pattern of right handedness and left hemispheric dominance for language (e.g. Knecht, et al., 2000a). However, evidence suggests that this typical pattern of hemispheric mapping is altered in individuals with neurodevelopmental disorders. Various studies report an increased proportion of left handedness in disorders such as dyslexia (Eglinton and Annett, 1994) and autism (Cornish and McManus, 1996) and data from individuals with language and reading impairments, such as Specific Language Impairment (SLI) and dyslexia, reveal reduced left hemisphere activation during speech production compared to controls (Whitehouse and Bishop, 2008; Illingworth and Bishop, 2009).

Developmental studies of the relationship between speech and motor function demonstrate differences in fine motor skill abilities in children with speech deficits (Visscher, Houwen, Scherder, Moolenaar and Hartman, 2007), as well as increases in bilateral cortical activation patterns underlying fine motor control in children with Persistent Speech Disorder (Redle et al. 2014) compared with controls. Furthermore, recent data from epilepsy patients demonstrates that the language dominant hemisphere can be identified and predicted by the differential motor performance between the preferred and non-preferred hand on a peg moving task (Flowers and Hudson, 2013).

This convergence of evidence indicates that hemispheric organisation of motor and speech functions are related, to the extent that the functional status of one is associated with the cortical representation of the other. This relationship has primarily been examined in cohorts with a predominant language disorder. To date this relationship has not been examined in individuals with a predominant motor disorder, such as those seen in Developmental Coordination Disorder (DCD), but without co-occurring language or reading impairments. This is a surprising omission in light of existing theories of how language and motor systems co-exist with regards the neural networks underpinning them (e.g. Goldenberg, 2013).

Developmental Coordination Disorder (DCD) is a neurodevelopmental condition affecting motor coordination and control often identified in childhood or young adulthood. It is estimated to affect 5-8% of the population (Gillberg, 2003) and is classified in DSM-V (American Psychiatric Association, 2013) as having difficulties with fine or gross motor coordination such that daily functioning is significantly affected. Importantly the motor coordination difficulties must not be the result of an underlying medical disorder (such as cerebral palsy). DCD is an idiopathic, stand-alone neurodevelopmental disorder, although in 25% of cases there is co-morbid presentation with other neurodevelopmental disorders, most commonly dyslexia or ADHD (Sugden, 2007). The exact cause of DCD is unknown and despite certain theories on possible neurological underpinnings (for review see Zwicker, Missiuna, Harris and Boyd, 2012), there has been relatively little neuroimaging research conducted with patients with DCD. Research investigating speech profiles in individuals with DCD suggests that language ability is often reduced in this group, and the co-occurrence of speech and language disorders in children with a DCD diagnosis is relatively high (see Hill, 2001, for review). The majority of research examining language and motor control disorders focusses on individuals with language impairments who also have motor coordination difficulties, but not necessarily a DCD diagnosis. The authors are not aware of any studies directly assessing the neural organisation of language within DCD populations.

The aim of this study was to establish whether there was reduced leftwards hemispheric lateralisation for speech production in a group of adult patients with DCD, but without co-occurring impairments in speech and language. It was predicted that due to the likely overlap between motor sequencing areas involved in fine motor control and in speech and language processes (Flowers and Hudson, 2013), the laterality profile displayed by the DCD participants in a speech production tasks would be significantly less left hemisphere dominant. To test this hypothesis an emerging technique in cognitive neuroscience was used; functional Transcranial Doppler (fTCD) ultrasound. fTCD assesses the relative changes in cerebral blood flow volume (CBFV) in each hemisphere whilst participants undertake a cognitive task and has been shown to reliably detect activation in speech paradigms (e.g. Bishop, Watt and Papadatou-Pastou, 2009).

6.1 Method and Materials

6.1.1 Participants

Participants were 12 adults with DCD aged between 18 and 43 years old (4 males; mean age = 25.33yrs, SD age = 9.01) and 12 adults without DCD aged between 18 and 28 years old (5 males; mean age = 20yrs, SD age = 2.66). All had normal or corrected to normal vision and gave informed consent prior to participating in the study. None of the participants had been diagnosed with a neurological disorder (aside from DCD in the patient group) nor were any taking medications known to affect the central nervous or circulatory systems. None had diagnosed impairments in speech, language or reading ability. All participants were Caucasian and all had English as a first and primary language. They had all completed compulsory and further education (which continues until age 18 in the UK) and all were either currently in higher education or full time employment. Participants were recruited through adverts placed on social media and around the University and were paid £6.00 for helping with the research. The investigation was approved by the ethics committee of the School of Psychology, University of Lincoln.

6.1.2 Sample Characterisation

All participants in the DCD group had received a diagnosis of DCD within the last 10 years from a clinician in the NHS. These diagnoses were self-reported by the participants. The speciality of the clinician providing the diagnosis varied between participants, with some having been assessed in primary care via their GP and others being referred to occupational therapists or neurological specialists. For the purposes of this study severity of DCD was assessed via the self-report Adult Developmental Coordination Disorder checklist (ADC), (Kirby, Edwards, Sugden and Rosenblum, 2010). The ADC is a screening tool for identifying DCD characteristics in adults. It is a short self-report questionnaire with 3 subscales, which focus on motor and coordination difficulties experienced in childhood and adulthood based around the DSM-V (American Psychiatric Association, 2013) criteria. The tool has been found to have high internal reliability and has been shown to have high discriminatory power at detecting individuals with DCD from controls (Kirby, Edwards, Sugden and Rosenblum, 2010). All participants in the DCD group met the criteria for significant motor difficulties during childhood, which is necessary for a diagnosis of DCD via this tool. In addition all DCD participants scored above the borderline threshold on the ADC, meaning that these individuals were in the ‘probable DCD’ category, as opposed to a milder form of the impairment. The ADC has a separate section on self-reported difficulties as an adult, although this does not focus solely on the motor domain and again, all DCD participants scored above the diagnostic threshold in this section.

The control group were selected from the general student and staff population, and were not specifically matched to the DCD group for age or gender.

6.1.3 Experimental Materials

All participants completed a series of assessments to ascertain their levels of motor, language and cognitive abilities.

Handedness Assessment: Hand usage was measured by a 21-item handedness questionnaire as described by Flowers and Hudson (2013). In short, respondents are required to indicate their preferred hand for executing 14 unimanual (e.g. hold a toothbrush) and 7 bimanual tasks (e.g. unscrew the lid of a jar). Participants were classified as left or right-handed if stating consistent hand preference for 90% of the tasks. Scores < 90% were classified on the basis of predominant left or right responses as either left or right ambilateral.

Nonverbal Reasoning: A shortened 9-item version (see Bilker et al., 2012) of the Ravens Standard Progressive Matrices (RSPM) test (Raven, Raven and Court, 2000) was included as a measure of general cognitive ability to ensure comparability between the patient and control groups. Bilker et al (2012) extensively modelled the 60 items in the original RSPM test and showed that a specific set of 9 items correlated highly with scores on the existing 60- item and 30 -item commercially available versions. The 9-item version also gave equivalent item and test level characteristics as well as a time saving of 75% against the administration time of the original version. In brief, participants are asked to choose which segment from a choice of 6 options best completes the pattern shown in a target box above. There are no time restrictions placed on this test and it does not require high levels of language or reading ability to complete, making it a good indicator of general nonverbal cognitive ability. For scoring purposes all items are equally weighted and a proportionate score based on number of correct responses is derived for each participant (see Bilker, et al 2012 for further details).

Language Assessment: Phonological processing and speech production abilities were measured using a sub set of tests from the York Adult Assessment-Revised (YAA-R) (Warmington, Stothard and Snowling, 2012). This test battery has been developed as a screening tool for diagnosing language and reading impairments, such as dyslexia, in students in higher education. Its inclusion here was to ensure comparable ability between patients and control on phonological and speech processing.

6.2 Experimental Procedures

6.2.1 Speech laterality

Language lateralisation was determined by measuring hemispheric changes in CBFV with fTCD during a word generation task. Word generation (WG) has been validated in numerous neuroimaging studies as an effective paradigm to elicit speech lateralisation (e.g. Somers et al, 2011; Benson et al., 1999; Bishop, Watt and Papadatou-Pastou, 2009). Within fTCD it has been used extensively by Knecht and colleagues (Knecht et al., 1998; Knecht et al., 1996) and the paradigm is described by Knecht et al. (1998). In brief, participants were seated in front of a computer screen with the fTCD headset fitted. Each trial began with a 5 s period in which participants were prompted to clear their mind (see Figure 1). A letter was then presented in the centre of the computer screen for 15 s, during which time participants were required to silently generate as many words as possible that began with the letter displayed. At the onset of the trial a 500 ms epoch marker was simultaneously sent to the Doppler-Box^{TM}. Following the generation phase, to ensure task compliance, participants were requested to report the words aloud within a 5 s period. The trial concluded with a 35 s period of relaxation to allow CBFV to return to baseline before the onset of the next trial. The WG paradigm consisted of 23 trials in total. Letter presentation was randomised and no letter was presented more than once to any given participant. The letters ‘Q’, ‘X’ and ‘Y’ were excluded due to their relatively uncommon occurrence in English. Verbally-produced words were recorded by the experimenter and the number of words per trial was calculated.

6.2.2 Motor Skill Handedness Assessment

To determine a more accurate measure of hand skill and motor co-ordination, and to serve as an additional confirmation of motor difficulties in the DCD group, the participants carried out an electronic version of the peg moving task described by Flowers and Hudson (2013). The dimensions of the board and peg movement procedure were identical, however, to improve timing accuracy the board was constructed to allow detection of peg lifting and placing via an electrical circuit in the board. This was connected to the PC’s Parallel Port, where a Visual Basic programme continuously monitored and recorded the times at which pegs were removed from or inserted into the holes

6.2.3 Data Analysis

Relative changes in CBFV within the left and right Middle Cerebral Arteries (MCAs) were assessed using bilateral fTCD monitoring from a commercially available system (DWL Doppler-Box^{TM}X: manufacturer, DWL Compumedics Germany GmbH). A 2-MHz transducer probe attached to an adjustable headset was positioned over each temporal acoustic window bilaterally. PsychoPy Software (Pierce, 2007) controlled the word generation experiment and sent marker pulses to the Doppler system to denote the onset of a trial. Data were analysed off-line with a MATLAB (Mathworks Inc., Sherborn, MA, USA) based software package called dopOSCCI (see Badcock, Holt, Holden and Bishop, 2012 for a detailed description). DopOSCCI makes a number of computations in order to summarise the fTCD data and advance the validity of measuring hemispheric differences in CBFV. First, the numbers of samples were reduced by downsampling the data from ~ 100 Hz to 25 Hz. Second, variations in cardiac cycle which may contaminate task-related signals were corrected using a cardiac cycle integration technique (Deppe, Knecht, Henningsen and Ringelstein, 1997). Third, data contaminated by movement or 'drift' were removed prior to normalisation. Normalised epochs were subsequently screened and excluded as measurement artefacts if activation values exceeded the acceptable range (± 40% mean CBFV). Fourth, to control for physiological process that can influence CBFV (e.g. breathing rate; arousal), the mean activation of the baseline period was subtracted from each individual epoch. Deviations in left versus right activity were therefore baseline corrected and reflect relative changes in CBFV. A laterality index (LI) was derived for each participant based on the difference between left and right sided activity within a 2 sec window, when compared to a baseline rest period of 10s. The activation window was centralised to the time point at which the left-right deviation was greatest within the period of interest (POI). In the present paradigm the POI ranged from 3 – 13 s following presentation of the stimulus letter (Bishop, Watt and Papadatou-Pastou, 2009). Speech laterality was assumed to be clear in all cases in which the LI deviated by > 2 SE from 0 (Knecht et al., 2001). Left-hemisphere or right-hemisphere speech dominance was indicated by positive or negative indices respectively. Cases with an LI < 2 SE from 0 were categorised as having bilateral speech representation.

6.3 Results

6.3.1 Diagnostic and Behavioural assessments

Table 1 shows the characteristics of the two participant groups on the behavioural tests. As expected the DCD group scored significantly higher than controls on the Adult Developmental Coordination Disorder (ADC) screening tool ($t(22) = 10.08$, $p < .001$, effect size reliability; $d = .9$). Notably, however, there were no significant differences between groups across the phonological processing assessments or the non-verbal reasoning test. The groups were similarly matched for age and nonverbal ability, and they did not differ significantly on handedness quotients as derived from the questionnaire; 3 of the DCD group and 1 of the control group had a handedness quotient at or below zero, denoting left-handedness.

Table 6.1 Mean *(Standard Deviation)*, t-statistic, significance value and effect size indicator for test scores across DCD and control groups. *denotes significant difference at p < .001.

	DCD Group (N = 12)	**Control Group (N = 12)**	**Statistics**		
	Mean *(SD)*	Mean *(SD)*	*t*	*p =*	*d*
Age (years)	25.4 *(8.91)*	20 *(2.66)*			
Handedness Quotient	50.8 *(62.2)*	74.6 *(46.3)*	-1.101	.283	.43
ADC Score	79.5 *(17.1)**	20 *(8.24)**	10.08*	.001*	.91
Ravens shortened Matrices score	.59 *(.27)*	.58 *(.20)*	.008	.993	.04
YAA-R Subtests:					
Spoonerisms Correct	.84 *(.23)*	.93 *(.14)*	-1.042	.309	.47
Spoonerisms Rate	.30 *(.19)*	.29 *(.16)*	-.057	.955	.05
Object Naming Rate	.41 *(.30)*	.56 *(.16)*	-1.629	.117	.62
Digit Naming Rate	.32 *(.29)*	.51 *(.24)*	-1.878	.074	.71

6.3.2 Motor skill task

As expected the DCD group displayed slower mean peg movement times across both hands on the motor skill assessment (see Figure 6.1) Interestingly this difference between groups resulted specifically from the performance of the non-preferred hand ($t(22) = 2.270$, $p < .05$, $d = .92$; DCD group mean = 27.7secs, SD = 5.65; Control group mean = 23.5secs, SD = 3.11). The effect size for this analysis was shown to be reliable ($d = .42$). The between group difference in the performance of the preferred hand was not significant ($t(22) = 1.59$, $p = .063$; DCD group mean = 25.03secs, SD = 4.97; Control group mean = 22.43secs, SD = 2.67), although the DCD group showed a greater hand asymmetry.

In addition, faster performance on the pegboard task (lower mean movement times) was correlated with higher scores in some of the language assessment components of the YAA. Table 6.2 shows a breakdown of these correlations.

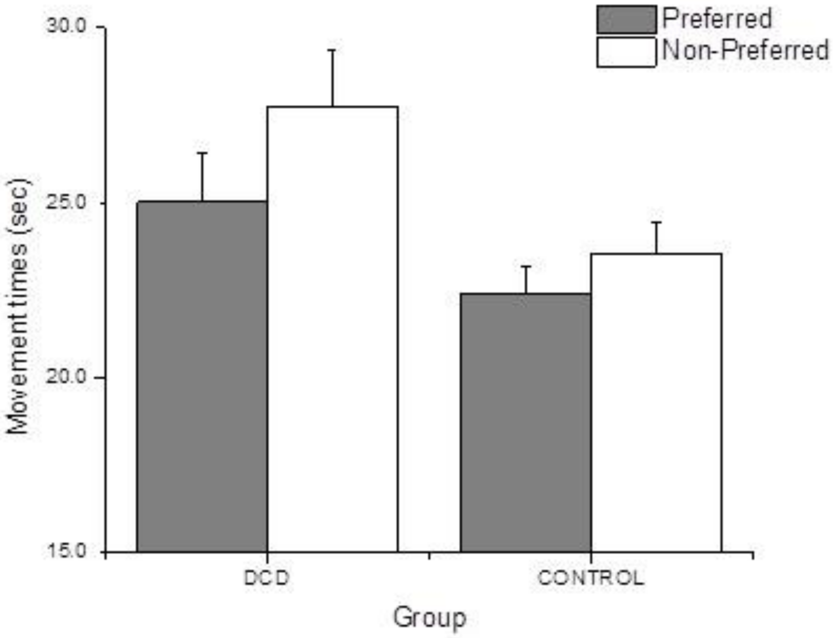


Figure 6.1. Bar chart showing the mean peg movement times for the preferred and non-preferred hands across each group.

Table 6.2. Pearson's correlations for the Pegboard motor skill task performance and language assessments across the whole sample (N=24). *denotes significant correlation

	Preferred Hand Performance		Non-Preferred Hand Performance	
	***r* =**	***p* =**	***r* =**	***p* =**
Spoonerisms Rate	-.34	.10	-.29	.16
Object Naming Rate	-.71	.001*	-.65	.001*
Digit Naming Rate	-.75	.001*	-.69	.001*
Mean no. words reported during fTCD	-.41	.05*	-.46	.03*

6.3.3 Speech lateralisation

Figure 6.2 shows a scatter plot of the laterality indices (LI) for the word generation paradigm for the DCD and control groups. There was a significant difference (*t*(22) = -2.2, *p* < .05) between the groups indicating that the DCD group (mean LI = 1.89, SD = 2.58) show less left hemisphere lateralisation during speech production than controls (mean LI = 3.77, SD = 1.42). A reliable effect size was found to support this result (*d* = -.41). This confirms the hypothesis that reduced leftwards lateralisation would be seen in the DCD group. In further scrutinising the spread of mean LI scores (see Figure 6.2.) it was observed that one left handed participant in the DCD group was more strongly right hemisphere lateralised than the remainder of the participants. Although this individual is not statistically an outlier, to check the possibility of this data point driving the interaction, we temporarily removed it from the sample and re-ran the analysis. Even without this participant there was a significant difference between the LI scores of the DCD group and controls (*t*(21) = -1.94, *p* = .03, one-tailed, *d* = .80) confirming the hypothesis that the DCD group (Mean LI = 2.44, SD = 1.87) would be significantly less left hemisphere lateralised than controls (mean LI = 3.77, SD = 1.42).

To ensure high internal reliability of the word generation LI scores computed for both groups, Split half reliability for word generation LIs was computed from Pearson correlations for the LIs from odd and even epochs. For the group as a whole, $r = .66$, $p = .001$, and specifically for the 12 individuals in the DCD group, $r = .79$, $p = .002$. It is clear that the reduced lateralisation in the DCD group is not the consequence of unreliability of the LI estimate.

To assess whether the range of ages in the sample contributed to the difference seen in LI score Pearson correlations of age in years and LI score were conducted across the sample as a whole and also separately for each participant group. None of these correlations were statistically significant: whole sample ($r(24) = -.19$, $p = .38$); DCD group ($r(12) = .01$, $p = .97$); control group ($r(12) = .14$, $p = .65$).

One possibility is that the reduced leftwards lateralisation in the DCD group could simply reflect poor ability on the word generation task. If the patients are less able to generate words, then they may not engage left-hemisphere systems as strongly (Illingworth and Bishop, 2009). There was a significant difference between groups in the mean number of words generated per letter: for controls, M = 4.2, SD = .66; for DCD patients, M = 3.5, SD = .48, (t(22) = -3.204, p < .005); with a reliable effect size ($d = .51$). A Pearson correlation of the LI from the word generation task and the number of words reported across the whole sample were not significant ($r(24) = .28$, $p = .18$), confirming that LI did not vary as a function of performance.

Finally, handedness preference as measured by the questionnaire did not correlate significantly with LI score ($r(24) = .209$, $p = .33$) and similarly performance on the motor skill pegboard task also did not significantly correlate with LI score ($r(24) = .163$, $p = .45$). This may be due to small sample size reducing power in this instance, however, the relationship between handedness and cerebral language lateralisation is considered to be weak and indirect, with inconsistencies in performance and inventory-based measures being reported in the literature (e.g. Groen, Whitehouse, Badcock and Bishop, 2013).

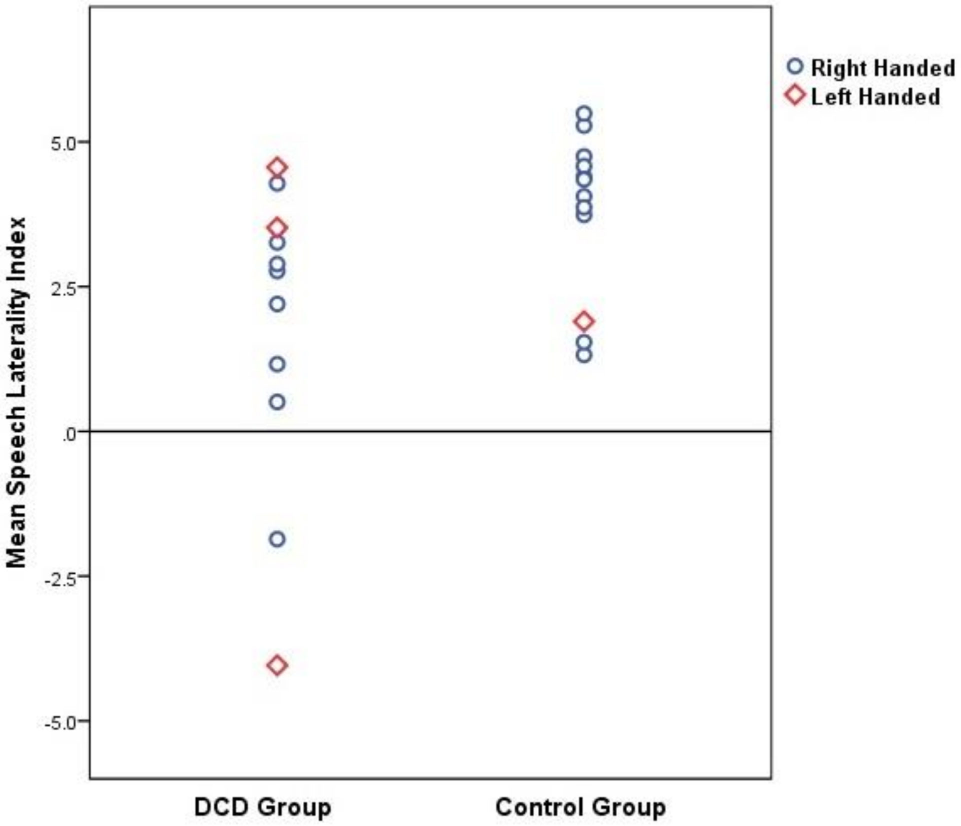


Figure 6.2. Plot showing distribution of mean speech laterality indices for DCD and control groups in the word generation task. Negative numbers indicate right hemisphere lateralisation and positive numbers indicate left hemisphere lateralisation.

6.4 Discussion

Previous research (e.g. Flowers and Hudson, 2013; Whitehouse and Bishop, 2008; Illingworth and Bishop, 2009) suggests that individuals with neurodevelopmental disorders affecting language and/or motor systems may show atypical hemispheric lateralisation patterns during speech production due to the common neural systems underpinning both functions. The aim of this study was to assess hemispheric speech lateralisation patterns in patients with motor coordination impairments, but with no known speech or language deficits. This was the first study of its kind to employ fTCD to assess speech lateralisation in patients with DCD, and the results supported the hypothesis that a reduced leftwards asymmetry would be observed in the DCD group.

One explanation for the link between the hemispheric control of speech and motor systems is that both functions employ sequencing components which are supported by the same neural network, located in the left hemisphere. Haaland, Elsinger, Mayer, Durgerian and Rao (2004) demonstrated that control of motor actions involving complex sequences are lateralised to left pre-motor and parietal areas, regardless of the hand used or the handedness of the participants. These regions have been shown to overlap with classic left hemisphere speech production areas (e.g Brodmann areas 44 and 45, see Binkofski and Buccino, 2004) meaning that the two tasks in this study may be relying upon the same region in the left hemisphere for their effective execution. Therefore we suggest that underlying DCD are impairments in motor sequencing, which not only affect the motor coordination abilities, but also the organisation of networks controlling speech production. Previous findings showing impaired motor timing and sequencing (unrelated to speech production) in DCD groups provide support for this view (Debrabant, Gheysen, Caeyenberghs, Van Waelvelde and Vingerhoets, 2013). In support of this explanation is our finding that motor performance is reduced in the DCD group specifically in the non-preferred hand. Left hemisphere control of the non-preferred hand (usually the left hand) has been demonstrated in previous studies during motor sequencing tasks (see Serrien, Ivry and Swinnen, 2006). The slower non-preferred hand performance in the DCD group may demonstrate a reduction in the strength of this ipsilateral pathway for complex motor action, to the extent that speech production processes relying on similar networks become atypically organised as well.

It is possible that the difference in laterality scores between the DCD group and the control group could result from the variances in age within the samples. Previous literature suggest that hemispheric lateralisation of speech shifts during development and that younger adults therefore may show a more bilateral speech representation (e.g. Holland, et al., 2001). However, that view is not supported by this data, as age did not significantly correlate with LI score. This finding is in line with previous fTCD work which shows no difference in laterality scores between children and adults (e.g. Lohmann, Drager, Muller-Ehrenberg, Deppe and Knecht, 2005; Groen, Whitehouse, Badcock and Bishop, 2012).

An aspect of this data that needs addressing, which may explain the difference in speech laterality indices found between the groups, is the differences in mean words produced by each group during the speech task. Crucially this sample of DCD patients display significantly different patterns of lateralisation than controls and yet do not differ significantly from them on tests for phonological and verbal processing or in their non-verbal cognitive function ability. Therefore the difference in word production rate could be the result of reduced task engagement by the patient group thus resulting in a poor representation of speech lateralisation.

It is worth considering though why the DCD group reported significantly fewer words, as it may provide insight into the nature of impairments in DCD and why this might impact on speech networks. One possibility is that the specific demands of the word generation task were increased for the DCD group, particularly in systems responsible for working memory and executive function, areas shown previously to be impaired in individuals with DCD (Pratt, Leonard, Adeyinka and Hill, 2014; Alloway and Archibald, 2008). These studies suggest that the motor impairments shown in DCD result from motor plans not being accurately held ‘online’ during the execution of a motor action, thus affecting the efficiency and accuracy with which the eventual motor response is made. The component of the word generation task which requires subjects to recall the words they were thinking of occurs after the letter stimulus has disappeared from the screen and so relies heavily on such working memory functions. However, if this task really implicated working memory functions to such an extent, then previous findings (Zwicker, Missiuna, Harris and Boyd, 2011) would indicate that increases in right hemisphere dorso-lateral prefrontal cortex activation would be associated with a more efficient working memory system, not a poorer one. This perspective would also suggest the DCD participants found the word generation task harder than controls, and the reduced leftward activation found could be due to a general slowed processing in this group. Cognitive control systems in speech production tasks have been shown to result in increased right hemisphere activation in patient groups compared to healthy controls (e.g. Brownsett, et al. 2014; Hodgson et al, 2014), however, as no previous imaging research has been conducted into speech production and DCD, it is difficult to extend this finding to our data.

However, whilst it remains a possibility that reduced left hemisphere activation is indicative of increased cognitive control processes, the performance data from the motor skill task gives support to the idea that it is complex motor actions which have parallels with speech production processes that are organised atypically, thus producing the differences in laterality profiles seen between the groups.

Potential limitations of this study are that it uses a relatively small sample and therefore this makes it harder to detect specific differences in performance on the motor task and how these may relate to direction of speech lateralisation. Furthermore the data is limited by the lack of participant information on environmental factors such as socio-economic status and lifestyle, which may impact upon the group differences seen. This study provides a good first step into exploring speech lateralisation in DCD, but more extensive studies should now be conducted with larger samples and a cross section of differing severity of motor impaired individuals.

In summary, this data demonstrates that individuals with Developmental Coordination Disorder affecting motor control also present with reduced left hemispheric dominance for speech production despite no behavioural deficits in that function. It is suggested that the two functions involve complex sequencing of movements which use similar neural systems, previously shown to lateralise to the left hemisphere. These results support the perspective that when atypical cerebral lateralisation occurs due to developmental impairment in either speech or motor control, this reorganisation extends to the related function, but does not disrupt it enough to impact upon the behavioural presentation of that related function. This data has implications for clinical practice as it demonstrates the sensitivity of fTCD to detect neurological differences between populations that are not evident through behavioural testing. This has potential application in the assessment of likely co-morbidities in individuals with developmental speech and motor impairments, but also extends our knowledge of the impact of neuro-developmental disorders on brain organisation and development

Chapter 7

Preface

The previous results chapters have explored the relationship between performance on the electronic pegboard task and speech lateralisation scores in a range of participant populations. In each case associations between this specific motor task and speech laterality have been displayed, and these have been explained in terms of the functional specialisation of the left hemisphere for controlling sequential motor output, of which both speech and motor skill measures make use. However, the results so far are unable to be more specific about which exact elements of the task are actually driving this relationship. Indeed, the literature on hand sequencing tasks and speech lateralisation yields very little in the way of an investigation along these lines. Some studies have compared handedness measures with direction of cerebral lateralisation for language, and yet these comparisons have focussed either on one measure of handedness or on distinguishing differences between performance and preference-based measures of handedness, rather than comparing a range of skill-based motor tasks (e.g. Badzakova-Trajkov et al., 2010; Groen, Whitehouse, Badcock and Bishop, 2013; Somers et al, 2015). Groen, et al., (2013) is the most closely mapped recent study, where 3 different motor performance tasks were compared with handedness inventory scores and language lateralisation. Overall they only found weak associations between handedness and speech lateralisation, and did not find a significant relationship at all for the single skill-based task used – the pegboard. The other two motor tasks tested were measures of hand preference rather than performance, which therefore does not further our knowledge of the component processes underlying motor skill and speech laterality.

This chapter presents a set of two experiments designed to fill this evidence gap by investigating motor performance on a range of skill-based tasks and assessing the relationship between these and direction and strength of speech lateralisation indices. To achieve this aim the chapter presents an innovative approach to this research question, on two fronts. Firstly in the deconstructing of the pegboard task itself. The purpose here was to test participants' performance on a set of hand skill tasks that are specifically derived from the motor processes incorporated in the pegboard task and see which of these best associates with speech lateralisation indices. The second novel aspect of this chapter is presented in experiment 2. Here a new fTCD paradigm has been developed to produce a laterality index of motor action, rather than speech, in order to measure whether motor action of either hand is controlled by increased left hemisphere activation during tasks more reliant on motor sequencing.

Deconstructing the Pegboard: imaging speech-related motor action

Strong left hemisphere asymmetry for language is a robust finding at the population level (e.g. Knecht et al 2000a). Similarly the cortical activation patterns of manual praxis, that is, the ability to generate, coordinate and perform learned gestures and intentional actions, also reveal a left hemisphere bias (Buxbaum et al, 2005; Haaland et al, 2004; Goldenberg, 2013). The association between praxis and language is longstanding in neuropsychology, with evidence revealing that left hemisphere lesions often lead to combined impairments in motor control and speech (Rasmussen and Milner, 1975; Goldenberg, 2013). As such, common neural mechanisms are thought to underlie both speech and manual action, especially action involving fine motor control of the hands. Evidence shows that classic speech production areas such as the pars opercularis and pars triangularis, also known as Broca’s area, are activated during motor tasks (Binkofski and Buccino, 2004) and that the motor cortex and pre-motor areas activate during language tasks (Sahin et al., 2009). These findings underlie the hypothesis that both functions share a common evolutionary origin and specifically that spoken language evolved from gestural communication (Corballis, 2003; Arbib, 2000, 2005).

Such neurological overlap between the praxis and speech is hypothesised to result from the two functions relying on similar processing mechanisms. One suggestion is that tasks which rely on sequential processing of complex actions will make use of similar cortical networks and will predominantly lateralise to the left hemisphere. The left hemisphere is recruited for complex sequential processing in a range of cognitive domains, and has been shown to be specifically involved in visuomotor control of action (Verstynen, et al. 2005). Furthermore, left hemisphere pathways activate more strongly than right hemisphere homologues during complex fine motor tasks, regardless of the hand that is moving or the participant’s handedness (Haaland, et al 2004; Serrien et al, 2006). It has been demonstrated that handedness tasks involving fine motor sequencing are related to the hemispheric lateralisation of speech activation (Gonzalez and Goodale, 2009; Hodgson, Hirst and Hudson, submitted) and even that performance differences between the hands on skilled motor tasks can predict direction of language lateralisation, as measured by the Wada procedure (Flowers and Hudson, 2013).

This study was designed to investigate whether the aspect of motor sequencing inherent in the pegboard task (as described by Flowers and Hudson, 2013) is the main factor driving the relationship found between hand skill and direction of speech lateralisation. Although there is agreement that sequential processing underlies the overlap in function between speech production and motor skill (Grimme et al, 2011), most studies examining this relationship use tasks which do not effectively tap into this mechanism. Furthermore, although it has been demonstrated that left hemisphere regions are crucial to the control of complex movement with either hand, it is not clear whether this activation occurs in response to discrete finger sequencing tasks, or more during gesture paradigms which rely heavily on communicative motions, and thus may be more likely to elicit left hemisphere activation due to overlap with speech production (e.g. Vingerhoets, 2013)

In addition to motor sequencing, some additional underlying component processes of the pegboard task were identified as having a role in the successful execution of the task: 1) Precision grip and release and grip strength; this skill is crucial in determining an individual's ability to pick up the pegs smoothly and accurately and release them as fast as possible. Evidence suggests that precision grip is one of the later aspects of hand manipulation skills to develop in young children (Scharoun and Bryden, 2014) and it has also been demonstrated that tasks which require use of the pincer grip motion are performed more accurately with the dominant hand (Gonzalez, Ganel and Goodale, 2006). A study by Annett, Annett, Hudson and Turner (1979) using stop-motion video analysis demonstrated that participants who had slower movement times on the peg board task actually deployed a less effective release motion of the peg, but were comparable on other aspects of the grasp action. 2) Finger dexterity; this skill involves the ability to quickly and accurately manipulate the fingers into different positions and move individual digits at varying speeds and angles, as required by the task. Models of corticomotoneuronal pathways indicate that crucial rostrocaudal connections which project bilaterally from the brain stem are heavily involved in finger dexterity, and severing these connections at various points limits digit mobility to varying degrees of severity (Isa, Kinoshita and Nishimura, 2013). As finger dexterity may rely more on direct cortico-spinal links tasks which isolate this may be crucial in differentiating ability on the pegboard task. 3) Arm movement; skilled manual tasks often require an element of upper arm motion especially if the task involves crossing the midline of the body. This additional element of gross motor function involves separate muscle and nerve groups which may vary the pattern of hemispheric activity. 4) Psychomotor speed; this function is defined as the ability to maintain focus on a task requiring manual/motor response by accurately integrating relevant cognitive processes. It relies heavily on aspects such as working memory, attention and other ‘top-down’ processes to maintain motor speed and concentration on a specific task. Patients with deficits in regulation of psychomotor speed have been shown to have lesions extending bilaterally through parietal and temporal regions (Goldenberg, 2013).

In order to explore the premise of additional underlying components being crucially involved in successful completion of the pegboard task, a set of experiments were conducted to assess overlap between speech production and motor output. The first of two experiments assessed whether the interactions between skilled motor performance and speech lateralisation are predominately dependent on the sequencing element of the required task, or whether the other identified component processes may also be important. Experiment 1 attempted to deconstruct these factors into separate tasks and then correlate left and right hand performance across these tasks with separately derived speech lateralisation indices. The hypothesis was that only tasks with an element of motor sequencing would correlate with speech lateralisation indices, based on the assumption that sequencing is a mechanism specifically supported by the left hemisphere, and common to both speech and pegboard performance. The second experiment then deployed a novel imaging paradigm using fTCD to derive lateralisation indices of *motor action* during three selected tasks. Previous work on imaging the motor cortex via fTCD has deployed simple finger tapping tasks to activate contralateral motor pathways as an indicator of functional relocalisation in stroke patients with aphasia and/or apraxia diagnoses (Silvestrini et al, 1993). This approach to measuring motor activation using fTCD has not yet been applied to skilled motor tasks or for comparison of motor and speech laterality. It is hypothesised that the tasks which correlate more strongly with speech lateralisation scores in experiment 1, will also display an increased left hemisphere activation bias for both hands (contralateral activation for right hand motion and ipsilateral activation for left hand motion), in comparison to a baseline task where it is expected that only contralateral action will be displayed.

7.1 Experiment 1

7.1.1 Participants

Forty adults aged between 18 and 40 years (17 males; mean age: 20.07yrs; SD age: 3.7) were recruited from the University of Lincoln. Participants gave informed consent prior to taking part in the study. All participants had normal, or corrected to normal, vision and none had history of neurological disorders or trauma, or any condition known to affect the circulatory or central nervous systems. All participants were Caucasian and had English as their first language. They received research credits in return for their participation. The study received ethical approval by the School of Psychology Research Ethics Committee, University of Lincoln. Participants completed a handedness questionnaire to determine their self-reported hand preference (See Flowers and Hudson, 2013), which revealed that 6 of the 40 participants were left handed, denoted by a handedness quotient at or below zero.

7.1.2 Motor Skill Tasks

All participants performed 6 separate manual praxis tasks. The ordering of task presentation was counterbalanced between participants. Each task was performed with both hands, alternating between right and left on each trial, with the self-reported preferred hand going first on each task. Figure 7.1 shows how each task corresponds to the component processes of the pegboard.

Task 1. Electronic Pegboard – This procedure has been described in detail in Chapter 3 of this thesis. In brief, 20 pegs were moved one at a time from a row of holes on one side of a rectangular board to a row of holes at the opposite side of the board. This task was performed as fast as possible and exact timings were measured by the electrical circuitry hidden in the board.

Task 2. Coin Rotation – Participants were asked rotate a British two pence coin (diameter = 25.9 mm, thickness = 1.85 mm, weight = 7.12 g) as quickly as possible among their thumb, index, and middle fingers. The time to perform 20 half turns was measured. The experimenter counted and timed the turns. This was performed 3 times with each hand. Performance was measured in seconds. This task has previously been shown to accurately measure manual dexterity in healthy adults (Mendoza et al, 2009) and patient groups (Heldner et al, 2014).

Task 3. Finger Tapping – Participants placed both hands flat on the table in front of them and were required to tap their index finger 10 times as fast as possible, whilst keeping their other fingers in contact with the table surface. This was performed 5 times with each hand. Taps were recorded by the experimenter and performance was measured in seconds.

Task 4. Grip strength – This was measured using a handheld dynamometer. Participants were required to sit with their feet flat on the floor and their arm at a comfortable right angled position by the side of their body. They were instructed to squeeze the device as hard as they could for 2 seconds and then release their grip. This was performed 3 times with each hand. Performance was measured in Kilograms.

Task 5. Dotting – This task was designed as a pen and paper version of the pegboard. Participants were asked to hold a short felt tip pen in a pincer grip and place a single dot inside circles laid out in two rows on a piece of paper (see appendix 2). They were instructed to do this as fast as possible and be as accurate as possible. The dimensions of the two rows of dots matched exactly the dimensions of the pegboard (see section 3.4) and the ordering of trial completion was also the same. Occasions where the dot was not inside the circle were classed as errors. Three trials were performed with each hand and the mean time and accuracy scores were calculated.

Task 6. Peg Sorting – Participants were required to sort 20 pegs from a pot placed at the side of a board into 5 cups arranged on the board. The cups were placed in a circle in grooved slots to ensure the exact dimensions were consistent across participants (see Appendix 2). Participants were instructed to ensure all 20 pegs were sorted as fast as possible, and they were explicitly told not to sort into the same pot on two consecutive pegs, or to use an adjacent pot to the one just selected on consecutive pegs. This rules were to avoid participants sorting into each pot in a circular manner or just making use of one pot.

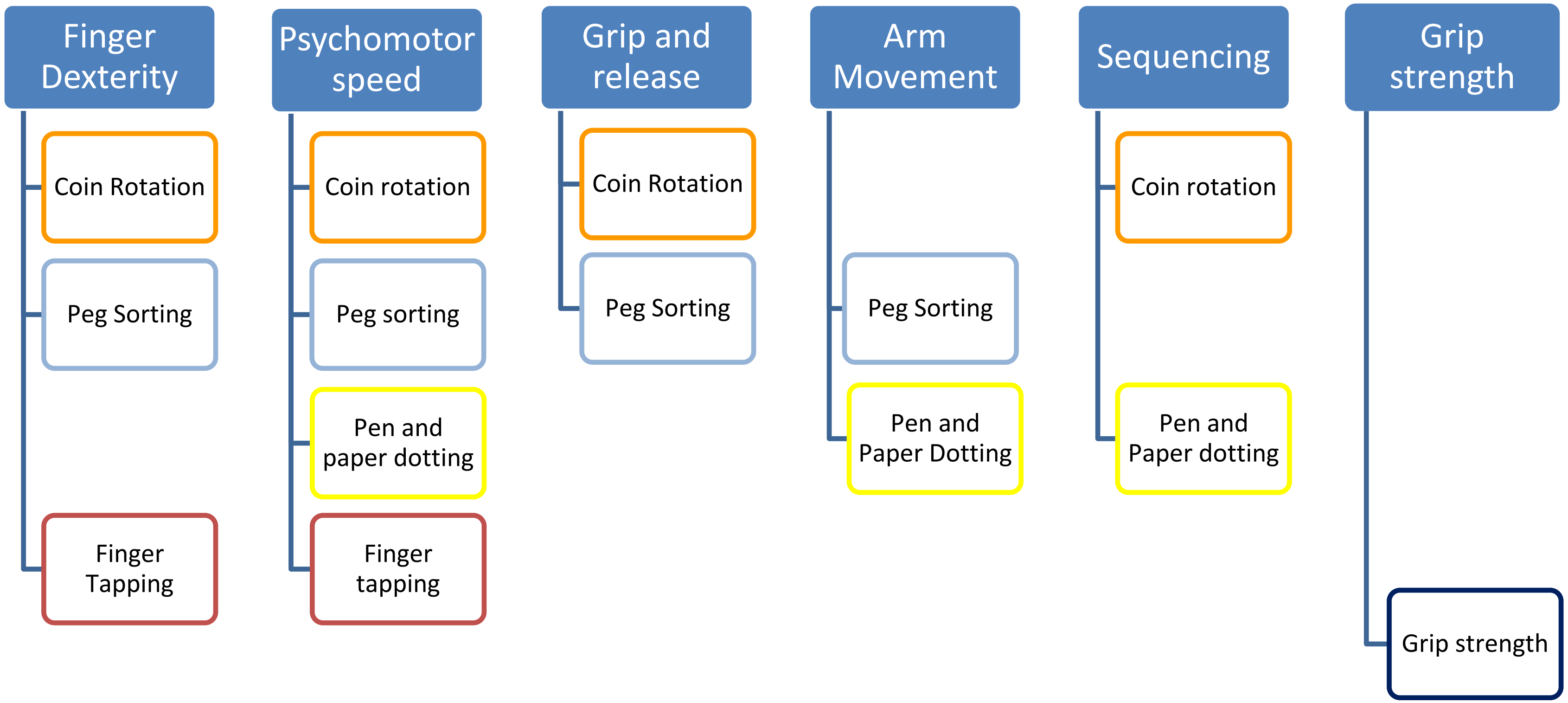


Figure 7.1 Schematic representing how each task corresponds to component processes of the Pegboard

7.1.3 Speech Laterality

Cerebral blood flow velocity (CBFV) was measured via functional transcranial Doppler (fTCD) sonography whilst participants completed a word generation task. This task involves the silent production of words corresponding to a stimulus letter displayed on a computer screen. The paradigm has been described in detail elsewhere, but briefly, participants receive a 5 s ‘clear mind’ message before a stimulus letter is displayed on the screen. At this point participants are asked to begin word generation silently inside their heads until they see the next instruction to repeat the words they were just thinking of out loud. This is followed by a 35 s rest phase. The task has been well used in language lateralisation studies (Knecht et al., 1998; Knecht et al 2000a) and is known to reliably elicit hemispheric activation. Measurements of middle cerebral artery blood flow velocity during the periods of silent word generation are compared with the rest phase of the trial. Participants performed 23 trials with a different letter presented each time.

7.2 Data Analysis

7.2.1 Motor Skill Tasks

Performance on 5 of the 6 motor tasks (Pegboard; Coin rotation; Dotting; Finger Tapping; Peg Sorting) was measured by the speed with which the tasks were completed. Mean movement times were calculated for preferred and non-preferred hand performance. For the sixth motor task, Grip Strength, performance was measured by the mean force squeezed in kilograms, for the preferred and non-preferred hands.

7.2.2 FTCD

Speech lateralisation indices were derived from measurements of cerebral blood flow velocity (CBFV) taken from bilateral insonation of the middle cerebral arteries whilst participants performed the word generation task. Recordings were made with a commercially available system (DWL Doppler-Box^{TM}X: manufacturer, DWL Compumedics Germany GmbH) via a 2-MHz transducer probe attached to an adjustable headset, positioned over each temporal acoustic window. PsychoPy Software (Pierce, 2007) controlled the word generation experiment and sent marker pulses to the Doppler system to denote the onset of a trial. Data were analysed off-line with a MATLAB (Mathworks Inc., Sherborn, MA, USA) based software package called dopOSCCI (see Badcock, Holt, Holden and Bishop, 2012 for a detailed description).

7.3 Results

7.3.1 Motor Skill Tasks

To assess the relative hand performance across each task non-parametric tests were deployed due to non-normally distributed data. Wilcoxon signed rank tests were performed to examine differences between the preferred and non-preferred hand performance across each of the 6 tasks. Four of the tasks revealed significant differences between preferred and non-preferred hand skill; the Pegboard task showed a significant increase in movement time between the preferred hand (median = 23.1 s) and the non-preferred hand (median = 23.9 s; $Z = -2.55$, $p < .02$, $r = -.29$). The coin rotation task similarly showed better performance with the preferred hand (median = 15.2 s) than the non-preferred hand (median = 17.9 s; $Z = -5.12$, $p < .001$, $r = -.57$), as did the Dotting task, where the preferred hand (median = 22.26 s) significantly outperformed the non-preferred hand (median = 26.02; Z = -5.44, $p < .001$, r = -.61). The fourth task to display significant performance differences was the grip strength measurement, where the preferred hand (Median = 26 kg) produced a greater force than the non-preferred hand (Median = 24.8 kg; z = -2.64, $p < .01$, r = -.29). There were no significant differences between the hands on the sorting task (PH Median = 35.3 s; NPH Median = 35.8 s; Z = -.66, p = .51) or the finger tapping task (PH Median = 1.78 s; NPH Median = 1.77 s; Z = -.96, p = .34).

7.3.2 Speech Laterality

Speech Lateralisation indices were obtained for 34 of the 40 participants. Six cases were unusable due to excess variability in the individual epoch recordings such that they had less than 50% acceptable trials recorded. LI values ranged from 5.49 to -2.70, mean = 2.51, SD = 1.8, with 4 cases classed as atypically lateralised (i.e. had right hemisphere or bilateral language distribution).

7.3.3 Motor and Speech Correlations

Due to a slight skew in the data Spearman correlations were conducted on the performance scores for the left and right hands from each of the 6 handedness tasks, and on the speech lateralisation indices. Results showed that there was good correlation across a number of measures, indicating that preferred (PH) and non-preferred hand (NPH) performance remained constant across all tasks. Correlations of handedness tasks and speech scores indicated that only two of the handedness tasks significantly correlated with speech LI scores; the pegboard (PH: $r_s(34) = -.35$, $p < 0.05$; NPH: $r_s(34) = -.43$, $p < 0.03$) and the coin rotation task (PH: $r_s(34) = -.49$, $p < 0.01$; NPH: $r_s(34) = -.42$, $p < 0.03$). Table 7.1 displays the correlation matrix.

Table 7.1 Spearman's Rho values for the 6 hand skill tasks and the Speech LI scores. * indicates p < 0.05; ** indicates p < 0.01

			Preferred Hand (Mean LIs)						**Non-Preferred Hand (Mean LIs)**				
		LI score	Pegboard	Dotting	Peg Sorting	Coin Rotation	Grip	Finger Tapping	Pegboard	Dotting	Peg Sorting	Coin Rotation	Grip
Preferred Hand (Mean LIs)	Pegboard	-.35*											
	Dotting	-.13	.44**										
	Peg Sorting	-.23	.35*	.51**									
	Coin Rotation	-.49**	.40*	.42**	.27								
	Grip	-.01	-.02	-.32*	-.13	-.10							
	Finger Tapping	-.13	.08	.56**	.25	.37*	-.38*						
Non-Preferred Hand (Mean LIs)	Pegboard	-.43*	.72**	.39*	.30	.50**	-.05	.24					
	Dotting	-.05	.30	.85**	.33*	.45**	-.29	.47**	.37*				
	Peg Sorting	-.32	.56**	.49**	.84**	.41**	-.02	.25	.52**	.33*			
	Coin Rotation	-.42*	.37*	.42**	.17	.85**	-.02	.30	.52**	.51**	.37**		
	Grip	.04	-.08	-.34*	-.15	-.17	.95**	-.37*	-.16	-.32	-.07	-.11	
	Finger Tapping	-.17	.13	.52**	.10	.42**	-.25	.91**	.21	.46**	.13	.34*	-.25

7.4 Experiment 2

7.4.1 Participants

A new group of participants were recruited for experiment 2. These were 22 adults aged 18-27 (5 males; mean age = 19.2; SD age = 1.92) recruited from the University of Lincoln. All gave informed consent prior to taking part and the study received approval from the School of Psychology Ethics Committee. All participants were Caucasian and had English as a primary language. None had history of any neurological or psychological disorders, nor were on medication known to affect the circulatory or central nervous systems. All had normal, or corrected to normal, vision and were right handed as measured by the handedness inventory.

7.4.2 Motor Skill Laterality Measurements

Two of the motor tasks from experiment 1 were selected to form the experimental conditions; the Pegboard and Coin Rotation. These tasks were chosen as they were the only ones to significantly correlate with speech lateralisation indices for both the right and the left hand in the previous study, indicating that they may best tap into the common processing mechanisms underlying speech and praxis. A third task from experiment 1, Finger tapping, was selected to serve as a control condition. A new paradigm was developed in order to measure the relative hemispheric activation during performance of these three motor tasks. Participants were seated at a computer screen with their hands placed on marked areas on the table in front of them. They were then instructed to keep absolutely still and not move their hands from the designated area until instructed to by the computer. A Psychopy software (Pierce, 2007) controlled computer program then ran the paradigm outlined in figure 7.2. This consisted of a 3 s pre-action ‘get ready’ phase, followed by a 12 s move phase, where the instruction of either ‘Left’ or ‘Right’ was given indicating the participants should start performing the task with the corresponding hand. These direction prompts were displayed in a randomly generated order, but always consisted of 15 ‘right’ trials and 15 ‘left’ trials, totalling 30 trials per task. This was followed by a final rest phase to allow the CBFV to return to baseline. The tasks were presented in block design, the order of which was counterbalanced between participants.

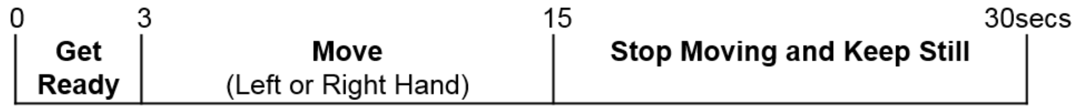


Figure 7.2 Schematic of the fTCD motor paradigm epoch timings

The task timings were controlled to correspond with the fTCD paradigm, which meant that participants performed the action for 12 seconds and then stopped. The Finger Tapping control condition was performed exactly as described in experiment 1 (see 7.2.2) using the index finger only. The Coin Rotation was set up so that the 2 pence coin was placed in between the marked areas where the hands were resting. At the instruction of either ‘Left’ or ‘Right’ the participant was required to pick up the coin with the corresponding hand, and rotate it as many times as possible within the 12 s window. The Pegboard task was the most adapted from the original version described in Experiment 1. In this paradigm only half the pegs on the board were used (10 in total) and the board was positioned ipsilateral to the moving hand on each trial. This was done to ensure that the board did not cross the participants’ midline, to minimise movement of the upper arm as this could confuse the laterality measurement (the board was repositioned on each trial by the experimenter via sliding it between the pre-designated placement areas).

7.4.3 Motor fTCD Data Analysis

Motor lateralisation indices were derived from measurements of cerebral blood flow velocity (CBFV) taken from bilateral insonation of the middle cerebral arteries whilst participants performed the three motor tasks described in 7.5.2. Recordings were made with a commercially available system (DWL Doppler-Box^{TM}X: manufacturer, DWL Compumedics Germany GmbH) via a 2-MHz transducer probe attached to an adjustable headset, positioned over each temporal acoustic window. PsychoPy Software (Pierce, 2007) controlled the experiment and sent marker pulses to the Doppler system to denote the onset of a trial. Data were analysed off-line with a MATLAB (Mathworks Inc., Sherborn, MA, USA) based software package called dopOSCCI (see Badcock, Holt, Holden and Bishop, 2012 for a detailed description). A set of 6 laterality indices (LI) was derived for each participant corresponding to left and right hand movement across each of the three tasks. These indices were calculated by extracting information from the Psychopy program to denote which of the 30 epochs were the 'left' and which were the 'right' trials, which were subsequently matched up to the LI values produced from the analysis. As with the speech paradigms, the LI values were calculated from the difference between left and right hemisphere activity within a 2 sec window, when compared to a baseline rest period of 10 s. The activation window was centralised to the time point at which the left-right deviation was greatest within the period of interest (POI). In the present paradigm the POI was taken from the 'move' phase of the paradigm and ranged from 5 – 15 s following onset of the trial. The baseline period was taken from the 'rest' phase.

Motor laterality was assumed to be clear in all cases in which the LI deviated by > 2 SE from 0 (Knecht et al., 2001). Left-hemisphere or right-hemisphere motor dominance was indicated by positive or negative indices respectively. Cases with an LI < 2 SE from 0 were categorised as having bilateral motor representation. Participants required a minimum of 15 acceptable trials (i.e. 50%) to be included in the analysis; all participants well exceeded this threshold.

7.4.4 Speech Laterality

Speech lateralisation indices were obtained for each participants following completion of the motor paradigm. This was to ensure that these participants were ‘typical’ in terms of their cerebral dominance for speech. Participants performed the word generation paradigm, the overview of and outline of the fTCD analysis procedure for this task was identical to that described in Experiment 1 – see section 7.2.3

7.5 Results

7.5.1 Lateralisation of Motor Skill Tasks

One participant was excluded from the analysis as their LI scores did not meet the quality thresholds required during pre-processing analysis and too many trials were unusable. For the rest of the participant’s data, paired samples t-tests were conducted to compare mean LI scores derived from activation during movement of each of the hands on each separate task. During the control finger tapping task there was a significant difference (t(21)= -7.063, p < .001, r = .68) in the LI scores produced by the right hand (M = 1.66; SD = 1.78) and by the left hand (M = -1.53; SD = 1.62), with each hand showing clear contralateral hemispheric activation. For the two experimental conditions there were also significant differences between the lateralisation indices produced by the right and left hands. The coin rotation task elicited contralateral activation patterns in the LI scores produced by the right hand (M = .813; SD = 2.15) and by the left hand (M = -

.321; SD = 2.34; t(21)= -2.093, p < .05, r = 2.45), although it should be observed this effect is weaker for the right hand, which is showing bi-lateral activation with a left hemisphere bias. Finally during the peg board task there was again a significant difference in the LI scores produced by the right hand (M = 3.17; SD = 2.77) and by the left hand (M = .453; SD = 2.66; t(20)= -3.93, p < .001, r = .44), however, during this task it was predominantly the left hemisphere which was controlling the action, indicating contralateral activation during right hand movement but ipsilateral activation during left hand movement.

Given that this is a new paradigm and therefore the reliability of the activation paradigm has not been previously assessed, the split half reliabilities of the odd and even epoch LI values were calculated for the left and right hand trials, across each of the three tasks. Pearson correlations indicated high internal reliability in all of these calculations see Table 7.2.

Table 7.2 Table of Pearson correlations calculating split half reliabilities of odd and even epochs, across each task and for both hands. * denotes significant correlation

	Left Hand		**Right Hand**	
	r	*p*	*r*	*p*
Pegboard	.54	.02*	.55	.019*
Coin Rotation	.77	.001*	.55	.021*
Finger Tapping	.47	.05*	.51	.03*

To assess the interaction between task type and hand used a repeated measures ANOVA was conducted using the variables ‘Hand’ (2 levels; left and right) and ‘Task’ (3 levels; coin rotation, Finger tapping and Pegboard). No outliers were identified, and the data met Mauchly’s test of sphericity, so significance values were taken from sphericity assumed categories. Results showed that there was a significant main effect of hand used, ($F(1,19) = 24.092$ $p < .001$) indicating that each hand produced a different mean profile of lateralisation, with the right hand producing a left hemispheric activation pattern (mean LI = 2.317; SE = .416) and the left hand a bilateral activation pattern with a right sided bias (mean LI = -.398; SE = .438; See Figure 7.3).

There was a significant main effect of task, ($F(2,38) = 8.804$ $p < .001$) demonstrating a difference between the hemispheric lateralisation indices depending on the task that was being performed; Coin rotation mean LI = .378 (SE = .495); Finger tapping mean LI = .144 (SE= .357) and Pegboard mean LI = 2.356 (SE = .53; See Figure 7.3). Finally, there was a significant interaction between hand used and task performed $F(2,38) = 6.785$ $p < .005$. This effect shows that the laterality indices produced by the left and right hand were significantly different across the tasks performed (see Figure 7.4).

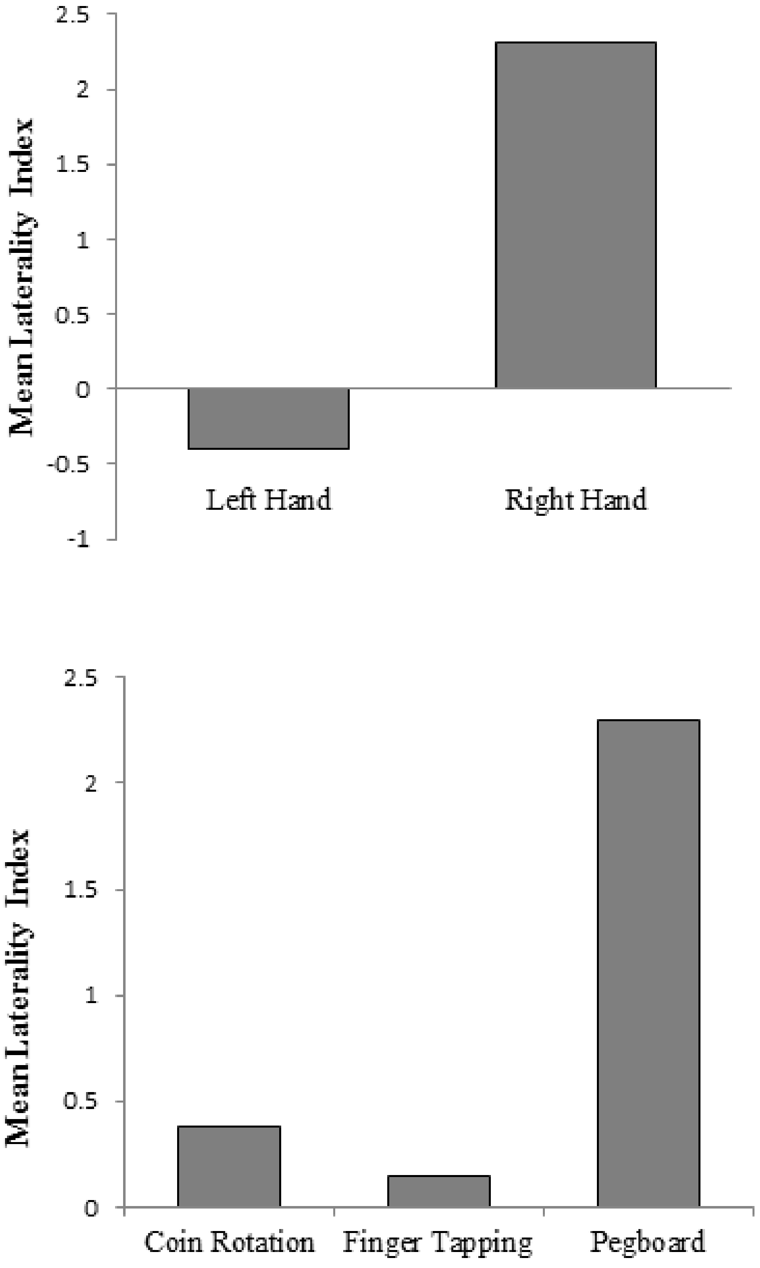


Figure 7.3 Bar charts showing the main effects of Hand (upper chart) and Task (lower chart). On both charts the 'y' axis denotes LI values, whereby –ve values are right hemisphere activation and +ve values are left hemisphere activation.

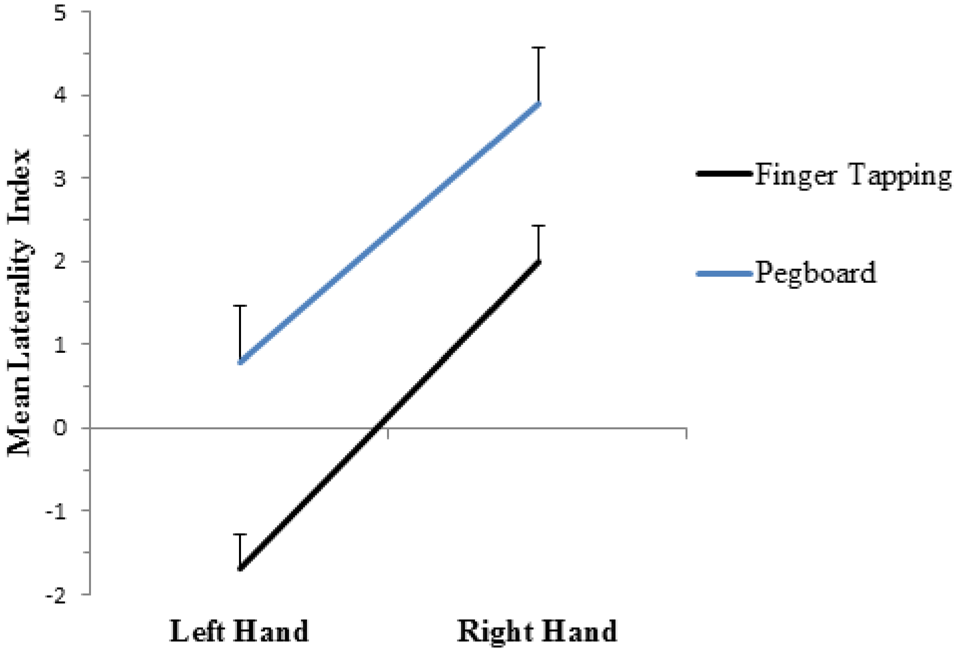


Figure 7.4 Plot showing mean LI indices during activation of Left and Right Hands during pegboard and finger tapping tasks

7.6 Discussion

Theories suggesting a common processing mechanism between praxis and speech are supported by evidence that shared neural architecture underlies both functions (e.g. Binkofski and Buccino, 2004). This set of experiments investigated a particular hypothesis for explaining the relationship between motor praxis and speech, namely that they are both reliant on complex sequential processing controlled by the left hemisphere (e.g. Grimme et al, 2011; Flowers and Hudson, 2013). In Experiment 1 performance on the pegboard task and five additional motor skill tasks sharing common processing requirements, were compared to speech lateralisation indices derived from a word generation task during fTCD sonography. Results indicated that only 2 of the 6 motor tasks correlated significantly with speech LI scores; the pegboard and the coin rotation task. These tasks were then used in Experiment 2 with an fTCD motor paradigm to derive lateralisation indices during movement of the left and right hands. This second experiment demonstrated that the right hand activated the contralateral (left) hemisphere for each of the tasks, whereas the left hand activated the ipsilateral (left) hemisphere during the pegboard task and produced bilateral activation during the coin rotation task. This was compared to a control condition task of finger tapping, with a single digit (index finger), during which both hands activated the contralateral hemisphere.

These results provide evidence supporting the hypothesis that motor sequencing tasks are most similar to speech production and that they are represented more strongly in the left hemisphere during activity of either hand. This is in contrast to tasks not reliant on sequencing, such as the control task, which elicited equal strength contralateral activation, and did not show a hemispheric preference. These findings are line with existing evidence on fine motor control of the left and right hands, which demonstrates predominant left hemisphere activation during such tasks (Verstynen et al, 2005; Serrien et al, 2006). The findings, however, extend previous work by indicating an integration of motor control with speech production pathways, supporting the assumption that they rely on the same left hemisphere networks.

Each of the tasks designed for Experiment 1 were accurate in distinguishing the dominant hand, although in two of the tasks this difference was not significant (Sorting Task and Finger Tapping). This gives validity to the tasks chosen as effective skill-based motor activities for measuring hand performance. If hand performance had differed in direction, rather than just degree, across each of these tasks then it would be concerning for the subsequent comparisons with speech indices in terms of making assumptions about the hemispheric control of each task. There were, however, some unexpected findings from the correlations between speech and motor performance across the 6 tasks. The first observation of interest was that the pen and paper version of the pegboard; the

Dotting task, did not significantly link with speech laterality. This is surprising because the only component it did not share with the pegboard was the grip and release mechanism of picking up the pegs (participants kept a constant hold of the pen during this task). Therefore this is an indicator that the sequential movement and manipulation of the fingers in the pegboard task may be a key factor regarding its common processing with speech. Support for this is provided by data from fMRI of finger movement tasks which show increased left hemisphere activation during sequential and non-sequential finger movements (Hayashi, et al., 2008).

The second observation from comparisons of each of these tasks comes from the fact that the sorting task also did not correlate well with speech scores, or indeed with many of the other motor tasks. This is likely due to the parameters of the task, as observations of participant behaviour during task execution suggested that it was more cognitively demanding than the other, more purely motor, comparators. For example, often participants hovered over a pot whilst deciding whether it would constitute an illegal move on that trial, before then making the peg placement. Thus it is clear that the task involved greater a working memory component than the other tasks, as well as a greater requirement for effective response inhibition. Such mechanisms are known to be controlled predominantly by the right hemisphere (Aron, Robbins and Poldrack, 2014), and so it is likely that a reduced left hemisphere network would be involved, even in right hand movement, thus reducing its relationship with speech indices. This, however, means it was a successful choice as a task in terms of one which eliminated motor sequencing, however, it was perhaps not as comparable with the other handedness tasks in terms of measuring a component of motor skill (as it seemed to rely on more cognitive motor planning mechanisms).

Experiment 2 demonstrated that the patterns of hemispheric activity resulting from motor skill tasks varied depending on how speech-related the tasks were. Two tasks were tested based on indications from Experiment 1 that they correlated best with speech laterality, the pegboard and the coin rotation task, along with a third task, finger tapping, which showed very poor correlation with speech scores, and so was used as a control condition. Results confirmed the hypothesis that greater left hemisphere activation would be seen in the experimental tasks regardless of the hand that is moving, although this was more pronounced for the Pegboard task than the coin rotation task. This is a novel finding as it demonstrates the left hemisphere bias for motor sequencing tasks in real time, and is an indicator as to why links between speech laterality and pegboard performance have been found in chapters 4-6. Furthermore the reliability of the fTCD data has been shown to be high in this new paradigm, thus these results can confidently assert that the activation profile seen is representative of motor networks. Figure 7.5 is a schematic representation of the results presented in Experiment 2. It indicates that in the control condition, finger tapping, predominantly contralateral activation was displayed, evidenced by the strong connections between each opposing hemisphere and hand. Weak ipsilateral networks are represented in order to account for the fact that some epochs present this type of activation (i.e. the LI is a mean score), which suggests that both hemispheres are working to greater or lesser degrees in support of task execution. This is the case across each task shown in Figure 7.5. The Coin rotation task is represented by less strong

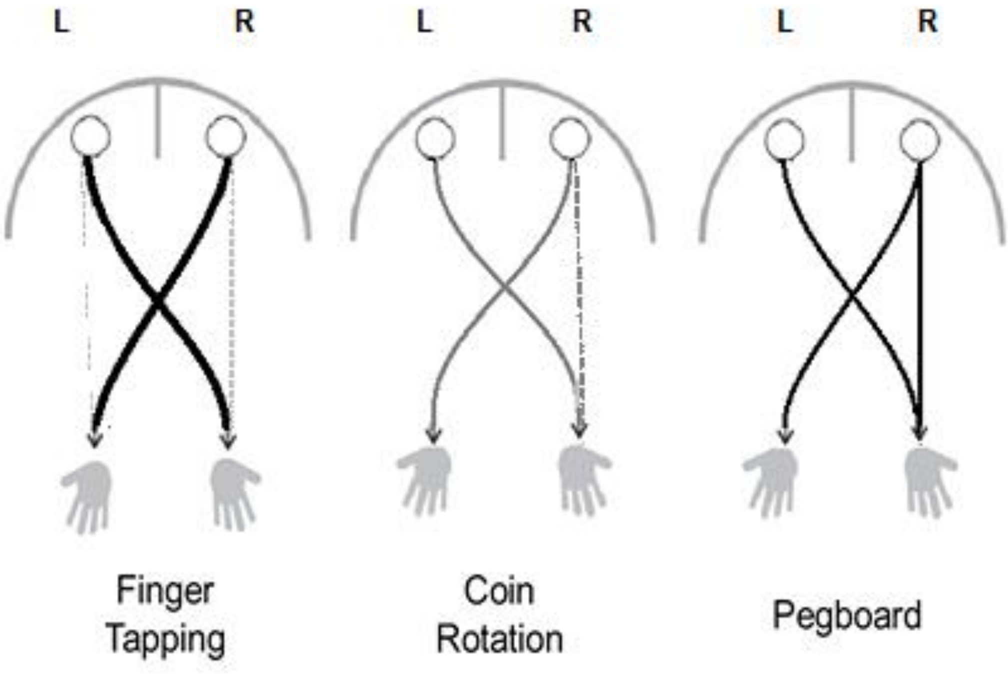


Figure 7.5 Schematic representing the activation patterns derived from the fTCD motor paradigm. Shading of the line relates to strength of activation. Dotted line indicates weak, but discernible activation.

contralateral activation and an increased role for the left hemisphere ipsilateral network, to reflect the mean LI scores being close to zero. Finally the pegboard task is represented by increased contralateral activation compared to the coin rotation task, but is also supported by much more activation in the left hemisphere ipsilateral network. This representation is supported by evidence indicating ipsilateral control exhibits a functional asymmetry between hemispheres whereby activation in left motor cortex during left-handed movements is stronger than activation in right motor cortex during right-handed movements (van den Berg, Swinnen and Wenderoth, 2011; Hayashi et al., 2008; Kobayashi, Hutchinson, Schlaug and Pascual-Leone, 2003).

Whilst Figure 7.5 is a plausible representation of the data, and indeed supports the hypothesis that left hemisphere specialisation has developed to control functions which rely on sequential motor ordering (Verstynen et al, 2005), it is important to consider the possible explanations for the pattern of results shown in this data, outside of the suggestion that the significant differences in speech-related motor tasks are due to shared neural processing. One of the factors inherent in the pegboard task is the reliance on visual processing in order to successfully complete the task. This differs from the requirements of the coin rotation and the finger tapping, where visual feedback does not inform the continuation of the motor action in the same way. For example, participants often reported it was easier to complete the finger tapping and the coin rotation by fixating the gaze at a point away from their hands. Due to the size of the pegs and holes of the pegboard task, it would not be possible to complete it accurately without the integration of visual information. Visual feedback has been shown to be integral to successful execution of handedness tasks (Smith, McCrary and Smith, 1960; Miall, Weir and Stein, 1985), and the disruption of accurate visual feedback during the grooved pegboard task has been show to neural processing speed and considerably impair performance (Fujisaki, 2012). Lateralisation of visuospatial control has reliably been shown to produce a right hemisphere bias (e.g. Whitehouse and Bishop, 2008; Flöel et al, 2001), which would not account for the predominant left hemisphere activation pattern seen in the pegboard task, which is more visually dependent than others in this study. However, evidence from grasping studies altering the visual properties of the target reveal that visuomotor mechanisms encapsulated in the left hemisphere play a crucial role in the visual control of action (Gonzalez, Ganel and Goodale, 2006), thus supporting the notion that the pegboard is more heavily dependent on sensory processing streams which also make use of specialised left hemispheric networks.

A final aspect for consideration is the lateral arm movement required in the pegboard task relative to the two other conditions. Although this was minimised in Experiment 2 by reducing the length of the board from 20 down to 10 pegs, and by positing the board on the ipsilateral side of space, there still involved some arm and shoulder movement relative to coin rotation and finger tapping. Evidence from studies of cerebral lateralisation of arm movement control suggest that each hemisphere activates a specialised system of control, resulting bi-lateral activation is at different stages of the movements (Mutha, Haaland and Sainburg, 2013). If this is the case, then it seems unlikely that excess arm movement will have impacted significantly on the pegboard task, as predominant left hemisphere activation, rather than bilateral, was found.

Chapter 8

Disrupting the speech motor mechanism: a Dual Task study

This thesis examines the sequential properties of speech production and motor skill, and has hypothesised that the two functions make use of common neural networks for this aspect of their execution. The results presented so far have demonstrated that pegboard performance is an indicator of atypical speech representation and that by focussing on the aspect of sequencing inherent to that task it may also be possible to infer what is happening in the left hemisphere during speech. This exploration of how these two modalities are linked in terms of their neurological underpinnings has indicated that there is functional overlap in the left hemisphere, and that this occurs both developmentally (Chapter 5) and in adulthood (Chapter 4 and 7). However, the results of this thesis so far have not been able to distinguish the exact roles of speech and motor processes in the generation of the left hemispheric activation patterns displayed.

It has been suggested that motor action forms the neurological basis of language and speech, evidenced by overlapping activation in cortical areas responsible for both processes (e.g. Binkofski and Buccino, 2004; Sahin et al , 2009). Furthermore theories suggesting a gestural origin to spoken communication (e.g. Corballis, 2003) propose that speech production skills may have developed by making use of existing, more ‘hard wired’, motor networks and pathways. One perspective in support of this theory suggests that the brain is inherently a motor system and that other only functions exist through the integration of particular aspects of this motor network (e.g. Wolpert, 2011). One way of examining this perspective in the context of commonalities in speech production and motor skill is to assess whether one function is more susceptible to disruption than the other. Such a finding would indicate that both functions are making use of similar neural networks, which, once overloaded may disrupt the less salient function first. This chapter presents a study investigating what happens to the processing of speech and motor skill when individuals are asked to perform two tasks simultaneously. The study hypothesises that motor and speech tasks linked by a common reliance on sequencing will be more likely to be disrupted during increased processing demands than tasks which are similar in properties but do not make use of information ordering and sequencing to the same extent.

When executing a cognitive task under challenging circumstances, success of performance particularly depends on the task-related circuits that enhance their processing capacities (Serrien, 2009). Performing two tasks concurrently will often result in overloading of the neural network designed to divide resources between competing priorities, such that capacity to perform concurrent tasks effectively then breaks down (Hellige, 1993). A successful technique to investigate this notion is the dual task paradigm. This approach is well used in cognitive psychology and has often been deployed to explore cerebral lateralisation of speech production and manual dominance (Medland, Geffen and McFarland, 2002). The paradigm requires participants to perform a pair of tasks, firstly doing each of them on its own, which forms the single task condition, and then performing both tasks simultaneously, which forms the dual-task condition. Theories propose that due to the increased cognitive load created by the requirement to attend to two tasks at the same time, performance on these tasks decreases, resulting in a so-called dual task effect, or performance decrement (McDowell, Whyte and D’Esposito, 1997). Studies exploring speech and manual dominance using this approach have revealed differences in processing capacity between the left and right hemispheres (Geffen, 1978; Pujol, et al., 1999) as well as evidence that preferred hand performance is more impaired under dual-task conditions than the non-preferred hand (Hiscock, et al., 1989).

However, previous studies examining the neural organisation of speech and motor control using a dual-task approach have either used tasks that are unrelated to each other, such as finger tapping and digit counting (e.g. Serrien, 2009), or they have been confounded by the analysis solely focussing on performance decrement in the task of interest, rather than examining the effects of dual tasking on both functions used (Medland et al, 2002). Therefore the present study aims to extend previous research in three ways, firstly, by comparing performance on behavioural dual task paradigm with direct measurements of cerebral dominance for speech production, obtained via fTCD. This is necessary to be able to make accurate predictions about how the dominant hemisphere is operating during dual-task conditions, rather than just relying on handedness to determine cerebral lateralisation.

Secondly, accurate assessments of dual-task interference will be made across both motor and speech performance to assess whether compensatory strategies vary between participants or whether there is a consistent breakdown of performance on one task. This study hypothesises that the latter will be the case, and that speech production will be more impaired. The third and final way in which this study extends previous work using dual-task paradigms to explore cerebral lateralisation is by deploying a design which contains both an experimental set of motor and speech tasks and a control set of similar tasks. This will enable distinctions to be made between the common neural architecture supporting the functions themselves (e.g. speech production and motor skill) versus the common networks supporting tasks specifically related by their sequential information processing requirements relying predominantly on left hemisphere networks. The experimental set of tasks used in this study were devised to reflect the common processing thought to be dependent on the left hemisphere, and these were then compared to dual task interference on a control set of tasks devised to match the experimental tasks for processing and execution requirements, but to be distinct in terms of their inherent properties and likely hemispheric processing (e.g. Lust et al, 2011; Andres, Seron and Olivier, 2007). The control condition was included to see if it were speech and motor interactions per se that caused an increased dual task effect, or whether, as hypothesised here, that only those with inherently similar properties of sequencing would be most impaired.

8.1 Method and Materials

8.1.1 Participants

Nineteen adults (7 males; mean age = 20.7 yrs; SD age = 4.6yrs) were recruited from the University of Lincoln. Participants gave informed consent prior to taking part in the study. All participants had normal, or corrected to normal, vision and none had history of neurological disorders or trauma, or any condition known to affect the circulatory or central nervous systems. All participants were Caucasian and had English as their first language. They received research credits in return for their participation. The study received ethical approval by the School of Psychology Research Ethics Committee, University of Lincoln.

8.1.2 Procedure

Handedness: Hand preference was assessed via the questionnaire described previously (see section 3.3.3). Measurement of hand preference by this means was necessary in order to make judgements about which hand should lead in the behavioural paradigm. Despite previous chapters preferring quantification of handedness in terms of relative motor skill (as measured by the pegboard task see section 3.3.2), it was a deliberate choice in this study not to use the pegboard task, to ensure that participants were not practised at the task prior to the Dual-task paradigm, which used the pegboard as one component.

Speech Lateralisation: In order to measure precisely the direction of hemispheric speech dominance to then make assessments of whether speech laterality had any impact on the dual task scores, participants performed the word generation task whilst undergoing fTCD imaging. This procedure was exactly the same as that described in previous chapters (see section 4.1.3). Importantly, in this study speech laterality was measured after all of the behavioural dual-task paradigm presentations, to ensure that speech lateralisation direction was not known beforehand to minimise possibly of experimenter bias in the behavioural paradigm.

Dual Task Paradigm: using a repeated measures design all participants completed 4 tasks, two speech tasks and two motor tasks. These were each undertaken separately to form the single task phase. These 4 tasks were then paired into an experimental set and a control set of tasks whereby participants then completed each set simultaneously, forming a dual-task phase. See Table 8.1 for the composition of the groups. Each task was performed continuously for two minutes and was scored based on the number of correct responses or movements made, with greater scores denoting better task performance. This deviates from the previous chapters in which better performance was associated with smaller scores (i.e. reduced movement times), but this change was made to ensure that calculation of dual task performance decrements in this study were consistent across all tasks. Following previous research suggesting practice effects could hamper the results in dual task conditions (Plummer and Eskes, 2015), single and dual task presentation was counterbalanced between participants, so some participants encountered the dual task conditions first and others did the single tasks first. The motor tasks were performed with the preferred and non-preferred hands. The specific requirements of each of the tasks are as follows:

Pegboard: Participants had to move as many pegs as possible within 2 minutes. They did each hand separately, starting with 2 minutes for the preferred hand followed by another 2 minutes for the non-preferred hand. The pegs started at the near side of the board, and participants were required to place them, in sequence, across to the opposite side. When the line of 20 pegs was finished participants were required to keep going by moving the pegs immediately back to the opposite set of holes again to ensure an unbroken pattern of movement. This continued until the time was up.

*Word Generation***:** This is an adaption of the verbal fluency paradigm used elsewhere in this thesis. Participants were required to generate words beginning with a given stimulus letter. Participants had two minutes to produce as many words as possible following verbal presentation of the stimulus letter by the experimenter. A new letter was presented every 15 seconds, giving a total of 8 letters for each participants. Letters were generated at random by a Psychopy script (Pierce, 2007) visible only to the experimenter. Responses were recorded and a mean word generation rate was calculated from across the 8 trials.

Box crossing: This is a pen and paper task developed by Della Sala, Baddeley, Papagno and Spinnler (1995; see also Baddeley, 1996) and requires participants to put an ‘X’ in a series of boxes joined together in a set path (see appendix 4 for a copy of the task). They did this for each hand separately, first with the preferred hand for 2 minutes and followed by the non-preferred hand for 2 minutes.

Digit Recall: Participants were required to repeat aloud a string of digits read to them by the experimenter. They had to repeat the string as fast and as accurately as possible and had to get through as many strings as possible within the 2 minute time frame. To ensure each individual was presented with digit strings within their working memory capacity, each person's optimal digit string length was calculated by a predetermined task during which strings of digits increasing in length are presented until they are no longer being accurately recalled. The optimum length is then the length used in the experiment. Scores are converted to proportions to reflect the differing number of presented strings versus correct answers between participants (this is required as those with a longer string capacity will take more time during string presentation and recall compared with shorter strings, which thus takes up more of the restricted 2 minute window).

Table 8.1. Overview of the tasks performed at each phase (single/dual) and in each condition (experimental/control) of the study

	Single Task		**Dual Task**
Experimental Condition	Pegboard	Word Generation	Pegboard & Word Generation
Control Condition	Box Crossing	Digit Recall	Box Crossing & Digit Recall

8.1.3 Data Analysis

Handedness: a laterality quotient was created from the responses to the handedness questionnaire described in section 3.3.3. This quotient was created using the following formula, where positive numbers indicate right handedness and negative numbers left handedness:

$$\text{Handedness Quotient} = (PH - NPH) / (PH + NPH) * 100$$

Speech Laterality: the process for analysis of speech lateralisation scores from the word generation task was identical to that described in the previous chapters (see sections 3.1.3; 4.1.3 and 4.1.4), whereby dopOSSCI software (Badcock et al, 2012) was used down sample and normalise the raw fTCD data in order to produce a lateralisation index (LI) for each participant denoting the direction of hemispheric dominance during speech production. Left-hemisphere or right-hemisphere speech dominance was indicated by positive or negative indices respectively. Speech laterality was assumed to be typical in all cases in which the LI deviated by > 2 SE from 0 (Knecht et al., 2001) and displayed left hemisphere activation. Participants displaying right hemisphere dominance or with an LI < 2 SE from 0 were categorised as having low lateralisation or bilateral speech representation and thus classified as atypical.

Dual-Task Paradigm: Initially differences in raw performance scores were assessed using paired samples t-tests to examine the prediction that dual task performance was significantly different from single task performance. This was done for each condition, and for each modality. Following this, the main analysis of the dual-task paradigm centred on the extent of the dual-task interference across conditions. In order to standardise the measurement of this interference due to the differing modalities tested and the varying scoring patterns across each of the tasks, a Dual Task Decrement (DTD) quotient score was produced for each set of tasks using the following formula:

DTD Quotient = [(dual task score – single task score) / Single task score] * 100

This DTD quotient was then used in a repeated measures ANOVA to determine extent and direction of dual task effects across the modalities of speech production and motor action.

8.2 Results

8.2.1. Handedness and Speech Lateralisation

All participants had acceptable fTCD recordings and so all were included in the analysis. The word generation task produced the expected left hemisphere dominant LI value across the sample as a whole; LI mean = 1.73, SD = 2.3. The range of mean LI scores was -4.43 to 6.04, and there were 3 individuals who were right hemisphere lateralised (mean LI scores of -4.43, -1.73 and -1.21 respectively) and 1 classed as bilateral (mean LI = .95).

Hand preference quotient scores ranged between -100 and +100, with 14 participants classified as right handed (mean = 85.03, SE = 5.4) and 5 as left handed (mean = -66.6, SE = 15.2). Six of the right handed participants had quotient scores of 100%, whereas only 1 of the left handed individuals had an equivalent score for left handedness (i.e. -100%).

8.2.2 Dual Task Paradigm

Performance in the dual-task phase was lower relative to the single task phase for each of the conditions and tasks. This difference was significant in 4 out of the 8 condition/task combinations, indicating that word generation was the task which displayed the greatest performance disruption under dual task conditions. Mean raw performance scores for the whole group across each of tasks and conditions are displayed in table 8.2.

Table 8.2. Means (Standard deviations), t-statistics, significance level and Pearson correlation values of raw scores from each task across each condition. *denotes significant result.

	PH		**Statistics**			**NPH**		**Statistics**		
	Single	Dual	*t*	*p* =	*r*	Single	Dual	*t*	*p* =	*r*
Word Generation	5.2 (.99)	4.3 (.77)	5.5	.001*	.75	5.2 (.99)	4.4 (.68)	5.3	.001*	.83
Pegboard	103.7 (7.2)	95.5 (12.7)	3.3	.004*	.53	97.68 (8.4)	93.4 (12.5)	1.9	.062	-
Digit Recall	79.4 (14.07)	75.5 (11.8)	1.4	.17	-	79.4 (14.07)	74.6 (14.2)	1.3	.22	-
Box Crossing	179.7 (19.8)	161.7 (28.3)	3.2	.005*	.54	99.9 (20.8)	97.4 (17.4)	.76	.46	-

Following this analysis, the DTD scores were calculated for each task to determine the extent of the effect simultaneous task performance had on each of the modalities tests. A 2x2 repeated measures ANOVA was conducted on the dual task decrement quotient scores firstly for the experimental condition and separately for the control condition. Both analyses used Modality (either speech or motor) and Hand Used (either preferred or non-preferred) as the within subjects variables, and LI score and hand preference as covariates. In the experimental condition (word generation and pegboard tasks) a significant main effect of Modality was displayed in the DTD scores, whereby the word generation task suffered a greater performance impairment than did the pegboard task (F (1, 18) = 4.21, p < .05; word generation mean DTD score = -12.96; SE = 1.9; Pegboard mean DTD score = -6.27; SE = 2.3). There was also a main effect of Hand Used, indicating that dual task performance was significantly more impaired when the preferred hand was doing the pegboard task than for the non-preferred hand (F (1, 18) = 5.72, p < .05; PH mean DTD score = -11.72; SE = 1.82; NPH mean DTD score = -7.5; SE =1.38). There were no significant interactions with speech lateralisation scores or hand preference in this experimental condition, removing the likelihood of a decreasing scale of DTD across different speech lateralisation profiles (see figure 8.1).

For the control condition (Digit recall and box crossing tasks) the same analysis was repeated and results showed that there was were no significant main effects of Modality or Hand Used, and neither were there any significant interactions between the DTD scores and direction of speech lateralisation or hand preference (see figure 8.1).

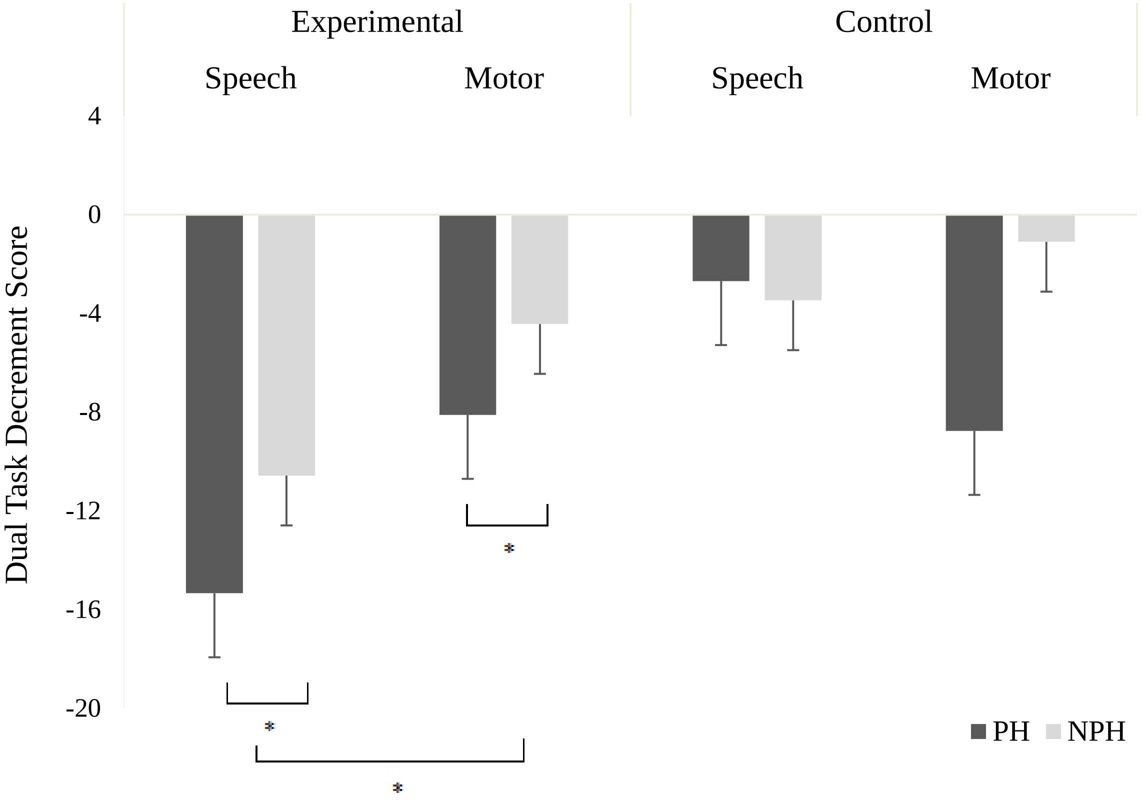


Figure 8.1 Bar chart showing mean dual task decrement scores for each modality (Speech or Motor) across each condition (Experimental or Control), sorted by hand used; PH = Preferred Hand; NPH = Non-preferred Hand. Lower scores denote greater dual task decrement. Significant main effects are highlighted; * = $p < 0.05$, Standard error bars are displayed.

8.3 Discussion

This study aimed to assess whether the neural links between motor and speech sequencing could be examined via a dual-task paradigm. Firstly it was hypothesised that speech production, as a comparatively ‘more recent’ neurological function (e.g. Corballis, 2003), would be more likely be impaired than motor skill under dual-task conditions involving tasks which were similar to each other in their properties and processing requirements, compared with tasks which were dissimilar. The results supported this hypothesis as speech production in the experimental condition, measured by the word generation task, was more impaired than speech production in the control condition. The study also hypothesised that performance on tasks reliant on sequencing, such as those in the experimental condition (pegboard and word generation), would be more significantly affected by dual task conditions compared to those in the control condition, which were not thought to rely on such similar processes (Andres et al, 2007). The results supported this hypothesis to a certain extent by demonstrating that motor performance was more impaired in the experimental condition across both the preferred and non-preferred hands, although this finding was offset by the non-preferred hand dual-task decrement score from the motor task in the control condition, which was significantly greater. Finally it was hypothesised that tasks within the experimental condition, which have both been shown to make use of similar processing requirements, would display greater dual-task impairments than tasks in the control condition. This finding was not displayed unequivocally, however, the experimental condition did show greater DTD scores than the control condition.

The results were not completely in line with the predicted outcomes, however. Firstly there was an unexpectedly large DTD score in the control motor task specifically for the non-preferred hand (the box crossing task), than in the experimental task. Given previous findings that preferred hand performance is usually more impaired under dual task conditions (Geffen, 1987), this was a surprising result. One possible explanation for the larger decrement in non-preferred hand performance compared to the preferred hand on this task, is likely due to the task being inherently reliant on writing skill. Performing box crossing with the non-preferred hand would represent a significant obstacle to successful completion, given that writing is a highly practised skill for the preferred hand (Perelle and Ehrman, 2005) and very rarely attempted by the non-preferred hand. However, the exact requirements of the task were to put an ‘X’ inside a small box (see appendix 4), and so this is not as technically difficult as writing letters or other complex shapes, which on balance may mitigate the practise bias of preferred hand over non-preferred hand writing ability. This does, however, raise questions regarding the selection of motor tasks for the control arm. The choice of task pairings was made difficult due to the range of features identified as having possible links to efficient pegboard performance in chapter 7. A balance had to be struck between selecting a task with enough similarity to the pegboard to ensure that the processing demands were equivalent, but also to avoid selecting a task which was too similar thus making the comparison ineffective. Box crossing was selected as it made similar demands on visual processing, arm movement and target matching, but did not require finger manipulation, grip variations or the same level of hand-eye coordination.

Another interesting omission in the data was that speech lateralisation scores did not significantly interact with the dual-task decrement scores. The hypothesis that word generation and pegboard performance would decrease under dual-task conditions reflected theories about the processing capacity of an integrated set of networks in the left hemisphere being over-stretched. It would therefore seem reasonable to expect that the extent of the interference experienced by tasks making use of this system would be linked to the direction of cerebral dominance for speech, primarily because both are purporting to be measuring the ‘same’ system, especially for those participants who are left hemisphere dominant for speech. It might be expected that the more left lateralised an individual is the greater dual task impairments they might suffer, but these results do not add any clarification on this point. A possible reason for the lack of effect here is small group size, as only a few participants had right hemisphere language. Therefore, this is a question for further research, perhaps to perform dual tasking across these functions whilst undergoing fTCD. Finally, whilst this data was in line with previous research showing that preferred hand performance is more greatly impaired than non-preferred hand (e.g. Medland et al, 2002), it didn't find the usual pattern of left handed participants being worse with their preferred hand than right handers with theirs, however, the fact that hand preference did not significantly interact in this analysis was likely due to the unequal group sizes resulting in only a few left handed participants.

Overall these results add to the set of studies presented in this thesis by providing further support for the notion that speech production and motor skill are linked by common neural processing, shown through the selective disruption to speech production under dual task conditions. This supports theories suggesting that left hemisphere control of speech and praxis is selectively dependent on the extent to which the functions make use of sequential ordering of information or component processes (Flowers and Hudson, 2013).

Chapter 9

General Discussion

The aim of this thesis was to examine the suggestion that handedness, as measured by motor skill, and speech production share common cortical processes and rely on common neural circuitry. This idea has been posited to explain the extensive links found between the two functions in terms of the lateralisation profiles that they display; a high degree of bias to the left hemisphere for language lateralisation, and the fact that the majority of individuals are right handed (Knecht et al, 2000a, b; Annett, 2002; McManus, 2002). Research to date exploring the links between these functions has provided a divergent picture, where results vary depending on measurement and classification approaches deployed (e.g. Groen et al, 2013). One perspective suggests that this relationship results from sequential processing, which is suggested to form the basis of common neural and cognitive networks underlying speech production and motor skill (Flowers and Hudson, 2013; Grimme et al., 2011) and is represented more extensively in the left hemisphere (Verstynen, et al, 2005).

The set of studies presented here had two main goals; 1) to investigate to the hypothesis that tasks making use of ‘sequencing’ are a useful indicator of links between speech lateralisation and handedness, and if so, in which populations? And, 2) to explain these links in terms of brain organisation, neurological function and developmental trajectory. The first set of studies explored the relationship between motor performance and speech lateralisation in different populations to assess how far this hypothesis extends. Following this, two further studies are presented which focussed on examining the component processes of the tasks used to elicit motor activation and present a novel paradigm using fTCD to measure hemispheric activation during different motor tasks, and a dual task paradigm to explore behavioural performance when the system supporting both functions is put under pressure due to competing task demands.

9.1 Summary of results

The first study was designed to extend work done with epilepsy patients by Flowers and Hudson (2013) to healthy adults. This study used a word generation task and a measure of motor skill, the electronic pegboard task, to assess patterns between performance on the handedness task and direction of hemispheric lateralisation for speech production. The findings, reported in chapter 4, show that handedness measured by skilled performance links to the direction of speech lateralisation and can significantly predict that direction. Specifically, individuals who show smaller performance differences between their hands are more likely to have atypical speech representation patterns. This provides clear evidence that the processes inherent to the pegboard task must be similar to those which are activated during speech production, such that performance on the former can predict the direction of the latter.

What is unclear from chapter 4 is at what point this relationship between hand skill and speech lateralisation develops. Previous literature has either focussed on patterns of cerebral lateralisation of language during development or on expression of hand dominance during development, but rarely are the two functions examined simultaneously in a developmental sample. Chapter 5 presents a study designed to use a cross-sectional approach to explore the relationship between motor skill and the development of speech lateralisation in children aged 3-10 years. Results demonstrated that mean speech lateralisation scores showed a significant leftward bias across all ages tested, giving indication that speech lateralisation is strongly represented in the left hemisphere at least by 3 years of age, in line with previous research (Bishop et al, 2014; Kohler et al, 2015). The data also revealed that hand preference was similarly well established by age 3, with all the children in this study showing a clear hand dominance effect on the 5-item preference score and the pegboard task. However, there was an age effect in the pegboard data, whereby younger children showed a greater performance difference between their hands compared with older children (see also Roy et al, 2003). Interestingly these results also showed that, in contrast to the adult data in chapter 4, children with a typical language lateralisation showed *larger* between hand differences in performance on the pegboard. These greater increases in performance differences between the hands was largely due to non-preferred hand skill, which improved to near adult like levels after about age 7 in this data.

Evidence from previous studies (Illingworth and Bishop, 2009; Whitehouse and Bishop, 2008) suggests that individuals with neurodevelopmental disorders affecting language and/or motor systems may show atypical hemispheric lateralisation patterns during speech production due to the common neural systems underpinning both functions. Therefore chapter 6 presented a study designed to assess hemispheric speech lateralisation patterns in patients with motor coordination impairments, but with no known speech or language deficits. This was the first study of its kind to employ fTCD to assess speech lateralisation in patients with DCD, and the results supported the hypothesis that a reduced leftwards asymmetry would be observed in the DCD group. This is an important novel study because firstly it suggests that the representation of atypical brain organisation is evident even in the absence of behavioural deficits in these individuals. And secondly it gives an indication about the point in development at which these deficits become apparent, i.e. for language laterality to be affected this must have occurred very early in the individuals development, as we know from data in chapter 5 that even 3 year old typically developing children show a left hemisphere dominance. The findings in chapter 6 are in line with previous suggestions that neurodevelopmental disorders reflect an immaturity of development, rather than a ‘damaged’ processing network (Hsu and Bishop, 2014).

The final two results chapters, 7 and 8, present investigations of the mechanisms underlying the relationship between pegboard performance and speech laterality indices. They were designed to examine which aspects of the pegboard are most crucial in causing the links with speech production scores seen in the previous chapters and to assess what happens to the functions when they are required to activate simultaneously under dual task conditions. Chapter 7 demonstrates that the pegboard and coin rotation task linked best with speech indices, and that when individuals perform these tasks under fTCD conditions, the left hemisphere is significantly more activated than the right hemisphere during motor action of either hand. This provides support for the notion that motor sequencing is a key component of the basis of speech production and hand skill, and that this is mediated by a left hemisphere specialised network. The dual task study equally provides support for this conclusion, due to the fact that during simultaneous speech and production and pegboard performance it was the language task which suffered a performance decrement, whilst pegboard times did not significantly reduce compared with single task conditions.

In summary the first three results chapters indicate that links between atypical speech representation and performance differences in skilled motor action are evident in healthy adults, typically developing children and individuals with DCD. They provide evidence that speech production and motor control are linked via a common developmental trajectory and to the extent that disruption of one function leads to atypical representation of the other function. The latter two results chapters provide evidence that sequencing seems to underlie relationship between speech lateralisation and handedness as they demonstrate that motor sequence tasks activate left hemisphere regardless of the hand moving, which is not the case with other motor tasks less reliant on sequencing. The mechanism underlying both functions supports theories describing a motor basis for speech production (e.g. Corballis, 2003), as language performance suffers greater decrement than motor performance in dual task conditions. The main novel findings are highlighted below:

Handedness:

- Preferred hand dominance was evident via the pegboard task across all ages tested, including patients with DCD.
- Younger children showed greater performance differences between their hands, with non-preferred hand being less skilled.
- Motor tasks with a higher degree of visuo-motor sequencing activated left hemisphere regions more strongly than right hemisphere regions, regardless of the hand moving.

Speech Lateralisation:

- Majority of healthy participants showed left hemisphere lateralisation for speech regardless of age
- Adults with DCD showed reduced left hemisphere lateralisation compared to controls

Interconnectedness of speech and handedness

- In adults with atypical speech representation between-hand performance differences are *smaller* than adults with left hemisphere lateralised speech
- In children with atypical speech lateralisation between-hand performance differences are *larger* than those with left hemisphere lateralised speech
- Adults with a motor coordination disorder perform worse overall on the pegboard task and display reduced left hemisphere speech lateralisation compared to controls
- Motor tasks involving visuo-motor sequencing correlate more strongly with speech laterality indices
- During dual task conditions speech production performance reduced more significantly than did motor performance

9.2 Pegboard Performance as an Indicator of Speech Lateralisation

Sequencing describes the ability to organise complex, but associated information in order to produce an accurate and meaningful response. Motor sequencing specifically relates to the planning and ordering of intended motor actions, and the process of altering intended action ‘online’ as required to execute the appropriate motor response (Serrien and Sovijarvi-Spape, 2015). Speech production shows similarities with this form of sequential processing, as language consists of complex sets of phonemes, syllables and words, alongside the necessary integration of syntactic and grammatical information required to communication coherently (Sahin et al. 2009). The working model of this thesis is that the left hemisphere is specialised for fine, complex motor control and specialised for language production, both of which contain elements of sequencing. It is suggested that this aspect drives the right hand/left hemisphere typical pattern of lateralisation seen at the population level (e.g. Knecht et al 2000a), and that the relationship between these two functions will be best examined when using tasks that tap into this component (Flowers and Hudson, 2013; Grimme et al, 2011). The data presented in this thesis supports this view point for a number of reasons. Firstly, links between speech laterality and performance on a motor sequencing task, the pegboard, were consistently found across different populations. This suggests that the reliance on sequencing by both of these functions is indicative of a fundamental principle of brain organisation, specifically in terms of the way information is being processed by each hemisphere (e.g. Ringo et al, 1994). Evidence from previous research supports this view by showing that hemispheric processing differs across information types, with complex and sequential stimuli producing increased left hemisphere activation (Grafton et al, 2002), and the integration of aiming and coordination of spatial information in guiding hand movements relying more on the right hemisphere (Goldenberg, 2013).

The developmental trajectory of motor and speech lateralisation is an intriguing one, with theories suggesting that the two functions are linked neurologically from an early age (Iversen, 2010) and that this continues throughout development (Alcock and Krawczyk, 2010). The similarities in developmental maturation of motor and language functions, as well as proficiency in these domains often being correlated to each other, suggests that these functions are co-dependent on underlying neurology. The data in this thesis supports this by demonstrating that performance differences on the pegboard are age dependent, and that they are also significantly predictive of direction of speech laterality (chapter 5). It is particularly noteworthy that the patterns of pegboard performance in the adults with DCD match those of the 3 and 4 year old typically developing children. This supports suggestions that neurodevelopmental disorders are reflective of an immature processing system (Hill, 2001; Hsu and Bishop, 2014) rather than an atypical one. This is an important distinction as it implies that factors affecting the successful integration and maturation of a developing language and motor system are causing the delay, rather than an abnormal neural organisation.

The second way in which the data in this thesis support the view that left hemisphere is specialised for fine motor control and speech processing can be seen when examining the patterns of speech lateralisation and motor performance across a range of skilled tasks; those with a higher degree of sequencing were more significantly related to speech indices (chapter 7). This goes some way to confirming theories that motor skill tasks and speech production are reliant on similar processes (e.g. Corballis, 2003), and is supported by existing data showing that disrupted verbal fluency ability and motor praxis of both hands are affected after left hemisphere brain lesions (e.g. Roby-Brami et al, 2012; Goldenberg, 2013). Finally, when both tasks were performed simultaneously it was speech production which suffered first, this is indicative of functions which make use of a related neural network, as dual task decrement affected one function more severely when the network was stretched beyond efficient processing capacity.

9.2.1 Integration of Sensory Processing

To effectively evaluate the suggestion that the pegboard task is a reliable indicator of speech laterality, and that using such a task is appropriate when examining the relationship between speech lateralisation and motor skill, it is important to consider other possible reasons why this pattern of results occurred. One factor concerns the role of sensory processing inherent to the pegboard task, in comparison to the requirements of other motor skill tasks tested, and in conjunction with sensory processing requirements of the speech production paradigm used. Chapter 7 discussed the role of the visual system in determining successful execution of the pegboard task. It was noted that although visuospatial processing has often been shown to be right hemisphere lateralised (e.g.

Whitehouse and Bishop, 2008; Flöel et al, 2001), components of visual feedback and integration with pre-motor action planning are controlled by the left hemisphere (Gonzalez, Ganel and Goodale, 2006). This reliance on visual information for successful completion of the pegboard task is a key aspect to understanding the neural processes underlying motor skill. Evidence from dual-task paradigms suggest that where vision is attenuated then performance breaks down more quickly across both speech and hand skill, not just for the more visually dependent motor task (e.g. Fujisaki, 2012; Cleland, Gaskell, Quinlan and Tamminen, 2006).

Similarly, the role of auditory processing is integral to speech production, and the ability to maintain fluent and correct speech production relies heavily on effective phonological monitoring. It is well established that there is a dominant left hemispheric lateralisation for processing of speech sounds (Schwartz and Tallal, 1980) and of acoustic stimuli with the same aural signature as speech, as compared to other acoustic or auditory non-speech stimuli (Zatorre, Belin and Penhune, 2002). The left hemisphere auditory cortex has also been shown to be more effective at processing sounds with quick temporal variations, such as those found in speech (Ringo et al., 1994).

This lateralised profile of auditory and visual processing indicates that the left hemisphere is specialised for integrating information from a range of sensory input modalities. This ability may underlie the reason for the pegboard being able to effectively elicit left hemisphere activation as it is a complex task, requiring visuospatial coordination, information processing at speed and sequential ordering, all of which are similar to processes underlying speech processing.

9.2.2 Role of ipsilateral network

One of the key features that becomes apparent when reviewing these data is the varying role played by the ipsilateral pathway in the control of motor performance. The variations between participants in the pegboard task tended to come about as a result of significant differences in non-preferred hand performance. The results in this thesis indicate that the links between handedness and language laterality occur on the basis that individuals who have atypically lateralised language also showed differences in their between-hand performance on the pegboard task. This difference in motor performance typically arose due to lower relative skill level in the non-preferred hand, rather than due to a worse performance with both hands. This pattern can be seen in each of the populations tested in chapters 4-6.

If theoretical explanations that hand dominance and speech both rely on similar processing strategies and common neural networks involving sequencing are correct, then the pattern of results seen in this data can be explained by speech and praxis being controlled by opposite hemispheres in these individuals (e.g. Vingerhoets, et al., 2013). This suggests that the ipsilateral motor pathway from the right hemisphere to the right hand must be very weak, if existent at all (Singh et al., 1998), which could explain the poor non-preferred hand performance in those with right hemisphere speech (i.e. poor right hand performance in the case of left handers – typically those who have atypical, right hemisphere speech). There is evidence from the neuropsychological literature showing that right hemisphere lesions leave the motor function of the ipsilateral (right) hand relatively unaffected, unlike the case of left hemisphere lesions which affects the function of the right and left hands (Goldenberg, 2013; Kimura, 1993). This supports the notion that the right hemisphere may have weak/insubstantial ipsilateral motor control pathways, whereas the left hemisphere is able to maintain functional support for both hands.

One of the brain structures implicated in the control of ipsilateral pathways is the Cerebellum. This structure is situated at the back of the head, under the cerebral cortex and contains many connections to the frontal, temporal and parietal lobes. The cerebellum is primarily involved in motor response preparation and execution, and has been shown to be integral in control of balance, position, muscle tone and sensorimotor control (Hallett, Shahani, & Young, 1975; Ito, 2002; Stoodley & Schmahmann, 2009) and it has also been demonstrated that each cerebellar hemisphere controls the ipsilateral side of the body (Eccles, 1967). The extent to which the cerebellum is connected to other regions of the cortex has been shown to mediate that effectiveness of skilled hand movements, leading to the suggestion that the cerebellum is a core structure in mediating controlled ipsilateral movements (Musalek, Shauroun and Bryden, 2015). Better cortical-cerebellar networks may facilitate motor action, response preparation and coordination, which in turn will strengthen the neural response to learned movement patterns (Musalek, Shauroun and Bryden, 2015). Furthermore the cerebellum has been shown to be involved in motor activation during speech (Hubrich-Ungureanu, Kaemmerer, Henn and Braus, 2002; Ackermann and Brendel, 2016), again suggesting the left hemisphere networks may be supported by other brain regions in the execution of complex sequential movements. The degree to which neural pathways are integrated across the brain will likely be an indicator of how effective this left hemisphere network is.

Associated with evidence that cerebellar-cortical network strength may be crucial in mediating fine motor control is the notion that sequencing itself may not necessarily be the common feature mediating ipsilateral activation. Verstynen et al (2005) suggest that rather than a left hemisphere network specialised for sequencing, it may be task complexity which is more relevant to determining lateralised hemispheric processing. They present evidence from fMRI showing that the recruitment of the left hemisphere ipsilateral pathway during finger movements did not require the task to involve sequential movements. Unlike in the control of contralateral movement, whereby sequencing was key to determining left hemisphere activation, the ipsilateral control of the left hand was similarly activated during sequential and non-sequential movements, as long as they were relatively complex. Simple sequential and non-sequential movements did not produce the same activation patterns. Similar results indicating left hemisphere specialisation for complex sequences were found by Haaland et al (2004). This suggests that ipsilateral control is a key component of a lateralised, combined speech and praxis network, and may explain why non-preferred hand action engages ipsilateral pathways less strongly.

9.3 A Model for Praxis and Speech

A suggestion in the literature is that the control of handedness/motor skill is mediated by a ‘praxis centre’ in the left hemisphere, responsible for specific control of complex motor-based sequencing tasks undertaken by either hand. First described in the unpublished PhD thesis of Pamela Bryden (1998, as cited in McManus, Van Horn and Bryden, 2016), and subsequently revisited by McManus, Van Horn and Bryden (2016), this model describes the functional relationship between the left hemispheric dominance in the control of complex motor output across the hands. It posits that although the contralateral pathways for control of the hands are still activated during handedness tasks, it is in fact a specialised region in the left hemisphere, a so called ‘praxis centre’, that mediates the control of this system. McManus et al. (2016) argue that extent of left hemispheric control of motor output is determined by the complexity of the motor task. Therefore low-skill tasks would be performed by the motor control centres in each hemisphere, which are directly connected to the contralateral hand. However, when motor tasks involve complex movements requiring sequential timing, visuomotor control and accurate integration of visual feedback the use of a lateralised praxis centre is required, which is typically in the left hemisphere. They suggest the praxis centre model can explain why non-preferred hand performance is usually worse, as it is said to rely on an 'inherently nosier' motor centre in the right hemisphere, which is dependent on transfer of information via the corpus callosum for control of the left hand. A schematic of this model is shown in Figure 9.1.

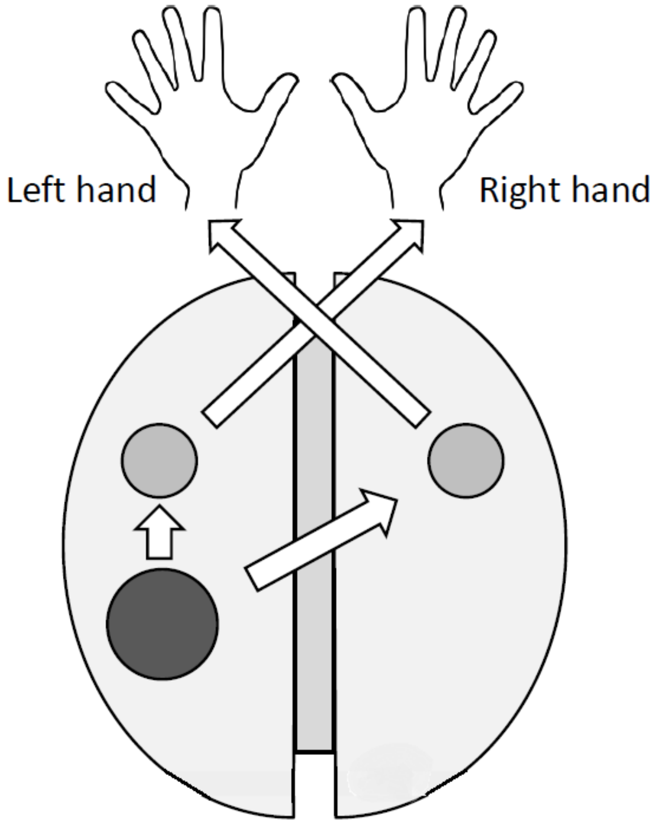


Figure 9.1 McManus et al (2016) Model of Left Hemisphere Praxis Centre

The data presented in this thesis concurs with suggestions about a specialised praxis centre in the left hemisphere. However, this data can also extend the model by integrating speech production into the network, in order to propose a specialised speech-praxis model which operates in a similar way to the outline in figure 9.1. The model can further be extended by the data in this thesis by the proposal that this speech-praxis centre in the left hemisphere becomes established via a developmental continuum of strengthening connections with increasing age, which can explain the motor and speech data from chapters 5 and 6. The data propose that the left hemisphere ‘centre’ activated by speech and motor control functions on a computational network basis of integration between ‘areas’ or ‘sets’ of neural connections involved in the processing of a number of key functions including; motor action, visuo-motor control, motor planning, phonological and auditory processing and sequential control of complex ‘higher order’ operations. Evidence from TMS studies lends support to this notion, for example it has been shown that the optimal site to elicit motor evoked potentials (MEPs) for the ipsilateral hand are in areas slightly lateral and ventral to the site of maximal contralateral MEP (Ziemann, et al, 1999). This shift in location within the left hemisphere for control of ipsilateral relative to contralateral hand movements has also been shown using neuroimaging (e.g. Cramer, et al, 1999). Furthermore recent evidence demonstrates that even within Broca’s area, the region classically thought of as the heart of speech production and, crucially, an area which is confined to a specific part of the left hemisphere, there are spatially and temporally separate processes which occur to support speech (Flinker et al., 2015; Sahin et al, 2009). Therefore a revised model of speech and praxis argues that the interconnectedness of these functions will determine the efficiency with which the left hemisphere is able to support motor control of both hands as well as speech production processes.

In light of emerging evidence about the structural and functional divisions within Broca’s area (e.g. Flinker et al 2015) it could be argued that strength or efficiency of callosal networks, responsible for transfer of information across between the hemispheres, is less important for the typical person who has left hemisphere speech and right hand dominance. For example, the speech-praxis centre model comfortably explains the data from a typical participant from this set of studies, who probably displays left hemisphere speech, left hemisphere activation during right and left hand use on the pegboard task and for whom both hands are able to perform complex sequential tasks relatively similarly (although a hand preference still exists). In such an individual, control of the right hand is excellent due to well integrated and frequently used contralateral motor pathways (e.g. Verstynen et al., 2005), and ipsilateral control of the left hand is good due to the effective networking of all of the aforementioned processes; put simply, the speech-praxis centre in the left hemisphere is better connected to relevant core functions and is integrated with pathways highly strengthened by speech processing which also makes use of them. This therefore allows for good control of complex, sequential motor action in the left hand, something not seen in the individuals who show greater performance differences between hands. For individuals who display atypical handedness or speech then the callosal pathway/inter-hemispheric transfer component of the model is more critical. The level of connectivity between the hemispheres becomes more integral to successful functioning, as intra-hemispheric networking may be poorer and so less able to operate independently. This would be an interesting area for further research.

An interesting finding from chapter 8 is that a dual task paradigm causes a decrement in performance on the word generation task before affecting performance of the pegboard task. This suggests that in this paradigm the motor control task is taking up more of the available network (i.e. demanding more integration from visual processes, sequencing, motor timing, planning) of overlapping processes in the left hemisphere, and less attention is therefore being paid to word production (e.g Serrien, 2009). This nicely supports an integrated speech-praxis centre model as the system appears to function well and is able to maintain low level activity in both domains, until it is overstretched, when the weights on connections between the component processes have to be diverted to one or other of the tasks. If one assumed a model whereby speech and praxis were relatively independently controlled in the brain, albeit in the same hemisphere perhaps, then the data from this dual task paradigm would not look like it does – there would be no specific decrement to one task over the other, there would instead be a greater variance in performance decrements between motor and speech tasks across individuals. It would also be possible to detect a temporal order to the performance decreases, as one area or set of connections would remain functional until the other competing set came online, this does not appear to be the case from the data in chapter 8, although it would be interesting to test such a paradigm using temporally sensitive techniques such as EEG.

One expectation of this model might be that individuals who have atypically lateralised speech, or left handedness, may be compromised in terms of their ability in these functions. However, there is evidence in the literature, and indeed data presented in this thesis, which suggests this is not true of most atypically lateralised people (see Bishop, 2013; Hugdahl, 2010). In fact this revised model can provide an explanation for this. It is possible to argue that atypical speech or handedness is not indicative of compromised processing or ability, but instead such individuals are making use of differently lateralised neural networks to produce the same behavioural outcomes. It is possible therefore to envisage a continuum of atypical processing which would depend on the interconnectedness of underlying key cognitive processes (as described previously), and the relative computational strength of supporting networks, where at one end the hemispheric representation of these processes is altered, but the connectedness is still strong, and at the other end the profile of lateralisation and connectivity of core components is poorer, which, in the worst cases would lead to developmental impairments in language processing or motor control, such as DCD or SLI (e.g. Hodgson and Hudson, 2016; Bishop et al, 2014). This would explain such idiopathic neurodevelopmental disorders where the impairments arise due to deficits in particular sets of cognitive processes, and where behavioural deficits occur in the absence of impairments to general intelligence or other sensory processes. Chapter 6 of this thesis presents a study with adults with developmental coordination disorder, which showed that despite no speech or language impairments, these individuals do in fact display atypical hemispheric lateralisation for speech. Similarly, the motor performance, whilst impaired as expected, was specifically worse with the non-preferred hand. As mentioned elsewhere, this data fits with handedness data from young children presented in chapter 5, and so lends support to the idea that where one function is affected it will have implications for the efficient development of processing of related functions.

9.4 Methodological Limitations

It is appropriate to consider the potential limitations of the results presented in this thesis in order to properly appraise the conclusions drawn. One of the main criticisms which could be levied concerns the effectiveness of the word generation paradigm, used here in the majority of the studies to elicit speech activation. Speech is complex process and one in which humans are very adept at altering and manipulating to suit different contexts and stimuli. The word generation task, whilst able to capture an essential feature of speech production, is not able to reflect the multiple other dimensions of language, such as syntactic function, phonemic distinction, sentence structure, prosody or intonation (Benson et al, 1999; Hertz-Pannier et al., 1997; Knecht et al, 2000a). Some of these other essential features of language also display specific patterns of lateralisation with findings reporting a left lateralised lexical-semantic system (Binder et al., 1997, 2000; Hickok and Poeppel, 2004; Price, 2000) and a right lateralised prosodic processing system (Ethofer et al., 2006; Meyer et al, 2002; Price, 2000), therefore in order to obtain a comprehensive understanding of functional specialisation for language, studies will need to examine differential patterns of activation across speech tasks. The notion that language is a unitary function and can be measured solely on the basis of verbal fluency tasks fails to understand the complexities of the skill and purpose of speech as a form of communication. Furthermore Bishop (2013) suggests that there could even be disadvantages to having different linguistic functions/processes distributed across the hemispheres, as such inefficient processing may reduce performance on speech/language tasks or even affect successful language development. But such questions have not yet been explored in detail and so it remains to be seen whether a more efficient processing network improves language ability, or whether language ability is determined by key component processes being either in the same or in opposite hemispheres.

A second methodological issue arises from the measurement of performance differences in hand skill and whether conversion of these scores to a laterality quotient is optimal and provides a more informative reference point across participants, than does a raw Right-Left (R-L) difference. The studies presented here report both approaches, although the analysis is done using the quotient scores derived from calculating the relative performance of each hand. However, McManus et al. (2016) argue that there is little mathematical basis for using a quotient score, if the intention through using such a measure is to obtain independent performance ratings for use in comparing between-hand differences across subjects. They present algebraic analysis demonstrating that using R-L score as a performance measure may be more informative as it is more likely than a quotient score to be statistically independent of overall performance (McManus et al, 2016). Applying this theory to the calculations of between-hand difference used in this thesis would only have the effect of increasing the statistical significance of these results. The laterality quotient measure of between-hand difference is perhaps a more conservative statistical measure, but does not qualitatively affect the results reported here.

Whilst this may be a technical issue which is unlikely to affect the characteristics of the results reported in this thesis, it highlights yet another point of contention in the field of laterality research in which the community has not yet come to a consensus about the best approach to measurement and classification of performance. This makes it especially crucial to report the data in a full a way as possible to ensure that terminology based difference do not cloud the actual understanding of the neural organisation of asymmetries in cerebral function and behaviour.

9.5 Future directions

One of the inevitable consequences of the studies presented in this thesis is that the data can naturally be extended in several directions, thus opening up further research questions which were beyond the scope of this body of work. This is particularly the case with the data arising from the developmental study (chapter 5) as well as the work with adults with DCD (chapter 6), as the later paradigms developed to examine motor laterality using fTCD would be very applicable to those groups. Therefore one of the key areas of future research is to look at the neurological development of motor lateralisation via fTCD imaging paradigms similar to those developed in chapter 7. This would enable the exploration developmental changes in laterality profiles by using a direct measure of neural activity, rather than continuing to infer brain development underlying motor praxis through observation of performance on handedness tasks. A longitudinal study, whilst logistically complex, would provide an intriguing picture on the possible changing lateralisation as hand performance stabilises and develops. This could start with very young children, as unlike the restrictions with measuring speech production in pre-verbal children, tasks which even 6-12 month old infants could do could be developed to be compatible with an fTCD paradigm.

In a similar vein, the findings in chapter 6 that altered representation of one neurologically linked function (motor control) has an effect on the neurological representation of another function (language lateralisation) suggests that links between motor and speech communication are intrinsically connected. This raises questions about the role of motor development supporting language acquisition in early infancy and it would be intriguing to measure whether early communicative gesturing is more limited/impaired in children who go on to receive a DCD diagnosis. Given the links between praxis and speech it could be hypothesised that motor communication would be less well developed in children who are developing atypical motor/speech skills, given the shared neurology underlying these functions. This area of research has much potential for extension, as the exploration of language organisation in children with motor disorders is very under-researched, as the functional link between speech and motor development is typically investigated in those identified with speech/reading disorders, who may also have motor deficits. The data in chapter 6 also presents scope for further examining the neurological impact of motor impairments on the development of other cognitive functions.

Finally the thesis has explored using fTCD as a methodology for exploring motor and praxis lateralisation. This work is some of the first to do this (although see Silvestrini et al, 1993) and so again there is much potential for developing this line of research further. Future projects could focus on examining the lateralisation of motor development and motor impairments in populations who find more invasive techniques, like fMRI, problematic; this would include patients with limited mobility, as well as young children.

9.6 Concluding Remarks

This thesis presents a series of studies demonstrating that sequencing-based motor and speech tasks share common properties and are likely mediated by an integrated neural network situated in the left hemisphere. It has explored this question in a novel way across a number of different participant groups and by using a novel paradigm to elicit neural activation of lateralised motor action. The data demonstrates that handedness as measured by a motor skill task can be predictive of speech laterality, both in typically developing adults and children. Furthermore it has shown, for the first time that individuals with developmental motor coordination impairments also show atypical speech lateralisation, providing further evidence that neurological motor and speech systems are intrinsically connected. This thesis also demonstrates the applicability of fTCD to neuropsychological research, and its usefulness in exploring the cortical representation of speech and motor lateralisation.

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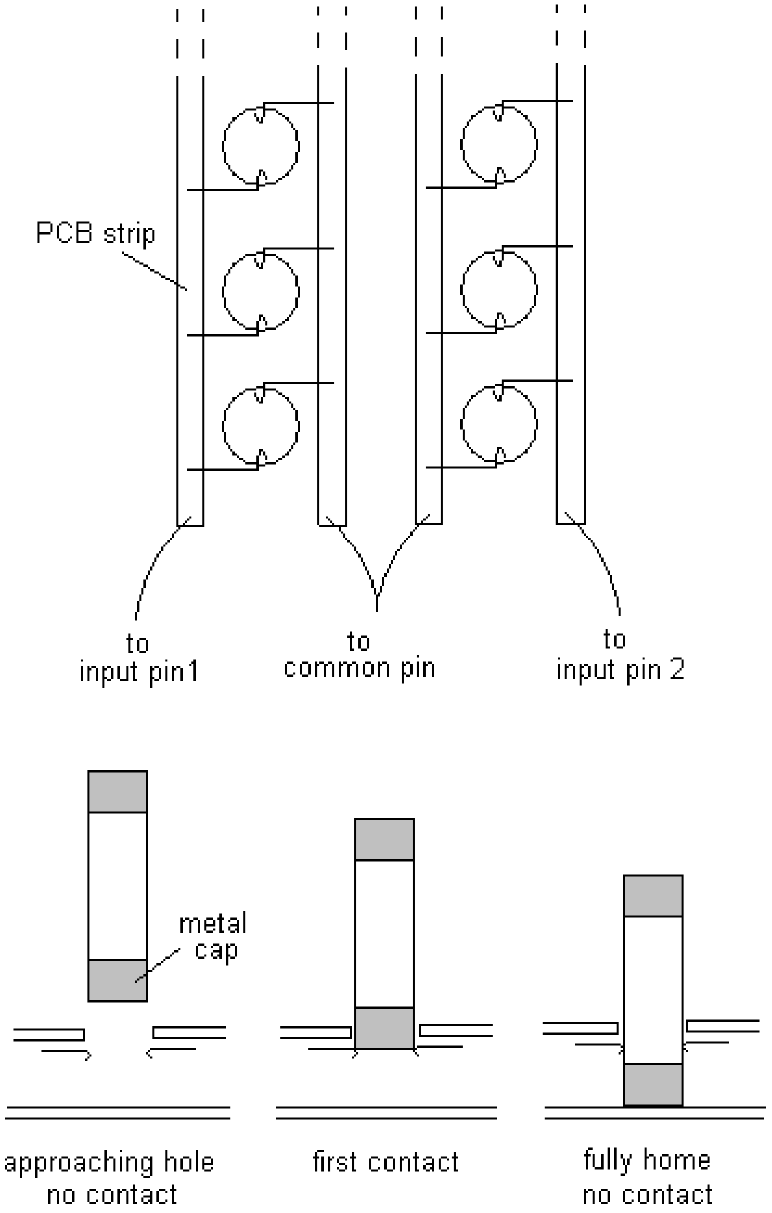
Appendix 1

Wiring diagram for the electronic pegboard



Appendix 2

Handedness Questionnaire taken from Flowers and Hudson (2013)

MOTOR-SPEECH LATERALITY

Id:	Sex:	Age:	Date:	Tester:

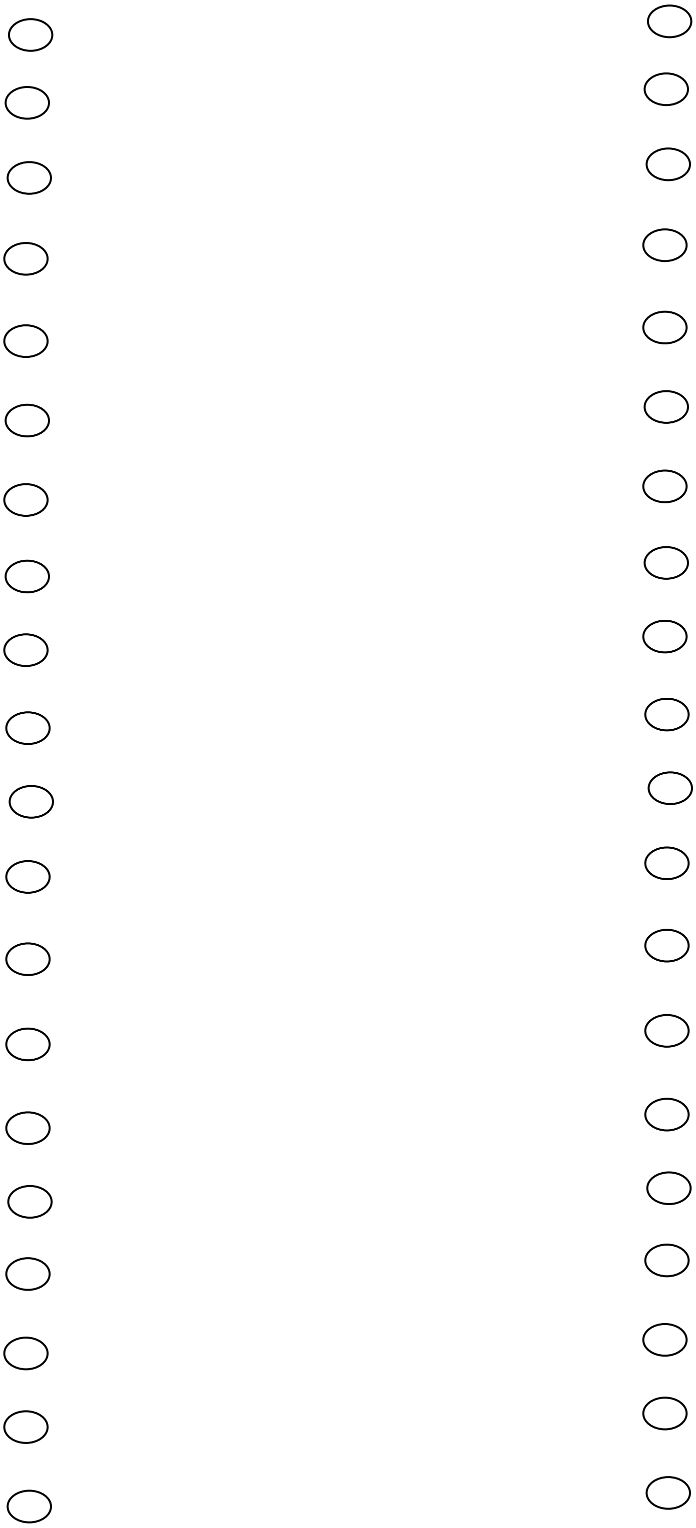
Do you consider yourself to be Right-handed, Left-handed, or ambidextrous, or other?

Which hand do you use to do the following? *Imagine yourself performing each activity in turn and place a tick under the appropriate column.*	*Right*	*Left*	*Either/ Uncertain*
Write with			
Draw with			
Throw a ball, dart, etc. to hit a target			
Play a game using a racquet (tennis etc.)			
Hold a toothbrush			
Hold a comb			
Hold a spoon for soup			
Hold scissors when cutting paper			
Hold a knife when sharpening a pencil			
Strike a match with			
Hold a hammer when hitting a nail			
Hold a screwdriver when mending a plug			
Hold a potato-peeler when peeling			
Deal out playing cards			
Which hand do you use when using two together to:			
Unscrew the lid of a jar			
Guide a thread through a needle (or a needle on to thread)			
Sew with thread			
Which hand do, or would, you use:			
At the top of a broom when sweeping			
At the top of a shovel when shovelling sand or snow			
As the lower hand when holding a cricket bat or golf club			
To pull the trigger on a rifle			

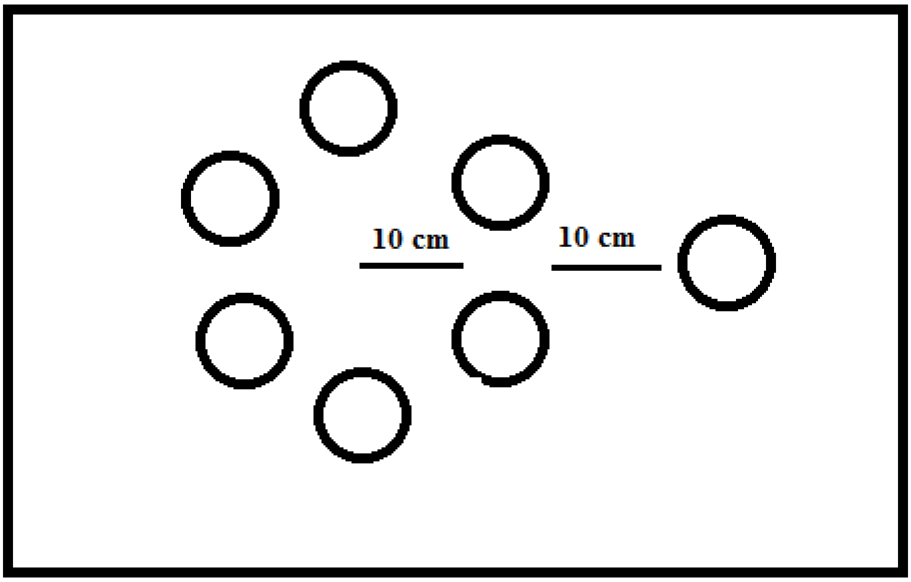
Appendix 3

Images of novel equipment used in motor tasks described in chapter 7

1. Pen and paper dotting task



2. Layout of Peg sorting task



Appendix 4

Box Crossing Task used in Chapter 8 (Della Sala et al, 1995)