Assessing language lateralisation using functional transcranial Doppler sonography

A thesis submitted for the degree of Doctor of Philosophy
UCL

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I, Heather Payne confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I am extremely grateful to Mairéad MacSweeney and Bencie Woll for their unwavering support and guidance through these projects. Thank you Mairéad for the extra chats, the 3pm chocolate fixes, and being an excellent role model. I am also extremely grateful to Nic Badcock for his guidance and for making my research visit to MacQuarie such an enjoyable and enriching experience.

Thank you to the past and present Visual Communication Group for being wonderful mentors, collaborators, and friends. Thank you Mum and Dad for keeping me going and helping to pick me up in the trickier moments. Thank you Yotam - during the course of this work we met, married, and started our little family. You have helped me think about things in new ways and reminded me what is important. My baby Jesse, thank you for being such a fun and happy little soul while I finished this work. Finally, this thesis is dedicated to my best friend and sister, Emily, for helping me to remember 'one day at a time'.

Abstract

This thesis uses functional transcranial Doppler sonography (fTCD) to investigate hemispheric asymmetries in brain activity during language processing. FTCD is a simple method that provides a measure of relative lateralisation. Given its portability and tolerance for movement, it allows physiological activity and behaviour to be measured simultaneously in understudied paediatric populations.

The first half of the thesis describes three methodologically motivated studies with adults. The results indicated that the strength of lateralisation is affected by experimental manipulations of task and stimuli. A particularly influential factor was the intensity of phonological lexical search required. There was also an effect of stimulus pace, suggesting that difficulty or effort may also play a role in driving the strength of lateralisation.

The second half of the thesis provides the main theoretical contributions to the literature in three developmental studies. The first found no evidence of increases in the strength of lateralisation between the ages of $3\frac{1}{2}$ years and $4\frac{1}{2}$ years. The second study found typical left-lateralisation during language production in a heterogeneous group of children born deaf. This study provides preliminary evidence that auditory input is not a contributory factor to the development of language lateralisation. The final study used a paced picture naming task with children. Concordance was measured between fTCD during this novel task and an established narrative task. The data also suggested that LIs measured by fTCD are most likely to relate to offline measures when the tasks share cognitive or linguistic demands.

In summary, this thesis contributes to a growing body of research demonstrating that fTCD is a useful tool to investigate hemispheric lateralisation. It is of particular use with those populations for whom other neuroimaging modalities are not suitable. It is often these groups of participants who can offer unique insights into language processing and the underlying neural systems.

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Chapter 1

Introduction

One of the most prominent figures in the study of language in the brain, Paul Broca (1824 – 1880), suggested that a general language faculty could be localised to a dedicated area of the brain, spatially and theoretically discrete from the sensory input and output systems through which language is conveyed. Subsequent theories of how the brain supports language have continued to attribute critical and dominant roles for frontal and temporal areas in the left hemisphere (Geschwind, 1970).

From broad domains of language processing (for example, speech production or comprehension) and large brain regions (for example, whole cortical lobes), descriptions of both language components and regions have become increasingly refined (Chang et al., 2015). Using different indices of brain function, key regions beyond the classic inferior frontal and temporal areas have been identified, both in other cortical areas and in subcortical structures (Tremblay & Dick, 2016). Nonetheless, hemispheric asymmetry remains embedded in the clinical literature and is a key feature of all models of language processing in the brain.

The phylogenesis of hemispheric dominance, that is, the development of the trait in humans as a species, is not well understood. Lateralisation is not unique to language, nor is it particular to humans. Other cognitive faculties have been proposed to show functional asymmetries. For example, visuospatial processing (Sperry, 1974; De Schotten et al., 2011), emotional processing (Tucker, 1981), and face processing (Kanwisher et al., 1997; McCarthy et al., 1997) show functional hemispheric lateralisation. Behavioural asymmetries have been observed in mammals, birds, amphibians, and fish (Karenina et al., 2017; Ocklenburg & Güntürkün, 2012). While evidence is mixed, task-dependent hand-preference asymmetries have been observed in certain primate species (Meguerditchian et al., 2013). Furthermore, there is a growing consensus that non-human primates show functional lateralisation of cognitive and emotional functions, including left-lateralised responses to species-specific vocalisations (Poremba et al., 2004; Gil-da Costa et al., 2006).

Causal factors involved in the phylogenesis of lateralisation are beyond the scope of this thesis. Briefly, it is possible that the presence of lateralisation across different species is due to shared ancestry, or that lateralisation has evolved independently in different species as responses to evolutionary pressure on other traits (for example, brain size – see Hopkins et al., 2015). Regardless of the origin, the existence of cross-species and cross-domain lateralisation suggests it serves an adaptive function. That is, it is likely that there are advantages of lateralisation, and accompanying disadvantages of atypical lateralisation.

There are some functional advantages of a strongly lateralised system, for example increased neural capacity and efficiency of information transfer between hemispheres (Vallortigara, 2006). These have been borne out in findings of improved performance in attention tasks in lateralised individuals (Vallortigara & Rogers, 2005). There are also survival advantages for species who display mixed (left for one function and right for another) and unequal lateralisation for certain behaviours at the population level (Ghirlanda & Vallortigara, 2004; Brown et al., 2004). At the other end of the spectrum, it is often suggested that atypical lateralisation may be disadvantageous. Indeed, low or right lateralised language processes have been linked to numerous developmental disorders of language and cognition, including autism (Herbert et al., 2003), SLI (Whitehouse & Bishop, 2008; de Guibert et al., 2011), dyslexia (Galaburda et al., 1985), schizophrenia (Crow, 1997), developmental stuttering (Foundas et al., 2003) and Williams Syndrome (Grice et al., 2001).

Explanatory mechanisms for the role of lateralisation in any of these disorders are lacking, perhaps because of a paucity of data on the development of typical lateralisation through the lifespan (ontogenesis). While genetic and non-genetic factors are thought to underpin the development of lateralisation, the complex interaction between maturation and learning and its relationship to lateralisation is poorly characterised. Understanding the factors that influence the development of lateralisation is a critical first step in understanding the relevance (if any) of atypical lateralisation. This thesis addresses questions relating to the development of functional lateralisation of brain activity associated with language processing. Specifically, it addresses whether the strength of lateralisation increases with age and proficiency in typically developing children. It also tests whether language lateralisation is affected by atypical language experience. Testing lateralisation of language processes in special populations offers a unique perspective on the relationship between exposure to language, proficiency, maturation and lateralisation.

The following two chapters are an overview of evidence which provides a backdrop to the studies in this thesis. Chapter 2 summarises evidence which demonstrates that language functions are lateralised in the majority of adults. Neuropsychological, intraoperative, behavioural, electrophysiological, and neuroimaging studies provide corroborative evidence for asymmetries in processing for numerous aspects of language. The complexities of quantifying the extent of lateralisation will also be outlined. Lateralisation of language in development is then considered, as well as experience-dependent factors which may play role in the development of language lateralisation. Chapter 3 provides an overview of functional transcranial Doppler sonography as a method for assessing lateralisation and isolates some aspects of the technique that would benefit from careful consideration. Chapter 4 ties these areas together to lay out the questions addressed by this thesis.

Chapter 2

Theoretical background

2.1 Language lateralisation in adults

2.1.1 Classical studies of language lateralisation

Speech and language faculties in humans have long been attributed predominantly to the left hemisphere. The historical roots of this observation lie in the field of neuropsychology, and in work with patients who presented with profound difficulties producing speech.

Between the 18th and 19th centuries, it was generally accepted that the human brain was anatomically, and therefore it was assumed - functionally, symmetrical (Xavier Bichet 1771-1802; in Finger & Roe, 1996). In this context, observations of a systematic relationship between the hemisphere of a brain lesion and symptomatology attracted understandable attention. There were several reports of patients presenting with disorders of speech and language (which were often erroneously considered to be one and the same) following stroke or traumatic brain injury, most notably reported in the work of Marc and Gustave Dax (1865), Paul Broca (1861, 1865) and Carl Wernicke (1874) (in Hellige, 1993 but see also Benton, 1984 for earlier clinical reports).

One of these reports described a number of individuals with ‘aphemia’ (defined as the loss of speech), all of whom showed lesions in the left hemisphere ‘third frontal convolution’ (left posterior inferior frontal gyrus) (Broca 1861, 1865). This finding was also reported in a larger group of patients with paralysis of the right side of the body, taken as evidence of a contralateral left-hemisphere lesion. Importantly, patients who had suffered right hemisphere damage typically showed well-preserved speech and language abilities (Dax, 1863; in Finger & Roe, 1999). The double dissociation between lesion site and language outcome was taken as evidence for a complete division of labour between the hemispheres, and as an indication that fluent speech (particularly the knowledge of articulatory speech actions) had been ‘successfully localised’ in the brain.

Carl Wernicke later reported patients with considerable deficits in understanding language and proposed an area in the first (superior) temporal gyrus responsible for processing sensory speech sounds. He combined this with the inferior frontal region described by Broca, to form a more comprehensive account of language processing (Lichtheim, 1885; Wernicke, 1903; described by Meyer, 1905). Wernicke also speculated that a deeper tract of white matter might exist that could link these two regions, damage to which could result in a ‘conductive’ loss linking reception and production of language (Meyer, 1905).

Numerous single-case and group studies of patients followed, further refining model of language processing in the brain. Visual field presentation and dichotic listening paradigms allowed a non-invasive way of testing lateralisation of language processing. These studies tested for asymmetries in reaction times and accuracy to stimuli presented to one or other hemifield or ear (Kimura, 1967, 1973; Shankweiler & Studdert-Kennedy, 1975; Caramazza, 1991). A number of studies involved patients who had undergone severing of the corpus callosum, meaning that transfer of information between the hemispheres was no longer possible (Gazzaniga et al., 1963). Stimuli presented to the right visual field (processed by the left hemisphere) could be accurately named, whereas those presented to the left visual field could not. These findings further fuelled the idea that the left hemisphere is critical, if not solely responsible, for language (Gazzaniga, 2000). Right hemisphere homologues of left hemisphere perisylvian regions were very much considered to play supporting roles (Caramazza, 1991). From solely explaining correlations between symptoms and lesions in patients, the field expanded to describing the language system in a functioning healthy brain (e.g. Caramazza & Berndt (1978)).

As well as functional asymmetries, post-mortem studies also showed anatomical differences between the hemispheres in healthy brains. Differences in volume of the planum temporale in post-mortem studies of healthy brains provided some of the first evidence that anatomical asymmetries could relate to asymmetries in function (Geschwind & Levitsky, 1968; Galaburda et al., 1978).

Intraoperative techniques for mapping areas of cortex critically involved in language processing enable clinicians to reduce post-operative effects on language in patients after cortical resection Hinz et al. (1994); Bassel (2007). Observations from patients undergoing surgery for intractable epilepsy provided further evidence for left-hemispheric dominance for fluent speech output. First, pre-surgical language difficulties were reported in patients whose seizures originated in left anterior temporal lobe Hermann & Wyler (1988). Furthermore, several studies reported object naming and verbal memory deficits in patients who had undergone left anterior temporal lobectomy (ATL) but little or no reduction in naming ability in those who had undergone right ATL (Ivnik et al., 1987; Sherman et al., 2011; Victoria & Butler, 2012).

Deficits in naming after surgery are less common in those patients who have undergone pre-operative electrocorticography (ECoG) (in combination cortical electrical stimulation) to identify areas that induce speech arrest when stimulated (Penfield & Roberts, 1959; Ojemann, 1991; Hinz et al., 1994) so that these areas can be spared. As well as being a useful clinical tool in this regard, direct stimulation of cortical areas to induce dysfluent speech *in vivo* provided further evidence for a critical role of left-frontal and temporal regions during language production. ECoG has spatial resolution to the order of millimetres, with some depth probes permitting measurement of action potentials from single neurons (Engel et al., 2005; Buzsáki et al., 2012). In one such study, Ojemann & Schoenfield-McNeill (1999) noted that disrupting single cells led to prescribed deficits in language abilities such as naming. However, when recording from groups of cells the picture was far less 'modular' – larger networks of neurons from across hemispheres appeared to be active during the same tasks (see Ojemann (1991, 2013) for reviews). I return to the difference between critical and involved (or necessary and sufficient – Price et al. (1999)) in 2.1.3.

The intracarotid amobarbital procedure, named the Wada technique after the physician who pioneered the practice, was developed as an alternative to intracortical stimulation or recording (Wada, 1949). This procedure involves injection of a barbiturate to the carotid artery supplying one or other hemisphere, whilst the patient is locally anesthetized (Wada & Rasmussen, 1960). The patient is then asked to complete a battery of memory and language tasks: traditionally this involved counting out loud prior to injection and noting if the patient is able or unable to continue. The patient would typically be asked to repeat spoken words, read words and sentences aloud, name pictures, and provide word definitions. Simple motor commands would also be given. In some cases, more complex linguistic tasks testing sequential language and verbal fluency would be given (Rausch & Risinger, 1990). Wada and colleagues observed that speech arrest during left hemisphere treatment was vastly more common than during right hemisphere treatment. This provided more evidence that left hemisphere cortical areas were more involved in language processing than their right hemisphere homologues.

Despite theoretical appreciation of the many subprocesses involved in language, expressive speech output was the focus of many early neuropsychological measures. The next section considers contributions made by neuroimaging, which allowed the measured variable of interest to be physiological responses rather than disruption of speech output alone. This has allowed the study of language functions to less ‘observable’ aspects of language processing such as activity associated with metalinguistic judgements or speech comprehension.

2.1.2 Neuroimaging studies of language lateralisation

Non-invasive methods for measuring lateralisation

Studying patient populations often necessarily involves atypical language functioning. The extent to which observations can be extrapolated to non-clinical populations is debatable. For example, epileptic patients may show differences in language representation in the brain prior to surgery, so examining language lateralisation in this group may not inform models of the neural systems supporting language in non-epileptic patients (Adcock et al., 2003). Lesion and patient studies can only take us so far in understanding the functioning of the healthy human brain (Rorden & Karnath, 2004).

Advances in medical imaging have permitted the measurement of dynamic brain function. Measuring brain activity crucially enables the recording of behavioural and physiological responses simultaneously to infer structure-function relationships with behaviour. As well as this, technological advances have drastically improved the resolution at which structural differences between hemispheres can be measured in patient and non-patient populations.

Measuring structural asymmetries in anatomy in vivo requires static images of brain tissue. The earliest such images were generated by Computerized Tomography (CT), which capitalises on the different absorption properties of bone, cerebrospinal fluid, and brain tissue when they are exposed to X-ray (Hounsfield, 1973). Lateralisation was not often quantified per se, but instead was restricted to descriptions of the site and laterality of a lesion and its relation to symptomatology (Damasio & Geschwind, 1984). However, it was one of the earliest research tools for assessing anatomical asymmetries in healthy living brains, by quantifying differences in size and shape of regions of interest (LeMay, 1976).

Structural images generated using magnetic resonance imaging (MRI) provided a way of imaging the healthy brain without exposing participants to the ionizing radiation associated with CT. Morphometry can be used to quantify hemispheric differences surface area, volume, or density of grey and white matter. This is done either manually across predefined regions of interest (usually larger anatomically defined structures) (Uchida et al., 2003) or using automated voxel-by-voxel methods (tensor- or voxel-based morphometry). Voxel-based morphometry (VBM), for example, spatially normalises structural scans to a template which allows individual differences in overall brain volumes (and other macroscopic differences) to be accounted for (Wright et al., 1995; Ashburner & Friston, 2000). The resulting images are then computationally segmented into grey matter, white matter and cerebrospinal fluid using probability maps and specialised imaging processing algorithms. Statistical comparison between volumes from each hemisphere allows asymmetries to be mapped without a priori hypothesis about anatomical structures.

Using an alternative MRI sequence of radiofrequency pulses and gradients can be used to more effectively display different types of tissue. For example, Diffusion Tensor Imaging (DTI) studies use a differently weighted scan image to increase signal intensity of water molecules and thus aids in mapping white matter tracts between different brain regions. Differences in microstructural properties of tissue between regions of interest in either hemisphere can be used as an index of lateralisation.

Turning to measures of brain function, a widely used and non-invasive technique is electroencephalography (EEG). Unlike intracranial recordings with patients, this method is not restricted to patient populations or the surgeon's positioning of electrodes. The fluctuations in electric currents associated with synaptic activity are detectable on the scalp and can be recorded without invasive surgery. Unlike single cell recordings, these fluctuations reflect activity over a population of neurons (synchronously in order to produce sufficient electrical energy) and are likely to reflect post-synaptic firing rather than action potentials (Rugg & Coles, 1995).

In language research, characteristic responses to presented stimuli (event related potentials – ERPs), observable in the recorded EEG, have provided a framework against which to test theoretical hypotheses. For example, the P600 component has been reliably observed across many languages, including signed languages, for grammatical violations (Friederici & Mecklinger, 1996; Capek et al., 2009). Having established that the P600 is a reliable indicator of grammatical processing, its presence or absence can be assessed in different populations, for example, early versus late learners, high versus low proficiency users, or in children of different ages.

An alternative way to index brain activity is to measure other physiological changes related to the electrical currents associated with neuronal spiking. Rapid progress in medical physics and radiography in the 1970s led to the widespread use of Positron Emission Tomography, and later, functional Magnetic Resonance Imaging (fMRI) for assessing functional brain activity

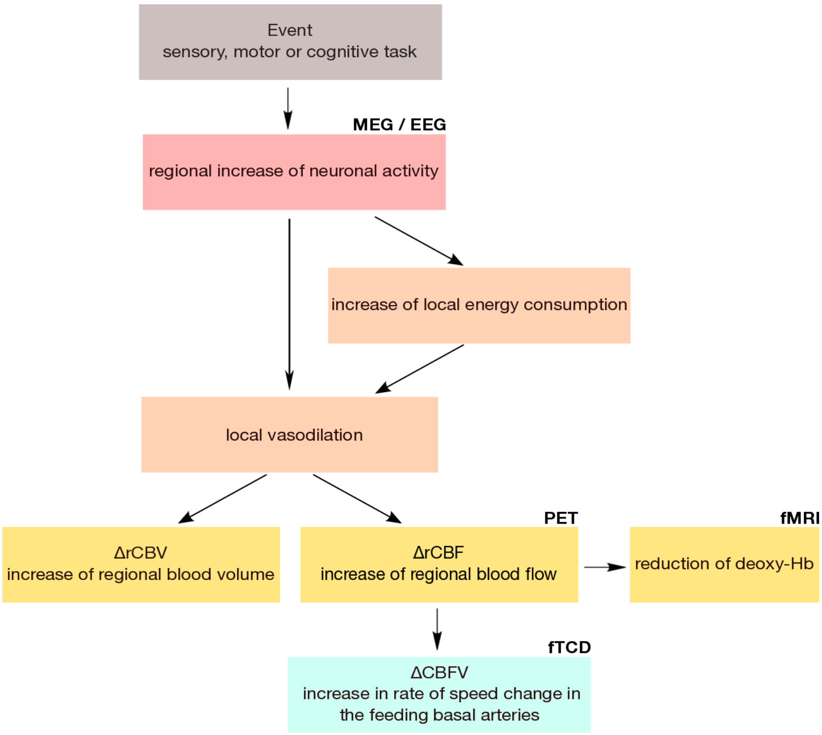


Figure 2.1: Physiological changes and the major neuroimaging methods. Adapted from Deppe et al. (2004)

using changes in cerebrovascular function as an index of brain activity (see Nutt, 2002 and Huettel, 2004, p.11 for historical accounts of PET an f/MRI respectively).

These methods capitalise on neurovascular coupling: the association between neuronal activity and changes in metabolic and vascular function which occur in tandem (Buxton et al., 2004). The mechanism for the coupling between neuronal activity and regional increases in blood flow is not fully understood (Petzold & Murthy, 2011; Attwell & Iadecola, 2002; Logothetis et al., 2001). Nonetheless, several associated indices of vascular changes can be measured and linked to changes in neural activity. These include blood flow volume, blood flow velocity, or the amount of oxygenated blood cells present. A simple diagram of physiological changes related to neural activity is shown in Figure 2.1.

In fMRI, changes in the blood oxygenation level dependent (BOLD) response can be measured for clusters of cells in the brain during language processing and be used to make inferences about location of neural activity. How well this reflects activity associated with the process of interest will be determined by the design, for example conjunction versus subtraction (Price & Friston, 1997) or statistical framework (Friston et al., 1996).

Of importance to developmental research, there are two other methods which will be referred to in this thesis. Magnetoencephalogaphy (MEG) permits similar time course information to be gathered as for EEG, but recording the magnetic fields induced by the electric currents affords a higher precision of source localisation. It has therefore been used in developmental studies of language lateralisation in children which will be discussed in Chapter 2.2. The second method is functional Near Infrared Spectroscopy (fNIRS), which measures the changes in oxy- and deoxygenated blood across several channels directly on the scalp. It uses infrared light to penetrate the skin and skull, and the reflected light received is used to calculate changes in oxygenation.

An alternative haemodynamic method, most commonly used in infants, and the imaging technique used in this thesis, is Functional transcranial Doppler sonography (fTCD). It will be introduced in further detail in Chapter 3. A short explanation is given here for clarity in the following literature review. fTCD is similar in principle to fNIRS, but is sensitive to blood flow velocity as opposed to level of haemoglobin in oxy- or deoxygenated blood. Blood flow velocity changes are measured from two key arteries which supply large portions of temporal and frontal cortices: the middle cerebral arteries (MCAs). Instead of several channels across the head as in fNIRS, fTCD uses two ultrasound probes to measure changes in blood flow velocity. Blood flow velocity change is one of the physiological changes in vascular activity associated with neurovascular coupling (see Figure 2.1). Lateralisation is measured as the maximum difference between changes left and right MCAs over a period of interest.

fMRI and PET studies of language lateralisation in adults

The use of CT scans to confirm lesion sites made it possible to study language structure-function relationships in living patients (e.g. Damasio & Geschwind (1984); Vargha-Khadem et al. (1985). Confirming classical neuropsychological studies, it was found that left posterior and inferior temporal lesions critically impair production and comprehension of language, and that there is partial dissociation between these skills depending on the site of the lesion (Naeser & Hayward, 1978). However, inferences on the function of a region were still being made from static anatomical observations rather than direct observations of their function. Functional imaging methods enabled concurrent correlations between brain activity and language processing.

Language clearly encompasses many stages of processing; users of a language are able to perceive, manipulate, make judgements on and produce various forms of their language without formal knowledge of its rules. Each aspect of language processing may or may not show consistent or related patterns of lateralisation. Early neuropsychological patient studies acknowledged that the type of processing required would have a bearing on which neural structures and computations were implicated (Geschwind, 1970). While contrasts between production and comprehension were made early on, later subdivisions led to a distributed model of the lexical system (Shallice, 1981; Allport & Funnell, 1981) reflected in more extensive but highly specialised networks (Caramazza & Berndt, 1978; Damasio & Geschwind, 1984).

The contemporary conceptualisation of language in the brain is less localisationalist than accounts from the latter part of the 20th century. Rather, the present view involves dynamic interplay between regions within a network. A broad overview of current understanding of functional asymmetries in language related processing in adults is provided below. For comprehensive reviews summarising neuroimaging contributions to understanding the neural basis of language, see Price (2010, 2012); Démonet et al. (2005); Poeppel (2014). These include subdivisions of language more refined than those here, .

Early fMRI studies described leftward dominance in functional responses to a number of language tasks. However, these studies did not directly quantify the extent of lateralisation (e.g. Petersen et al. (1988); Frith et al. (1991); Binder et al. (1997), at most providing qualitative descriptions of 'pixels' activated (e.g. Pujol et al. (1996)). fMRI studies directly testing and quantifying lateralisation tended to adopt tasks from the clinical literature to provide comparisons to measures such as the Wada procedure. For example, Springer et al. (1999) used a forced-choice decision task in which participants had to make semantic category judgements. Activation during this task was compared to that during a tone decision task. Using a statistically determined cut-off point for defining lateralisation categorically, the authors reported that 96% of their typical group showed left-lateralised activity; the remaining 4% showed symmetrically distributed activity.

Tasks designed to test expressive language skills (production) have included verb or word generation, picture naming, and silent speech production (see Price, 2012 for an overview). Contrasts have included low-level baselines of speech-like motor movement. For example, Braun et al. (1997) used PET to compare various speech production tasks to orofacial and laryngeal movements, reporting consistent leftward asymmetry. Depending on the exact contrast chosen, these were observed as extensive activations in frontal opercular regions, prefrontal, superior and middle temporal gyri, inferior angular gyrus and paralimbic regions.

More recent fMRI studies reinforce and refine these findings, indicating lateralised responses in cortical and subcortical regions during overt articulation and in covert articulatory planning (Price, 2012). Tremblay & Small (2011) directly tested differences between hemispheres in two regions of interest (ROIs), a frontal ROI encompassing inferior frontal regions and a mesial ROI which included motor and pre-motor regions. They found that generation of novel sentences showed more pronounced left-lateralisation than repetition of sentences in frontal ROIs but similarly lateralised responses in generation and repetition in mesial ROIs. This suggests that lateralisation is not driven only by articulation or speech motor planning, but is a feature of generating language during speech production.

As well as language production, neuroimaging studies of the perception of language suggest varying extents of asymmetries in processing. Lateralisation depends on both the nature of the task (e.g. passive listening, judgement tasks) and the stimuli presented (phonemes/words/sentences). Speech perception in listening tasks involves regions in the superior temporal gyrus, and superior temporal sulcus extending to the supramarginal gyrus (summarised in Démonet et al. (2005)). The extent to which activity is lateralised has been much debated in the literature (Rauschecker & Scott, 2009; Hickok & Poeppel, 2007) but with consensus that at least some aspects of speech perception show preferential responses particularly in left primary auditory and association areas.

Passive listening to connected speech recruits a more extensive left than right portion of temporal cortex, specifically in posterior superior temporal sulcus and gyrus (Crinion et al., 2003), though it is reported to be bilateral in several earlier studies (Dehaene et al., 1997; B. M. Mazoyer et al., 1993). Mixed results in lateralisation could be due to differences in the stimuli used these studies. Tasks requiring judgements on aspects of prosodic processing, such as intonation, recruit right hemisphere perisylvian homologues (Ross & Monnot, 2008). Therefore, assessing passive listening to connected speech with a great deal of prosodic information could lead to reduced lateralisation given the presence of certain top-down processes (such as a focus on intonation versus searching for communicative intent). Peelle (2012) describes lateralisation of speech perception as dependent on the cognitive and linguistic processes required to complete the task. It is suggested that perception and processing of unconnected to connected speech becomes increasingly left-lateralised, with greater left-lateralisation with increasing linguistic task complexity.

In line with this view, metalinguistic and receptive language tasks more reliably show left lateralisation of brain activity. Significant left- greater than right-hemisphere activity along superior temporal gyrus has been found for phonological decisions on auditory speech compared to tone decision tasks

(Burton et al., 2000). Similar findings are reported for rhyme decisions on text stimuli compared to perceptual categorisation tasks using visually unfamiliar strings of characters (Seghier et al., 2004). Accessing meaning from auditory stimuli gives rise to left-lateralised responses which extend anteriorally, laterally, ventrally, and posteriorly from Heschl's gyrus (see Price, 2012 for a review). For example, semantic decisions on visually presented words compared to perceptual judgements on unfamiliar characters show reliable left dominant activity (Seghier et al., 2004). Even the type of responses required can influence the degree of lateralisation measured. When participants are asked to perform grammaticality judgments on connected speech, peaks in activation occur along superior temporal gyrus more prominently on the left. However, when asked to judge sentences and repair ungrammatical sentences covertly, right hemisphere homologues and clusters around inferior frontal gyrus are recruited – thus the effect of hemisphere diminished when participants are asked to manipulate sentences grammatically (M. Meyer et al., 2000). Therefore, the type of task required of participants can directly affect any assessment of the extent of lateralisation.

Functional TCD studies of language lateralisation in adults

Functional TCD has been used with adults, both to answer questions about the validity of the technique as an alternative to invasive methods, and as a tool for large scale studies testing distributions of lateralisation in relatively large populations. To date numerous fTCD studies have reported left lateralisation of cerebral blood flow during language related processing in the majority right handed adults (Knecht et al., 1996, 2000, 2001; Lust et al., 2011; Rosch et al., 2012).

The most commonly used task to elicit 'language-related' activity using fTCD is a phonological fluency task. During phonological (often called verbal- or word-) fluency tasks, the participant is presented with a series of letters one at a time and asked to generate as many words beginning with the letter as possible within a given time. It is used extensively in the neuropsychological literature with patient populations, for example in individuals with acquired lesions (Baldo et al., 2001), dementia (Monsch et al., 1994), and schizophrenia (Frith et al., 1995). Results using fTCD and phonological fluency are in line with a meta-analysis of functional MRI studies of fluency tasks reporting the greatest number of peaks in activation around left inferior frontal gyrus (Costafreda et al., 2006). FTCD studies report between 82 - 92.5% of right-handed participants as showing left hemisphere dominance, while only 7.5 – 9.5% show right hemisphere dominance (Knecht et al., 2000, 2001).

Stroobant et al. (2009) explored a range of language tasks within participants. They measured fTCD signal during: 1) covert phonological fluency; 2) sentence construction (from a series of words presented in a mixed order); 3) reading aloud fragments of natural text and 4) semantic decision, (deciding which of three words was not synonymous with the others). All tasks were left lateralised at a group level; however, the percentage of left lateralised participants differed depending on the task: sentence construction (90%); phonological fluency (80%); reading (73%) and semantic decision (67%). Production tasks tend to produce stronger left hemisphere lateralisation than receptive tasks as measured with fTCD (Badcock, Nye, & Bishop, 2012; Buchinger et al., 2000; Stroobant et al., 2011), and fMRI (Gaillard et al., 2004).

2.1.3 Variability in language lateralisation

There are several potential sources of inter- and intra-subject variability in lateralisation for language that ought to be considered. While they are peripheral to the questions addressed in this thesis, they nonetheless have implications for interpretation of lateralisation data collected here. The following section considers 'biological' (relatively fixed) sources of variation, and what I have termed 'situational' (relatively unfixed) factors, which are those that depend on the current environment or conditions of testing.

Biological factors

Variability in structural anatomy, handedness, and gender have been linked to variability in lateralisation. A full discussion of these factors is beyond the scope of this thesis. However, several key points are considered here.

Differences in surface area and volume of cortical structures may be expected to entail differences in functional activity, due to the configuration of neurons, the number of synaptic connections and the types of connections groups of neurons have with other regions (Zatorre et al., 2012). Therefore, asymmetries in structure between left and right hemispheres, particularly in perisylvian regions important for language processing, could go some way to explain variability in functional lateralisation. Indeed, significant differences have been reported for various indices of structural morphology at macro- and microscopic levels in anterior temporal, temporo-occipital and frontal regions: all key regions implicated in language processing. The most robust findings are asymmetric protrusions of the right frontal and left occipital lobes which are characteristically 'twisted' about the Sylvian fissure, a phenomenon known as Yakovlevian torque (Toga & Thompson, 2003). Similarly, the angle of the Sylvian fissure is reported to slope more steeply upward in the right hemisphere and this has been reported using a range of methods (Geschwind & Galaburda, 1985; Thompson et al., 2001).

Differences in grey matter size and volume of the planum temporale, originally observed in post-mortem studies (Geschwind & Levitsky, 1968), have been confirmed with CT scans (LeMay, 1976) and in subsequent MRI studies (see Hervé et al. (2013) for a review). Heschl's gyrus, adjacent to the planum temporale, is highly variable between individuals, though there are leftward asymmetries found in most studies (Penhune et al., 1996; Chance et al., 2006; Dorsaint-Pierre et al., 2006; Warrier et al., 2009). Anterior language regions most usually associated with Broca's area have shown mixed results in whether they display structural asymmetry (Foundas et al., 1996; Amunts et al., 1999; Good et al., 2001; Watkins et al., 2001). In addition greater left than right volumes have been reported in the angular gyrus, and the anterior insula shows greater right than left volume (Watkins et al., 2001; Chiarello et al., 2013). Differences in the integrity of white matter fibre tracts in left and right hemispheres are also observed. The integrity of the arcuate fasciculus which links posterior temporal with inferior frontal regions is significantly greater in the left than right hemisphere (Catani et al., 2007).

Despite convergent evidence that structural asymmetries exist in areas fundamental to the language system, it is not clear how these asymmetries relate to functional activity. If structure explains functional lateralisation a stronger correlation between the size of a structure and extent of lateralisation would be expected. Some supporting evidence comes from the finding that structural asymmetry in the volume of the insula related to the direction and moderately to the strength of functional lateralisation during word generation (Keller et al., 2011). However, this study used mixed methods for determining LIs (fTCD and fMRI) which were collapsed where insufficient data were collected. This raises questions about the reliability of the Lis. Furthermore, analyses of activity across regions which covaries (functional connectivity) have shown hemispheric differences even when accounting for differences in structure (Nielsen et al., 2013), which is suggestive of fluctuations in lateralisation which are not direct consequences of anatomical differences.

The structural asymmetries in grey matter volume and surface area in areas of the cortex central to speech processing (e.g. planum temporale) that have been observed in adults have also been observed in foetuses at 26-28 weeks gestation (Wada et al., 1975; Habas et al., 2011) and in newborns (Witelson & Pallie, 1973; Chi et al., 1977; Duboc et al., 2015; Dubois et al., 2008, 2010; Hill et al., 2010). The very early presence of differences in anatomy suggests that to some extent structural asymmetries may be under genetic control (Josse & Tzourio-Mazoyer, 2004). If indeed anatomy explained some variance in functional lateralisation, developmental studies of changes in lateralisation would need to take into account individual differences in structure as well as the gradient of change in structure.

Other traits which show asymmetries have also been linked to language lateralisation. Perhaps most prominently, handedness has been considered a proxy for language lateralisation in some studies (for discussion see Bishop (2013). Handedness has long been linked to language lateralisation, given the observed association with stroke site in early neuropsychological patient studies. Gustave Dax noted that right-side hemiplegia was used to diagnose the presence of a left-sited lesion, while Paul Broca suggested a common basis for handedness and language dominance in anterior regions of the left hemisphere (in Finger & Roe (1999). Hécaen & Sauguet (1971) found corroborative evidence for this idea, reporting that left hemisphere lesions were less predictive of aphasic symptoms in left-handed patients. Similarly, using the Wada procedure described above, Rasmussen & Milner (1977) reported a lower proportion of left-handed than right handed adults who were left lateralised for language (70% versus 96%). Hinz et al. (1994) report a similar pattern in paediatric surgery patients, where atypical language dominance was found in left-handers. However, the relationship between language lateralisation and handedness is not a straightforward one. This is evident from the high proportion of left-handers who nonetheless show left lateralisation for language. In a large study of 297 adults, handedness and hemispheric dominance for language did not concord more often than chance would predict, except for in a highly unusual subgroup of the population: those with strong left hand preference who showed strong right lateralised responses during sentence production. This indicates that handedness is not a suitable proxy for language lateralisation, although this has been used in developmental studies and with special populations for whom other methods may be unfeasible (Crow et al., 1996; Mandal et al., 1999).

Finally, sex has been considered to play a role in individual differences in lateralisation for language. Alleged behavioural differences in performance on language and visuospatial tasks between genders have been hypothesized to relate to differential patterns of lateralisation (Witelson, 1976; Gur et al., 2000). However, the literature on gender differences and lateralisation is highly inconsistent, with stronger lateralisation being associated with both better (visuospatial task: Gur et al. (2000)) and poorer (verbal task: Shaywitz et al. (1995)) performance. Hence there is an unclear association between lateralisation and putative processing advantages. Furthermore, the presence of differences in performance in language tasks, cortical structural asymmetries or function between males and females has been largely discredited due to the low power of many early studies (see Wallentin (2009) for a review).

Situational factors

Factors specific to the chosen methodologies and experimental conditions can lead to important differences in lateralisation which are unrelated to questions about the development of lateralisation or the role of input. These include the choice of imaging modality, methods of calculating lateralisation, and the choice of language task.

Variability in lateralisation indices in functional studies may relate to whether methods are testing areas *critical* or those *involved* in a given language process. These have been referred to in the literature as *necessary* versus *sufficient* (Price et al., 1999). Neuropsychological case studies or studies of patients to determine hemispheric dominance prior to surgery (using EcOG or the Wada procedure), in general aim to localise areas that cause critical impairment to language processing when disturbed, the assumption being that they are necessary for typical function. The ability to perform a task given damage or temporary incapacity in an area provides evidence only that the area is sufficient for task execution. In contrast, neuroimaging measures of healthy brains tend to provide measures of activity in all or many of the regions involved in a process, though they may not be critical to its execution. In these cases, suitable conjunction or subtraction contrasts of tasks are often used to attempt to isolate processes core to the function of interest. This distinction is important in considering intra-individual variability of lateralisation in adults. While the overall direction of dominance for critical regions of the cortex may be consistent between imaging methods, there may be variability in those areas involved in the process, and to what extent, depending on the specific demands of the task.

The way lateralisation is calculated from neuroimaging data could also lead to observations of differences in lateralisation. For example, in terms of strength or extent of lateralisation, both the Wada and cortical stimulation mapping techniques have tended to discretise cerebral dominance, deeming cortical regions associated with language as either left- or right- dominant. Calculation of relative dominance in the form of lateralisation indices or asymmetry indices has not been a common feature of these types of studies (although some have used an index and applied an arbitrary cut-off to categorise individuals as right or left- lateralised).

Quantifying lateralisation in PET or fMRI requires the comparison of activation in each hemisphere (or ROI within it). This is non-trivial, given that activation depends critically on the thresholding and correction level applied, as well as the extent of region being examined (see Seghier (2008); McGettigan et al. (2012); Peelle (2012) for discussions). However, many studies will often report activation in one or other hemisphere without a direct contrast with the contralateral region, preventing any conclusions about lateralisation being drawn.

Quantifying lateralisation in ERP or EEG studies involves determining the source of the generated electrical currents. This is a nontrivial task given the 'inverse problem', that is, the many possible mappings between generator(s) of the signal and recordings at the scalp (Michel et al., 2004). Nonetheless, attempts to source localise have advanced, and been validated against other methods such as fMRI. Combining the good temporal resolution of EEG recordings with source localization is used to draw inferences about processing differences between the hemispheres. For example, source-derived hemispheric differences in N1 responses to two auditory stimuli presented with varying inter-stimulus time windows, suggesting differential processing mechanisms in left and right auditory regions (Clunies-Ross et al., 2015). Laterality tends to be estimated in EEG studies from the comparison of amplitude magnitudes at electrodes in either hemisphere following source localisation. As with EEG, quantification of lateralisation for MEG data uses source localization to test for hemispheric differences in the number of unit dipoles with activation over a threshold in the ROIs (or magnitude of amplitude) (Tanaka et al., 2013).

The choice of language task will also lead to intra-individual differences in lateralisation. Many studies will determine 'hemispheric dominance for language' using one language task. This is problematic given the lack of correlation between the strength of lateralisation across language tasks, and difficulties in keeping task difficulty consistent and well operationalised across different domains of language processing. Evidence from pre-surgical assessment of language lateralisation shows that considering a battery of language tasks and calculating a composite lateralisation index confers a greater consistency with intraoperative mapping techniques in patients with intractable epilepsy (Gaillard et al., 2004) and improves reproducibility and reliability of lateralisation indices (Ramsey et al., 2001; Rutten et al., 2002; De Guibert et al., 2010; Wilke et al., 2010).

2.2 Language lateralisation in children

2.2.1 Neuroimaging studies of lateralisation in children

During early childhood, gains in language ability are made at remarkable speed (e.g. Gopnik & Meltzoff (1975)), and so it should be borne in mind that the physiological processes supporting language are unlikely to be static. Investigating lateralisation during development is therefore likely to shed light on the factors which constrain the mature adult system.

Sensitivity to the sounds of speech has been reported in young babies, using an orientation method: babies gaze more readily to the sounds of their native language than to non-speech sounds (Vouloumanos & Werker, 2007). The neural systems supporting this skill have been investigated using fMRI in very young sleeping babies. Findings of more extensive activity in left temporal regions including the superior temporal sulcus (STS), planum temporale, temporal pole and angular gyrus in 2-3-month-old babies exposed to speech versus silence suggest that language lateralisation is established very early in life (Dehaene-Lambertz et al., 2002, 2006). Some results indicate that this lateralisation is specific to speech, for example, activity in the left angular gyrus is greater for forward speech than backward speech (Dehaene-Lambertz et al., 2002). Similarly, activity is greater over temporal fNIRS channels for forward speech greater than backward speech (Peña et al., 2003) and native languages greater than non-native languages and other types of non-human vocalisations (Yasuyo et al., 2011). Left-lateralised responses to forward greater than backward speech are also reported for 3 year olds (Eyler et al., 2012). These findings suggest that the neurobiological underpinnings of low-level auditory speech perception are in place very early in life.

These findings have been put forward by some as evidence for a 'continuity between infant and adult systems' (Dehaene-Lambertz et al., 2006), with the implication that language-related hemispheric dominance is innately specified (as suggested in Szaflarski et al. (2006)). However, a mechanism by which left-lateralised speech perception gives rise to left-lateralised speech production (or other, higher order language functions) is not yet evident from the literature. Even language skills overtly related to speech perception, such as comprehension of auditory speech may not show similar patterns of lateralisation to findings with passive listening in babies. It is possible that findings of left-lateralised speech perception in babies are not precursors of, or related to, higher order language comprehension but driven rather by the general auditory processing of complex communicative sounds (evidenced by left-lateralised responses to a variety of human vocalisations as in Lloyd-Fox et al. (2012), or specific only to speech perception and not to other domains of abstract language learning. Put another way, it is possible that leftward dominance for processing the complex sounds of speech is unrelated to the leftward dominance observed in adults across other domains of language. Clearly, there is more to successful mastery of language than perceiving speech sounds.

Beyond passive speech perception, accessing meaning from speech or comprehending single words also appears to show left hemisphere dominance in infants. K. E. Travis et al. (2011) used MEG with 12-18-month-old infants and demonstrated more pronounced 'adult-like' (N400) ERP responses over left hemisphere sites. Contrasting words with signal correlated noise, the authors showed that the N400 was modulated by semantic priming with congruous and incongruous pictures, providing further evidence that the left-lateralised responses are associated with accessing meaning (lexico-semantics) (K. E. Travis et al., 2011). While this study suggests early lexical processing may be left-lateralised, the authors did not directly test for statistical differences between ROIs in each hemisphere, and as such there is the possibility of quantitative differences in lateralisation between infants and adults (i.e. the conclusion of an 'adult-like' lateralisation could be an over-interpretation of the data). Research which focuses on language lateralisation in children has been hampered by the strict movement constraints of most neuroimaging techniques. Consequently, other than research on speech perception with babies and infants, studies have generally taken place with children older than the age of 4 years. In school-aged children, a variety of receptive, expressive, and metalinguistic tasks have been used.

Skills relating to auditory speech processing such as categorical perception (of phonemic versus non-phonemic stimuli) involve more extensive left frontal regions, including left postcentral gyrus, anterior superior temporal gyrus (STG) and superior temporal sulcus (STS), and sub-cortical structures (Conant et al., 2014). Studies of lateralisation for receptive language processing in response to connected speech, (for example, narrative processing) are inconsistent. Some studies suggest bilateral patterns of activity (Booth et al., 1999; Schmithorst et al., 2006; Szaflarski, Altaye, et al., 2012; Sroka et al., 2015) or fewer significantly lateralised participants (Lidzba et al., 2011) while others adopting similar tasks and age ranges find hemisphere effects in posterior temporal areas (e.g. Ahmad et al. (2003)) or for a specific inferior frontal network identified as an independent component (Karunanayaka et al., 2007). Given the more extensive network of regions (and cognitive processes) involved in narrative comprehension, differences in the choice of regions of interest and baselines may contribute more strongly to different patterns of results than when a more constrained language skill is targeted.

In contrast, expressive language and metalinguistic tasks, where they have been attempted with children, show more consistent leftward dominance. Using fMRI, verbal fluency (Holland et al., 2001, 2007; Gaillard et al., 2003; Szaflarski et al., 2006), vowel identification (Everts et al., 2009; Lidzba et al., 2011) and semantic lexical decision (Everts et al., 2009) all show stronger and more extensive activity in left hemisphere perisylvian regions. In the first study of its kind with 3-year-old children, Sowman et al. (2014) used source-localised MEG during picture naming and tested lateralisation across three ROIs. Activity in ROIs centred on inferior frontal, supramarginal gyrus and STG all showed significant left greater than right activity. Similarly, in 3-6-year-old children performing semantic fluency, Paquette et al. (2015) using fNIRS showed a hemisphere by region interaction in changes in oxy-haemoglobin (HbO). These revealed greater changes in concentration of HbO in inferior frontal than temporal channels in the left hemisphere.

The portability and tolerance to movement of fTCD make it a strong candidate for a feasible way to look at brain activity in young children and populations for whom well-established imaging techniques such as fMRI are unsuitable. In light of this, several fTCD studies have contributed to this literature, establishing reliable left lateralisation in young children using expressive language tasks (Lohmann et al., 2005; Stroobant et al., 2011; Bishop et al., 2009; Groen et al., 2012; Haag et al., 2010; Bishop et al., 2014; Hodgson et al., 2016).

In the earliest of these, Lohmann et al. (2005) devised a picture description task designed to elicit language without the tight constraints of verbal fluency. Each trial consisted of a single picture being displayed and a 25s period in which the child could describe it. The resting phase consisted of 30s during which children were asked to close their eyes. The next trial was signalled with a cueing tone. Significant left lateralisation in 13/16 participants between the ages of 2;3 and 9;8, with an average lateralisation index of 3.91% difference between left and right MCAs. Retesting a month later showed that the direction of lateralisation was consistent in all children. Stroobant et al. (2011) used a similar trial set-up with single picture stimuli to elicit story telling about an object in 26 children aged 4;0 – 9;5. The authors found significant left lateralisation in 24 out of 26 children, and an average lateralisation index of 3.45% difference between left and right MCAs. Discrepant results have been reported for picture description however. Haag et al., 2010 used a picture naming task and reported much greater variability in lateralisation than Lohmann et al. (2005) or Stroobant et al. (2011). While 14/23 children showed left-lateralisation, the mean difference in blood flow change was not statistically significant from 0 (0.74%). The authors do not report split-half odd-even reliability or intra-class correlation coefficients so it is difficult to assess the reliability of the data collected in this study compared to other studies. With large variation in Laterality Indices (-9.89 to 11.16) and no behavioural data reported, it is possible that there was a great deal of variability in the children's ability to perform the task.

An alternative paradigm for eliciting connected speech in children is the animation description task developed by Bishop et al. (2009). This differs from previous fTCD task procedures in that the baseline is not a period of inactivity, but requires the child to watch a cartoon silently. In the original study, 4-year-old children showed an average LI of 1.9, with 62% of the children significantly left-lateralised. This was replicated in a different sample of 4-year-olds who had an average LI of 3.0, with 74% showing significant left lateralisation (Bishop et al., 2014).

As has been found using fMRI, fTCD studies of receptive language tasks have shown a lesser degree of left lateralisation and poorer test-retest reliability than production tasks. For example, Stroobant et al. (2011) tested 4 – 10 year olds on both an expressive (storytelling) and receptive (story listening) task. They measured a similar extent of left-lateralisation for the expressive task as other fTCD tasks (2.84% difference between left and right MCAs) but no significant difference at the group level for the receptive task (0.89%). Categorically, 92% of children showed significant left dominance for expressive language, while only 61% did for receptive language. The latter task also showed poorer test-retest reliability (Stroobant et al., 2011). These are in line with fTCD data from adults performing receptive tasks which show reduced (Badcock, Nye, & Bishop, 2012) or no significant lateralisation (Stroobant et al., 2009).

In summary, there is complementary evidence from a number of imaging methods that expressive language tasks show robust left-lateralisation in children with typically developing language. The next section considers whether there are changes in lateralisation during development.

2.2.2 The developmental trajectory of lateralisation

The neural systems involved in language processing undergo global changes and refinement during development (Bonte et al., 2016). In this thesis however, the focus is solely on changes in lateralisation of neural activity through development, either at the whole hemisphere level or within particular regions of interest.

Section 2.2.1 described how babies, infants, and children show left lateralised responses to speech sounds, and that older children show (to varying degrees) left lateralisation for expressive and metalinguistic language processing. However, it is not clear from these separate studies whether the extent of lateralisation changes from early infanthood through childhood and into adulthood and whether this is consistent over different domains of language. Longitudinal or at least cross-sectional studies using the same tasks are required to truly address questions about the development of hemispheric lateralisation.

Differences between newborn and 6-month-old babies in inferior frontal responses to speech sounds have been found using MEG (Imada et al., 2006). The authors suggest this could indicate that language processing activity in regions in the left temporal areas extends to frontal areas in the first 6 months of life, potentially leading to changes in the extent of lateralisation. Forwards speech contrasted with backward speech showed differential effects in 2 and 3-year-old sleeping children (Redcay et al., 2008), though in this study lateralisation was not explicitly tested and additional activity in either hemisphere was region specific. Further evidence for shifts in lateralisation in infants comes from studies which have found group differences in the lateralisation of ERP responses to known and unknown words between 13 and 20 months (Mills et al., 1997, 2006). The authors here report that an initially bilateral distribution of activity becomes more lateralised with age. Aside from these changes in perception in infants, changes are also reported for higher order language tasks in older children.

Several of the studies with older children have used cross-sectional or correlational designs tested whether there are changes in lateralisation during development. The resulting picture is mixed. Some studies have found that lateralisation elicited by a covert verbal fluency task (fMRI: Holland et al. (2001, 2007); MEG: Kadis et al. (2011)) or a vowel detection task (fMRI: Everts et al. (2009)) is not as strong in children as in adults, suggesting some form of consolidation through development. In contrast, Gaillard et al. (2003) and Wood et al. (2004) found no association between age and lateralisation in large groups of children between 7 and 14 years old performing verbal fluency tasks.

In the fTCD literature, Lohmann et al. (2005) did not find a correlation between lateralisation and age. However, the behavioural responses of the children to each picture were not analysed so it is possible that differences in task performance may have obscured any effects of age. Nonetheless, in a more recent study in which behavioural responses were taken into account, Groen et al. (2012) tested children using the animation description task described in section 2.2.1. In a group of 60 typically developing children aged 6 – 16 years old, they found that age was not a significant predictor of the extent or direction of lateralisation. Similarly, in a group of 38 children aged 3 – 10 years, Hodgson et al. (2016) did not find a correlation between the strength of lateralisation and age.

Many of the studies testing developmental changes in lateralisation, using a variety of brain imaging methods, have limitations. First, in many, the youngest participants were 6 years old, by which time much of the steepest gains in language development have been made (Goldfield & Reznick, 1990). Maturationally, the period of potential change in functional lateralisation may have been missed, as many changes in brain metabolism, structure, and functional connectivity occur in the preschool years (Johnson, 2001). In terms of task performance, most 6 to 7-year-olds will be competent and proficient users of their native language(s) and while there will be inevitable variability in proficiency, the types of tasks may not sufficiently test the child's abilities.

A further limitation is that studies have nearly exclusively used cross-sectional or correlational designs. With considerable individual variability in terms of both the extent of lateralisation and language abilities, it is possible that developmental effects could be under- or over-estimated in a correlational design. These studies also often have a small number of children representing each age group which, given individual variability, is likely to provide insufficient power to detect effects of age. Only one of the studies with children is longitudinal in design (Szaflarski et al., 2012). In this study both a verbal fluency and passive story comprehension task showed increases in lateralisation, however, importantly changes in performance were not accounted for (Szaflarski et al., 2006; 2012).

In a recent in depth systematic review of fMRI studies of language lateralisation in development, the authors concluded that evidence for a strong and unified increase in strength of lateralisation through development is not convincing (Weiss-Croft & Baldeweg, 2015). Where small changes were observed, for example increases in leftward lateralisation for phonological decision making in premotor (inferior frontal) regions (Lidzba et al., 2011), the authors suggest such findings are confounded with improved task performance. Indeed, in one such study that identified a correlation between activation around inferior frontal gyrus and age (Holland et al., 2001), the authors suggest that maturational change could be expected globally, and therefore increased proficiency in task-related cognitive and linguistic skills may underlie changes in the strength of lateralisation. In several studies, it is not possible to test this possibility given the lack of online task performance data (e.g. Lohmann et al., 2005; Everts et al., 2009).

While there is good evidence for aspects of language processing in children to be left-lateralised, it does not appear to show a simple developmental trajectory. To consider lateralisation as 'emerging' or strengthening through development is an assumption which has not been adequately addressed given the complexities of lateralisation. The study described in Chapter 9 of this thesis, uses functional TCD to assess potential longitudinal changes in hemispheric dominance. The next section considers evidence that both maturational and experiential factors may affect the development of lateralisation of language.

2.3 Factors affecting the development of lateralisation

2.3.1 Atypical hemispheric dominance in development

Right lateralised or bilateral processing is often referred to as 'atypical' lateralization. Atypical lateralisation has been reported for children and adults with disorders of language and literacy, such as SLI (De Guibert et al., 2011; Whitehouse & Bishop, 2009), dyslexia (Illingworth & Bishop, 2009) and developmental stuttering (L. E. Travis, 1978). This raises the possibility that left-lateralisation may be the hallmark of proficient language. However the directionality of this association is unknown. It is possible that a failure to develop left-lateralised language underlies poor language outcomes. Alternatively, language deficits may lead to the atypical patterns of language organisation in the brain (for example, through altered sensory input or feedback). Delineating the causal relationship between lateralisation and disorders of speech and language is not possible without prospective cohort studies of children at risk for language and literacy disorders. However, to our knowledge, no such studies exist.

Clinical conditions that severely damage or disrupt left hemisphere processing, such as lesions or epilepsy, can offer unique insights into the neural plasticity for language processing (Bates et al., 2001). Children with left temporal lobe epilepsy (Powell et al., 2007; Adcock et al., 2003) or left hemisphere brain tumours or vascular malformations (Fakhri et al., 2013) show significantly more right hemisphere dominance for language than would be expected from the distribution of hemispheric dominance in the general population (Knecht et al., 2001). Importantly, children with early lesions or early onset epilepsy are more likely to show right lateralisation for language than those who are affected by these conditions later in childhood (Springer et al., 1999). These studies highlight the importance of the brain's maturational state (i.e. age) on the reorganisation of language processing in the brain.

However there is not a straightforward link between age, direction of lateralisation, and language proficiency. Good language outcomes are found in the context of both right-hemisphere language dominance (in children with very early left hemisphere lesions), and bilateral language dominance (in children who acquire left hemisphere lesions in later childhood) (Lidzba et al., 2017). Though deficits in language may be subtle or go undetected due to imprecise measurement, it is nonetheless clear that language ability and the direction of lateralisation are not tightly linked, and that the notion of early damage linking to right hemisphere compensation and better recovery may be an oversimplification of the data (Levine et al., 2015). Other factors such as the location of the lesion relative to inferior frontal language regions show a more consistent relationship to right-hemisphere dominance than do clinical observations of language proficiency (Liégeois et al., 2004).

Research from children with epilepsy or those who have sustained damage to the brain gives unique insights into the neural systems supporting language under extreme circumstances. The studies provide evidence for plasticity, the extent of which is modulated by maturation (age). Another way to examine the parameters that influence the development of lateralisation in the healthy brain is to consider a population with atypical sensory experience. In Chapter 10 of this thesis, I will consider the influence of atypical sensory and language experience on lateralisation, the background to which is reviewed in the following section.

2.3.2 The role of sensory input

To what extent does information which the brain encounters during development alter the course of lateralisation? Investigating the role of experience, in particular sensory and language experience, could help bridge the apparent gap between the findings demonstrating very early functional specialisation of left hemisphere regions for speech perception (Dehaene-Lambertz et al., 2002, 2006; Blasi et al., 2011) with the extensive plasticity of lateralisation observed following brain injury or severe epilepsy.

Studies from congenitally blind individuals indicate reduced left lateralisation during language processing in children born blind, driven by increased right hemisphere involvement (Lane et al., 2017). This may be evidence for the importance of visual information in the ontogensis of lateralisation. However, the authors point out that the language input is not permanently altered in the case of blindness. Indeed, any delays in language abilities in blind children are short-lived. An alternative explanation is that extra-linguistic visual information to map vocabulary to concepts is be unavailable during the period of steep language learning in early childhood. Therefore any effects on lateralisation may be driven by the timing of the sensory deprivation. In this case the state of maturation as well as the presence of sensory input may be involved in the development of lateralisation. This could explain why reduced left-lateralisation is observed resolved cases of language disorder (Bishop et al., 2014) and childhood aphasia (Elkana et al., 2011).

Another source of language related sensory input is motor movement associated with language, for example orofacial and upper limb proprioception. If this type of input was involved in the development of typical lateralisation, one would expect atypical language dominance in children with speech disorders. While structural studies of speech apraxia suggest bilateral abnormalities in brain morphology (Liégeois & Morgan, 2012), functional studies of lateralisation in this population are lacking. Limited evidence for sensory input affecting lateralisation of language also comes from individuals with congenital brachial plexus injury who show reduced left-lateralisation correlated to the extent of their right-hand function (Auer et al., 2009).

Language lateralisation has long been linked to auditory sensory input. An early theory on the origins of functional lateralisation suggested that the prenatal environment has an important role (Previc, 1991, 2007). This theory suggested that position of the uterus and placenta in the majority of foetuses causes craniofacial asymmetries and a subsequent right ear advantage for sounds of certain frequencies. Animal studies provide corroborative evidence that prenatal sensory experience relates to later functional lateralisation. For example, chicks with differential exposure to asymmetric light during incubation show different patterns of asymmetries in pecking behaviour (Rogers, 1996). The key point is that prenatal sensory experience could influence hemispheric specialisation.

A related idea is that auditory speech perception plays a role in the development of typical functional lateralisation beyond the prenatal period. One prominent theory suggests that cortical asymmetries in processing temporal properties of speech are (causally) related to a downstream specialisation for language in left hemisphere regions. This hypothesis specifically relates to properties of primary and association auditory areas in posterior superior temporal gyrus (Zatorre, 1989; Zatorre et al., 2002; Efron, 1963). There have since been several accounts of hemispheric asymmetries in auditory speech perception, for example Peelle (2012); McGettigan & Scott (2012); Giraud et al. (2007); Boemio et al. (2005); Poeppel (2003); Brown & Kosslyn (1993). These have been controversial in at least two ways. First, whether or not lateralisation has reliably been observed at different stages of speech perception (e.g. prelexical or lexical). Second, the relative importance of temporal or spectral processes underlying speech perception is debated (Scott & McGettigan, 2013). The details and subtleties of theories of asymmetries in low level auditory speech perception are beyond the scope of this discussion. Rather, it is relevant that none provide mechanistic or developmental accounts of how or why lateralised perceptual processing could cause downstream lateralisation in other regions of the language network. Similarly, theories that posit a deficit in auditory processing in the development of language disorders (Tallal & Piercy, 1975; Tallal, 2004) lack a mechanistic account of how atypical lateralisation of sensory processing causes disorders primarily affecting subprocesses of language other than phonological processing. Perhaps most importantly for the current thesis, the accounts which place a central role for hemispheric asymmetries of speech perception in language lateralisation fail to account for lateralisation for other types of language input. A special case of this, where auditory speech information is unavailable (or less available), is individuals born deaf. This is considered in the following section.

2.3.3 Deafness as a model system

One way to understand the importance of auditory input for lateralisation of language is to consider atypical experience of auditory input. In this way, deafness has provided a model system to look at effects of language experience (MacSweeney, Capek, et al., 2008). There are several different ways in which an individual born deaf may access linguistic information, and the relative weightings of importance of each of these is likely to fluctuate through development and into adulthood. The main channels of language input include signed language, speechreading, and reading (a visual representation of the spoken language). Outputs are by way of sign, speech, and written text. A number of studies of individuals born profoundly deaf, particularly those who are fluent users of a signed language, have provided evidence for the robustness of left lateralisation of language processing. Supporting patient and neuroimaging data are reviewed below.

Relationships between aphasic symptoms and lesion site appear to manifest themselves similarly in users of signed and spoken languages. For example, left frontal lesions have been associated with dysfluent sign production, telegraphic utterances, and paraphasic errors with relatively unimpaired comprehension (Poizner & Tallal, 1987; Hickok et al., 1996). Importantly, these production errors were unlikely to be a result of general motoric problems, given that errors were produced with either hand, i.e. regardless of hemiplegia or minor visuospatial deficits common in patients with left hemisphere lesions (Corina & Blau, 2015). Also, left posterior superior temporal regions classically associated with comprehension deficits in the speech aphasia literature similarly affect deaf signers. In a relatively large group (n=19) of unilaterally damaged American Sign Language (ASL) users, a significant interaction was found between damaged hemisphere and the involvement of the temporal lobe in simple sentence comprehension, such that left hemisphere damaged patients with posterior temporal lobe damage performed significantly more poorly than any other group (Hickok et al., 2002).

As well as similarities in the profiles of left hemisphere damage between speech and sign, right hemisphere damage in signing patients is associated with difficulties in pragmatic language difficulties, for example atypical ordering of events in a story, attention to small details of a story, or difficulties with cohesive conversations (Emmorey et al., 1993; Poizner & Kegl, 1992).

Despite commonalities between lesion-symptom relationships in speech and sign, there are also areas where supporting neural systems diverge. For example, while classic posterior temporal damage has been associated with difficulties in sign comprehension, there also appears to be a role for the left parietal lobe in processing signs. Evidence for this comes from the observation that in many cases the temporal lesions may extend to left parietal lobe including the supramarginal and angular gyri. Indeed, in several patients with profound sign comprehension difficulties, lesions were restricted to this area leaving posterior temporal regions intact (Chiarello et al., 1982; Poizner & Tallal, 1987). More recently, patient studies have also raised the possibility of a critical contribution of the right hemisphere to certain aspects of sign language processing specifically. In locative relationships expressed using classifier constructions, and in the comprehension of the orientation of classifiers to represent spatial relations (Atkinson et al., 2005) and in comprehension of a particular type of negation involving non-manual (facial) features (Atkinson et al., 2004). In a task designed to elicit both lexical and classifier signs in ASL, patients with right hemisphere damage made a significantly greater number of classifier errors than left hemisphere damaged patients (Hickok et al., 2009).

Functional neuroimaging studies with deaf adults using a range of language tasks confirmed a largely leftward bias in processing. During the production of single signs, a left lateralised fronto-temporal network of associated regions is observed, similar to that observed for spoken word production (Petitto et al., 2000; Corina et al., 2003; José-Robertson et al., 2004). A similar pattern is observed whether participants produce 'whispered' signs at the side of their body (Emmorey et al., 2007), overt signs in standard sign space (Corina et al., 2003), or imagined signs (McGuire et al., 1997). These studies report task-related activation in a network of classical language areas focused around the left inferior frontal gyrus, compared to a variety of high and low-level baselines. Importantly left lateralised activity is reported regardless of the hand generating the signs, suggesting that lateralised motoric processes do not drive the observed hemispheric asymmetries (Corina et al., 2003). Instead, these findings are evidence that modality-independent lexical access is associated with activity in the left medial temporal cortex and left inferior frontal gyrus.

Tasks involving sign comprehension have consistently showed posterior temporal activation analogous to that found for speech comprehension (Neville & Bavelier, 1998; Petitto et al., 2000; Capek et al., 2010). To test whether comprehension of BSL and spoken English are similarly lateralised, MacSweeney and colleagues used audio-visual English stimuli compared to videos of BSL sentences, to match as closely as possible the prosodic and visual elements of the stimuli (MacSweeney et al., 2002). The authors reported similar activation patterns for the two sets of stimuli in native users of the respective languages, with greatest activation in bilateral superior temporal regions and inferior prefrontal areas. It seems then that when natural language stimuli that contain similar levels of higher-level prosodic information are used, neural correlates of signed and spoken languages are highly comparable. It is likely that naturalistic language comprehension, regardless of modality, relies on bilaterally distributed areas. This is in line with fMRI data reporting bilateral activation during comprehension of sign language discourse (Newman et al., 2010).

Although there are marked differences in the processing of sensory information linked to the modality of the language being used, there are clear left-lateralised networks engaged when adult signers process signed language. It is therefore possible that some neural systems involved in language processing, and by extension, involved in lateralisation of language processing, are to some extent modality independent. Evidence from deaf adults using signed and spoken languages suggests lateralisation during language processing is not dependent on auditory input and that other forms of linguistic input (speechreading, sign language) are sufficient to initiate left-lateralised language. The logical conclusion of these types of observations are that hemispheric dominance is related to 'linguistic' input rather than auditory speech per se (Corina et al., 1992).

There is some evidence that highlights the complex interaction between linguistic input and maturational changes and how these may impact on language lateralisation. Several studies show differences between early and late deaf learners of sign language (Neville et al., 1997; MacSweeney, Waters, et al., 2008; Mayberry et al., 2011). The first of these showed less lateralised responses in deaf-native signers than deaf signers who learned later in life and attributed this to an increased role for the right hemisphere in native signers (Neville et al, 1997). MacSweeney et al (2008) found that non-native signers engaged left posterior inferior frontal cortex to a greater extent than native signers during rhyme and location judgements on words and signs (MacSweeney et al., 2008). Importantly, task performance and proficiency were accounted for in these analyses, implying that group differences in lateralisation were indeed driven by the different language backgrounds of the participants. While these studies did not explicitly test differences in lateralisation, they highlight the possibility that a complex combination of language input and age of exposure to input are likely to result in measured changes to lateralisation.

So, given adequate linguistic input, left lateralisation for language processing seems to be robust. However, the studies detailed above with deaf individuals almost exclusively recruited fluent adult sign language users so results could be accounted for by a complex combination of maturation and learning, to some extent independent of the form of the signal by which it is delivered. Examining functional lateralisation in children born profoundly deaf could help to disambiguate between effects of exposure to alternate language input and other potential causal factors such as proficiency and maturation. Chapter 10 addresses this question using fTCD to test lateralisation for expressive language in young children born deaf.

2.4 Chapter summary and research questions

The aim of the research in this thesis is to investigate potential contributory factors to left hemispheric dominance for language processing. This will be achieved by using a method that allows us to measure lateralisation in previously understudied populations. Research in young children and those with additional learning needs has been hampered by practical difficulties of the methods such as fMRI and PET. For example, movement restrictions can make it difficult to assess expressive language leading to receptive or subvocal tasks being used. Compliance in younger children for these types of tasks may be difficult to ensure. High costs of fMRI can lead to small, underpowered group sizes. Furthermore, young children may not be sufficiently still leading to high drop out rates (e.g. 42% in Holland et al. (2001)). fMRI is usually unfeasible for multiple testing sessions which has led to a paucity of longitudinal data. Therefore, in the current thesis I will use functional transcranial Doppler sonography which is appropriate for use with children.

Chapter 3

Methodological background

3.1 Transcranial Doppler sonography (TCD)

3.1.1 Basic principles

Transcranial Doppler sonography (TCD) uses ultrasonic waves sent from and received by a transducer probe to measure changes in cerebral blood flow velocity (BFV) through a target artery (Aaslid et al., 1982). Examining an artery using ultrasound is referred to as 'insonation'. The technique relies on the Doppler effect, which was discovered and formalised by the physicist Christian Doppler in 1894. The effect refers to the change in frequency that occurs when wave or oscillation makes contact with a moving object and is backscattered towards the receiver. The change in frequency, or 'shift', of the received wave is proportional to the speed of the moving object. Therefore, if the initial frequency of the wave and subsequent shift are known, the speed of the moving object can be calculated.

One caveat of this approach is that the derivation of BFV velocity depends on the angle of the moving object relative to the transducer. In transcranial Doppler, this 'angle of insonation' is not known. If the angle is not 0°, the speed of the blood will be under- or over-estimated (Martin et al., 1995). For this reason, relative change in blood flow speed is measured, an issue which is discussed in more detail later in this chapter, and in the General Discussion (Part 12).

In the case of TCD, the moving objects are the erythrocytes in the blood stream. A 2MHz ultrasound wave is emitted from the probe in pulses. The same probe acts a receiver for the returning wave and samples it at a rate of 100 measurements per second (100Hz). Pulsed- as opposed to continuous-Doppler allows different depths inside the head to be targeted, giving greater reassurance that the artery of interest is being insonated. During transcranial ultrasound, a frequency of 2 MHz is most often selected because a lower carrier frequency sufficiently reduces the attenuation (energy loss) of ultrasound when it makes contact with tissue or bone. 2 MHz waves allow for successful insonation of arteries through the thinnest parts of the skull with an acceptable signal-noise ratio (Aaslid et al., 1982; Padayachee et al., 1986; Spencer et al., 1990). This frequency is a compromise between improved resolution (higher frequencies) and lower attenuation (lower frequencies) (Alexandrov et al., 2011).

Power, the amount of energy carried by an ultrasound wave can be adjusted to improve signal to noise ratio. However power per cm^2 (intensity) is a key factor in determining safety of ultrasound, as increased intensity is associated with bioeffects such as heating of bone or tissue (Shankar & Pagel, 2011). At the power levels used in fTCD there is a very low risk of heating effects. For working with children, given less attenuation of the ultrasound through thinner skulls, the power required to record from the MCA with reasonable quality is significantly lower than adult levels.

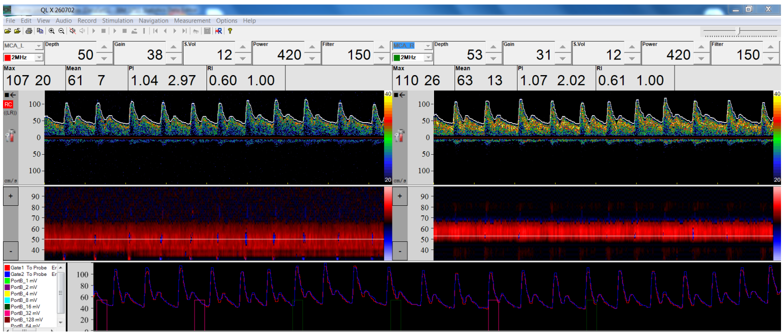
A Thermal Index is calculated and displayed on diagnostic ultrasound devices during monitoring. For TCD, a Thermal Index Cranial (TIC) is used and provides a threshold at which any increase in power may result in heating effects of the insonated bone and tissue. For the commercially available Doppler boxes used in research, a TIC of <1.0 is adopted and the ALARA ('as low as reasonably acceptable') principle is adhered to (British Medical Ultrasound Society, 2010; American Institute of Ultrasound in Medicine, 2011). A recent review suggested that for postnatal scanning these guidelines are conservative (Harris et al., 2016).

TCD is able to measure blood flow velocity in the major cerebral arteries via the transorbital (eye socket), transforaminal (occipital) and transtemporal (at the temples) acoustic windows, where skull thickness is permeable by ultrasound (Kassab et al., 2007). The posterior, anterior, middle, internal carotid, ophthalmic, vertebral, and basilar arteries can be targeted via one or more of these windows.

3.1.2 Visualisation of the TCD signal

To ensure the insonation of the artery of interest, and in turn the correct placement of the probes, a fast Fourier transform (FFT) of the ultrasound signal is displayed to the experimenter (Figure 3.1). Changes in cerebral blood flow are shown for left and right probes. The white line at the top of the blood flow envelope indicates the values recorded by the software for each sample point.

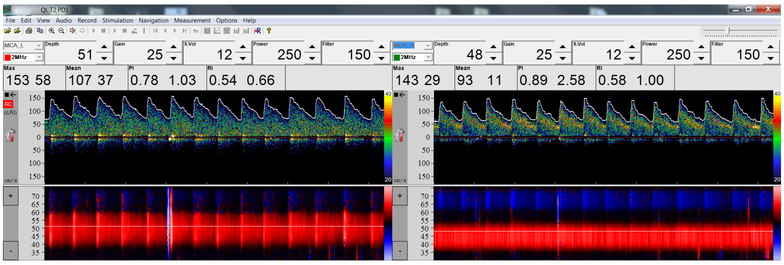
Since the blood flowing is not a single object but cells suspended in fluid,



MCA_L 2MHz
Depth 50
Gain 38
S.Vol 12
Power 420
Filter 150
Max 107 20
Mean 61 7
PI 1.04 2.97
RI 0.60 1.00

MCA_R 2MHz
Depth 53
Gain 31
S.Vol 12
Power 420
Filter 150
Max 110 26
Mean 63 13
PI 1.07 2.02
RI 0.61 1.00

Figure 3.1: Screenshot of QL monitoring software.



MCA_L 2MHz
Depth 51
Gain 25
S.Vol 12
Power 250
Filter 150
Max 153 58
Mean 107 37
PI 0.78 1.03
RI 0.54 0.66

MCA_R 2MHz
Depth 48
Gain 25
S.Vol 12
Power 250
Filter 150
Max 143 29
Mean 93 11
PI 0.89 2.58
RI 0.58 1.00

Figure 3.2: Screenshot of QL monitoring software with m-mode window.

the TCD signal made up of component speeds with different weightings (intensities) (Forster, 1983, in Deppe et al., 2004). 'The FFT decomposes the signal into its constituent parts, providing information about the distribution of speeds at any particular time point. The FFT spectral image shows velocity (cm/s) on the y axis, time on the x axis (sec) and the intensity in colour (higher intensities are shown in yellow, lower are in blue). The intensity reflects the distribution of speeds present at that cross section of artery – so for each speed, we can see what proportion of the blood is flowing at that speed. If we are in the middle of the artery, we expect the highest speeds to be the most prevalent (intense).

In recent years, the display window also contains a power m-mode display thanks to the development of multi-gate power m-mode Doppler (Spencer et al., 1990; Moehring & Spencer, 2002). This allows the display of spectrograms at multiple depths simultaneously, reducing the amount of time taken to identify a temporal window. The m-mode image shows depth at which the blood flow speed is being sampled on the y axis, time on the x axis, and the direction of flow as red (towards the probe) and blue (away from the probe) (see Figure 3.2).

The characteristic appearance of the spectrogram in particular target arteries helps the experimenter determine the optimal signal. Guidelines for expected flow velocities and depth ranges for each of the arteries give the experimenter more tools to help in deciding the optimal placement for the probes (Ringelstein et al., 1990). Recommendations for the steps of identifying key parts of the vessels are also available and provide a good set of landmarks to ensure insonation of the desired artery (Alexandrov et al., 2011).

3.2 Functional TCD

3.2.1 Physiological basis of the fTCD signal

Functional TCD (fTCD) measures changes in cerebral blood flow velocity (BFV) in response to cognitive or sensory tasks. It capitalises on neurovascular coupling, the biological mechanism by which local cerebral blood flow adapts to changing metabolic neuronal activity (Villringer & Dirnagl, 1995; Rosengarten et al., 2012). This is the mechanism thought to underpin task-dependent localised fluctuations in oxygenation levels in the blood measured with fMRI (Kuschinsky, 1991) and fluctuations in blood flow volume measured in PET (Raichle et al., 1976).

The multiple systems supporting regulation of regional blood supply undoubtedly complicate the interpretation of changes in BFV. However, the diameter of larger vessels remains relatively unchanged and so this is unlikely to be the driving factor behind measured differences in flow velocity (Duschek & Schandry, 2003; Giller et al., 1993). Similarly, the influences of blood pressure and heart rate (Kelley et al., 1992; Silvestrini, Troisi, et al., 1994), respiratory rate (Stoll et al., 1999; Sturzenegger et al., 1996) and CO_2 pressure (Kelley et al., 1992; Sturzenegger et al., 1996) are reported to have little impact on the cerebrovascular changes measured by TCD during sensory or cognitive tasks. Therefore, increases in BFV can be interpreted, at least in a large part, to the neural-cognitive activity related to the task. Some additional reassurance is gained by analysing relative differences in BFV between two arteries, given that physiological changes unrelated to the task at hand are unlikely to influence one or other side independently.

For functional TCD, it is usually the transtemporal windows that are targeted. The transducer probes are placed at the temporal window (the thinnest part of the skull, several millimetres above the cheekbone). The Middle Cerebral Arteries, the largest branches of the internal carotid, are targeted for measurement. Measurement from one artery only is uncommon for functional TCD studies because of the unknown probe angle (and hence

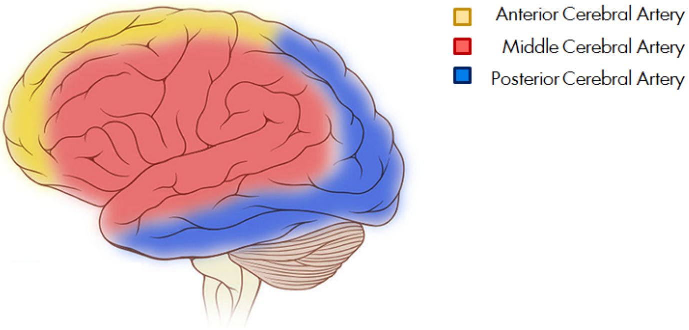


Figure 3.3: Vascular territories of the major cerebral arteries.

possibility of over or under estimating velocity) (Deppe et al., 2004). For example, measuring velocity in the basilar artery through the occipital window would allow only interpretation of the absolute BFV in that artery – this is subject to bias given the unknown angle of insonation of the probe.

Bilateral measurement from the MCAs allows a comparison of BFV change in between left and right hemispheres. For reference, Figure 3.3 shows the approximate areas of cortex supplied by the middle cerebral arteries, indicating areas where neural activity leading to an increase in BFV would be picked up by insonating these arteries. The MCAs serve a much larger area than posterior or anterior cerebral arteries and carry much of the blood required by the cortex (Roach et al., 2010).

3.2.2 Experimental protocol

Paradigms and testing approaches using fTCD to study cerebrovascular responses to cognitive or sensory events have inevitably changed over the past 25 years. However there are some general features of task designs that are worth mentioning here. Several fTCD studies, for example, Silvestrini, Cupini, et al. (1994), Vingerhoets & Stroobant (1999), and Bracco et al. (2011) have contrasted a baseline period of rest with single 'active' periods each 60 – 120s in duration. Mean flow velocity during rest and active periods were compared to test for task-induced changes in blood flow speed. It is now much more common to minimise signal-to-noise ratio by averaging over multiple trials. This approach was standardised by the introduction of AVERAGE software (see below) (Deppe et al., 1997). The vast majority of recent fTCD studies follow 'blocked' designs in which stimuli are presented and/or responses are elicited for approximately 5 – 30s depending on the nature of the task (e.g. auditory naming: 5s, Badcock, Nye, & Bishop (2012);

spatial judgement task: 27.5s, Dorst et al. (2008)). The number of trials varies, but approximately twenty is common.

3.2.3 Data analysis protocol

Several ways of quantifying task-related changes in CBFV have been used, though many of these were based on historical constraints on computing power and have largely been abandoned in favour of the following pipeline, which has remained relatively unchanged since the original software AVERAGE (Deppe et al., 1997), and forms the framework for the widely used dopOSCCI toolbox (Badcock, Holt, et al., 2012). Vadikolias & Tsivgoulis (2011) provide a brief summary of earlier analysis methods.

From the spectral recording, it is possible to save several features of the blood flow, including peak (systolic) and end (diastolic), mean and maximum velocities, as well as any time-locked triggers from stimulus presentation. The maximum velocity 'envelope' (depicted by the white line in Figure 3.1) is exported and used for analyses in most fTCD studies. The first step of data analysis is usually downsampling of the left and right spectral envelopes. The rationale for this step is that 100Hz is an unnecessarily high sampling frequency considering the temporal resolution of the haemodynamic response. The signal then undergoes a simple transformation whereby values within each heart cycle are replaced with the cycle average to form a step-function. Accounting for these systemic fluctuations of BFV due to the heart cycle maximises the likelihood of finding task-related changes in the signal.

Artefact rejection can feasibly occur at any stage of the pipeline, but is usually done after heart cycle integration and before trial segmentation. Thresholds for artefact rejection are chosen heuristically in two ways: trials where the blood flow velocity measured is below or above the mean by more than 30%, and the maximum difference between left and right channels does not exceed 20% of the average flow velocity (Badcock, Holt, et al., 2012).

With this transformed signal, time locked triggers allow the segmentation of the data into trials. Data from left and right channels are normalised either using an average speed of the whole recording or on a trial-by-trial basis for that channel. Each of the trial's blood flow envelopes are also baseline corrected on a trial-by-trial basis to a rest period before stimulus presentation, typically between 4 and 8 seconds.

It is standard practice to obtain a Laterality Index (LI) for each participant. Following Deppe et al., (1997, 2004), the LI is calculated from the baseline corrected CBFV signal. Given that the signal has been normalised, the units are % change from baseline, relative to the average speed of the trial (or the entire session, depending on the chosen normalisation parameters).

The difference curve between right and left channels is given by:

$$\Delta V_i(t) = dV_{i,left}(t) - dV_{i,right}(t) \tag{3.1}$$

This is averaged over the number of trials:

$$\overline{\Delta V}(t) = \frac{1}{N}\sum_{i=1}^{N} \Delta V_i(t) \tag{3.2}$$

The time in seconds at which this averaged difference reaches its maximum provides the value of the 'peak latency' and is denoted here by t_{max}. This is usually restricted to be within a predefined period of interest (POI), in case the maximum difference should fall too 'early' in physiological terms, for example before stimulus presentation.

The LI for a single epoch is given by:

$$LI_i = \frac{1}{t_{int}} \int_{t_{max}-0.5t_{int}}^{t_{max}+0.5t_{int}} \Delta V(t)dt \tag{3.3}$$

,

where t_{int} is the integration window and is usually fixed to 2 seconds (Deppe et al., 2004). The data series are recorded by the DopplerBox at 100 samples per second (Hz). Therefore in real terms the calculation in Formula 3.3 is calculated using the difference between left and right channels averaged by the number of sample points in the integration window.

The overall LI for an individual is calculated as an average over all epochs:

$$LI_{fTCD} = \frac{1}{N}\sum_{i=1}^{N} LI_i \tag{3.4}$$

This LI can be treated as a continuous dependent variable, or used to categorise individuals by direction of lateralisation. This is typically determined using a one sample t-test to test whether the LI value is significantly different from 0 in either direction.

It should be noted that the vascular response to neural activity is orders of seconds longer than this, with a peak in haemodynamic changes thought to be 4-6s after stimulus exposure (Bandettini et al., 1993). For this reason, baselines and periods of interest are often shifted to several seconds after the event marker.

This section aimed to provide an initial overview of the most widely used data processing steps for fTCD. However, normalisation, baseline correction, and calculating a lateralisation index will be discussed in more detail in Chapter 12.

3.3 Methodological issues to consider

3.3.1 Reliability of fTCD for assessing language lateralisation

Section 2.1.2 described the contributions from fTCD studies to the investigation of language lateralisation, and the convergence and divergence of results from different methods of assessing language lateralisation. These types raised issues of validity and inter-method reliability. This section describes studies of the reliability of fTCD. This will include within-test reliability and test-test reliability. Possible sources of measurement error are described.

Several ways of estimating internal (within-test) reliability for fTCD have been used in the literature. The most common is to calculate a Laterality Index for each epoch (though whether this is based on the peak latency from the grand average or the peak latency epoch-by-epoch has not been standardised) and to calculate the correlation or consistency between odd and even epochs, or a selection of random epochs.

Depending on the distribution of the LIs, both parametric and non-parametric correlation coefficients have been used to assess internal reliability. Cronbach's alpha, usually a measure of rater-reliability for continuous data has been calculated as has an intraclass correlation coefficient (ICC). Correlation coefficients such as Pearson's r only test for an association between the odd-even epochs, allowing for systematic differences as long as they are consistent (e.g. odd epochs always 5% higher than even epochs). Cronbach's alpha (or the ICC) can be used to give a more stringent measure of whether odd-even epochs are consistent and similar in their LIs. For Word Generation, the most commonly adopted fTCD paradigm, moderate to good split-half correlation coefficients have been reported from studies with adults ($r = .89$: Bishop et al. (2009), $r = .61$: Whitehouse et al. (2009), Cronbach's alpha = 0.52: Badcock, Nye, & Bishop (2012)). Picture description and animation description tasks have also shown good split-half reliability ($r = .93$ and .91: Bishop et al. (2009)).

Tasks with children have shown promising within-test consistency. For example, Stroobant et al. (2011) compared the first and second half of testing sessions for a story telling and story listening task with school-aged children. They reported ICCs of 0.66 (good) and 0.58 (fair) for these tasks respectively, indicating consistent patterns of lateralisation through the recording session. For an animation description task with children, split-half correlations of $r = .88$ (Bishop et al., 2009) and $r = .80$ (Chilosi et al., 2014) have been reported.

As well as within-session reliability, test-retest reliability has also been estimated for TCD to test whether LIs are consistent at different testing sessions. Absolute CBFV at rest has shown moderate to good reliability (range r = .71 - .95) (Baumgartner et al., 1994; Bay-Hansen et al., 1997; Maeda et al., 1990; Totaro et al., 1992). For functional TCD studies, some have tested reliability of the LI elicited during a task, others whether categorical direction of laterality remains constant from test to test.

In adults, word generation has shown good test-retest reliability ($r = .95$, $p < .001$, with no subjects showing significantly different LIs, regardless of the interval between testing sessions (which ranged from 1 – 14 months). Testing the same subject on 10 consecutive occasions showed small fluctuations in LI that were within the standard error range and hence deemed to be expected stochastic variability (Knecht, Deppe, Ringelstein, et al., 1998). Similarly no trend in lateralisation was found in a separate study repeating word generation over 10 sessions (Lohmann et al., 2004), though decreases in lateralisation were found for fMRI scans of this individual performing the task on ten different occasions. In children, Lohmann et al. (2005) measured test-retest reliability for a picture description task with 16 children, reporting a correlation between LIs from the first and second testing session of r = 0.87, $p < .001$. Only one child showed a significant difference in a paired Wilcoxon test from 1st to 2nd testing session.

3.3.2 Limitations of fTCD

The major limitation of this method is that the resolution (i.e. the territory of the MCAs) is far larger than the scale of possible subtle differences in lateralisation we might expect from the neural systems that support language. fMRI data has shown regional variations in the extent of lateralisation within hemispheres, for example differences between the angular gyrus and ventral precentral gyrus (Seghier et al., 2011). Global measures of laterality will mask these differences. Nonetheless, this criticism also holds for the Wada test which is considered clinically to be the gold standard of establishing hemispheric dominance for language. Furthermore, as a tool for testing special populations and testing task or stimuli specific effects on lateralisation which could warrant further investigation, fTCD remains a viable tool.

A second general limitation is that because the angle of insonation will always be unknown, the only reliable task-induced changes in CBFV will be relative differences between left and right only. It is not viable to interpret absolute CBFV in a single MCA because of its dependence on angle of insonation. In combination with the large territories of the MCAs, the consequence of this is that it is not possible to be certain whether changes in LI are due to fluctuations of blood flow in the left or right hemisphere.

Relatedly, fTCD study designs rely on blocks of activity with multiple stimuli and the need to allow CBFV to return to baseline to prevent an additive effect over time. With this approach to experimental design and analysis, it is not possible to consider the CBFV response to single events.

In terms of using fTCD to examine language lateralisation, there are several areas that warrant further investigation. The number of controlled experimental manipulations that have been attempted with fTCD is small, which leaves some questions about unrelated factors which could influence the fTCD signal measured.

Chapter 4

Outline of the thesis

4.1 Research questions

This thesis focuses on the following areas:

- The developmental trajectory of lateralisation in a longitudinal cohort:
    - Does lateralisation of language processing increase with age in young hearing children?
- Behavioural relevance of lateralisation:
    - Do changes in the strength of lateralisation over time (if any) relate to gains in language proficiency?
- Atypical language input and its effect on lateralisation:
    - What is the effect of impoverished input of spoken English on lateralisation for spoken language?
- Profiles of language lateralisation:
    - Do sub-processes of language show different patterns of lateralisation within participants?
    - What is the relationship between lateralisation for different language tasks?

These primary research questions are, to some extent, dependent on a better understanding of fTCD as a method for measuring lateralisation. Therefore several studies were designed to further our understanding of the physiological TCD measurement in controlled language paradigms. These first studies will not directly inform the broader theoretical questions detailed above. Rather, they focus on refining our understanding of fTCD as a measure of hemispheric dominance. Therefore, these methodological studies are carried out with hearing adults. The specific aims of these first studies are:

- To establish reliability of Laterality Indices (LIs) during paradigms other than verbal phonological fluency
- To investigate the effects of task demands on the TCD signal
- To test whether strength of lateralisation relates to extraneous measures of task performance such as the number of words articulated

These will be addressed in three studies with adults described in Chapters 5 - 7. The first contrasts overt and covert responses in two types of verbal fluency task. The second uses a novel passive judgement task as a way of manipulating task difficulty. The third uses consistent stimuli and rates of presentation and response, differing only in the demands the task places on language-related processes (the need to generate novel tokens).

4.2 General procedure for Chapters 5 - 7

For all studies in the following section, hearing adults were recruited from two participant pools which have a mixture of students and members of the wider community. All adults were tested in a quiet room at the Deafness, Cognition and Language Research Centre. Ethical approval for the studies was granted by the UCL Research Ethics Committee (ID:3612/001). Participants gave written informed consent and were aware they could withdraw at any time. Each session lasted between 45 - 150 minutes.

Participants were seated facing a laptop computer upon which time-locked stimuli were presented using Cogent toolbox (www.vislab.ucl.ac.uk/cogent) (Chapter 5) or Psychtoolbox (Brainard & Vision, 1997; Pelli, 1997; Kleiner et al., 2007) (Chapters 6 and 7) for MATLAB (Mathworks Inc., Sherborn, MA, USA). Triggers were sent from the presentation PC via a parallel port to the Doppler-Box at trial onsets. These were recorded on a separate data acquisition computer with the TCD signal, allowing the analysis of stimuli-related changes in cerebral blood flow.

Chapter 5

The effects of overt articulation and fluency type on lateralisation

This study has been published elsewhere: Gutierrez-Sigut, E., Payne, H., & MacSweeney, M. (2015). Investigating language lateralization during phonological and semantic fluency tasks using functional transcranial Doppler sonography. Laterality: Asymmetries of Body, Brain and Cognition, 20(1), 49-68.

5.1 Introduction

Chapter 2.1 described research which has tested the sensitivity of fTCD to detecting lateralised language functions in adults. It was noted that the 'gold standard' task for use with fTCD is phonological fluency, also referred to in the literature as 'verbal fluency' or 'word generation'. Due to the characteristics of our experimental design in this study, here we use the term phonological fluency.

Fluency is usually performed covertly, that is, participants think of as many words as possible beginning with the target letter. Task adherence is usually assessed in one of two ways: participants either respond with a button press each time they think of a new word (Krach & Hartje, 2006; Stroobant et al., 2009) or are required to verbally report some of the generated words in a later *report* period (see Badcock et al., 2012, Whitehouse & Bishop, 2009).

In the context of the research questions to be addressed in this thesis, the use of this task raises some concerns. Producing a consistent flow of words may also be problematic for young children. Typical verbal fluency is also an unsuitable assessment of English language for deaf children who may have poor expressive phonological skills in the context of good English comprehension speech reading skills, for example. Additionally, phonological fluency alone is unlikely to give a full picture of language lateralisation, since language is not a monolithic skill but made up of many component skills, as has become increasingly clear from fMRI studies using batteries of language tasks to assess lateralization (Wilke et al., 2006; Niskanen et al., 2012). Here we examine the potential benefits of using an overt word generation task and examine the use of a fluency task in a domain other than phonology: semantics.

Covert versus overt tasks

The predominance of covert tasks in the fTCD literature has largely been driven by the wish to minimise movement artefacts in the TCD signal (e.g. Knecht et al., 1996; Stroobant et al., 2009). However, covert fluency is not ideal for use with children, given that there is no online measure of task compliance. One possibility is to ask participants to whisper their response (Vingerhoets & Stroobant, 1999; Lust et al., 2011), however even this may be difficult for young children. The desire to use fTCD with children has already led to the development of overt production tasks which show good within task reliability (e.g. Bishop et al., 2009; Lohmann et al., 2005). Bishop et al. (2009), asked right handed adults and children to overtly describe pictures and video animations. They reported left hemisphere lateralisation during these tasks, and good task reliability using split half correlations, suggesting that lateralisation can indeed be evaluated with fTCD using tasks that require overt speech.

However, no previous study, to our knowledge, has directly compared strength of lateralisation when the same task is performed covertly versus overtly. In the current study we directly compare covert and overt word generation during word fluency tasks (phonological and semantic). This allows us to directly evaluate the impact of overt versus covert speech production on hemispheric lateralisation. Bilateral (primary) motor cortices are necessarily involved in overt, more than covert, speech production (Price, 2010; Palmer et al., 2001). One possibility therefore is that we will find covert speech is more strongly left lateralised than overt speech, measured using fTCD.

Overt speech production tasks are not only easier than covert tasks for children and special populations, they also permit a more reliable assessment of the relationship between task performance and strength of lateralisation. Studies to date that have used covert production have either not reported correlations between lateralisation indices and number of words generated (e.g. Deppe et al., 2000) or have reported non-significant correlations (Knecht et al., 2000; Krach & Hartje, 2006; Stroobant et al., 2009; Lust et al., 2011). One possibility is that the lack of such a correlation is, at least in part, due to the indirect measure of the number of words produced during the covert period. This is either assessed at the same time as covert generation, by requesting a button press to represent the generation of a new word (Stroobant et al., 2009), or by the number of words reported at the end of the silent generation period (Knecht et al., 1996; Deppe et al., 2000; Badcock et al., 2012). Lust and colleagues (2011) did use an overt version of task which permitted a direct measure of the amount of words generated, however the participants in that study were given fluency instructions from the Controlled Oral Word Association Test (Ruff et al., 1996) which does not permit repetitions, proper nouns or numbers as responses. Under these conditions, participants only produced a mean of five words in a response window of 20 seconds. We adopted a more lenient approach to scoring output in the current study, which we argue more accurately reflects the natural fluency of participants.

By measuring lateralisation as well as the behavioural responses during overt word generation, we will test the hypothesis that there is a positive correlation between the number of items produced and the strength of hemispheric lateralization during a word generation task.

Phonological versus semantic tasks

While lateralisation for expressive phonological tasks has been confirmed by these early studies, it is less clear whether fTCD gives reliable results for other domains of language. The literature suggests that tasks that tax phonological skills such as rhyme generation (Krach & Hartje, 2006) and the gold standard phonological fluency task (Knecht et al., 1998, 2000) appear to drive left hemisphere lateralisation more than phonologically less demanding language tasks.

Studies that have assessed semantic processing have adopted more receptive measures as opposed to the production tasks typically used to assess phonological processing (Rihs et al., 1995; Vingerhoets & Stroobant, 1999; Buchinger et al., 2000; Stroobant et al., 2009). These semantic tasks have included listening to a short passage and answering multiple choice questions, listening to a word definition and generating the target word (Badcock et al., 2012) and semantic decision (Stroobant et al., 2009). Because of the conflation of production type and language task (phonological tasks being expressive and semantic tasks being receptive) the contribution of language task to the observed lateralisation is difficult to estimate. Here we avoid this confound between language domain and language task, by using a word fluency task to assess both phonological and semantic processing.

Summary

In this study we compare lateralisation in phonological and semantic fluency tasks during overt and covert speech production. It is predicted that the overt conditions will elicit a greater number of rejected trials due to movement artefacts. We predict left lateralisation at a group level in all tasks, in line with previous fTCD literature discussed above.

We test the hypothesis that the strength of lateralisation index, as measured by fTCD, is modulated by whether covert or overt production is required. If overt speech production is largely driven by activation in bilateral motor cortices, then we would observe a lower laterality index during overt than covert speech. Second, we test the hypothesis that there is a positive relationship between strength of laterality index and the number of words produced. The inclusion of an overt speech condition allows a more accurate assessment of this potential relationship, since both are direct measures which are taken concurrently. Finally, contrasting phonological and semantic fluency tasks allows us to examine the strength of hemispheric dominance across different language domains. Based on previous studies, we predict a stronger lateralisation index for phonological than semantic fluency.

5.2 Method

General design and procedure

We used a 2 (production type: covert vs. overt) x 2 (language task: phonological vs. semantic) design. The resulting four conditions were presented in separate blocks, the order of which was counterbalanced across participants: phonological-covert, phonological-overt, semantic-covert and semantic-overt.

Covert blocks: The covert condition of this task was based on the standard fTCD word generation paradigm (e.g. Knecht et al., 2000). Each trial began with a three second preparation period during which 'clear your mind' was displayed on the screen and participants were instructed to focus on the screen (Figure 5.1 shows a scheme for the trials). The cue, either a single letter or a semantic category, was then displayed for 12 seconds. Participants were asked to silently generate as many words as possible beginning with the letter/belonging to the category displayed on the screen. To ensure compliance with the task, at the end of the covert phase participants were asked to overtly report as many of the words they had generated as possible. This period lasted for five seconds, as in previous studies. Then 'relax' appeared on the screen for 10 seconds.

Overt blocks: The overt blocks proceeded in exactly the same way as the covert ones, except that the participants reported the words aloud as soon as the stimulus had been presented (see Figure 5.1). In this case, the stimulus was displayed for 17 seconds.

Participants' responses were recorded and transcribed for scoring offline. In the phonological conditions, items were considered incorrect if they were phonologically incorrect. Orthographic errors (e.g. psychology for /s/ were allowed). In the semantic conditions, items which were in any way linked to the category were allowed. However, describing phrases, for example *'good for you'* in response to the target *'vegetables'* were disallowed.

Participants

Twenty-nine adults (13 male) took part in the study. All were native English speakers and reported being right handed, which was confirmed using an adapted Edinburgh Handedness Inventory (Oldfield, 1971). Three participants were excluded due to difficulties in locating a signal. There were 26 remaining participants (12 male) ranging from 19 - 46 years old (mean 27.2 years).

Materials

Phonological task

Ten letters were chosen (A, B, C, F, H, M, O, S, T, W) and repeated, resulting in 20 trials which were presented one at a time in a pseudo-randomised order. The overt condition proceeded in the same way, except that the participants immediately reported the words aloud once the stimulus had been presented. In this case, the letter was presented for 17s and they generated for this period. In the analysis, only the first 15 seconds were counted, as for the covert condition.

Semantic task

For the semantic trials, participants were instead presented with a semantic category and asked to name as many things that belong to that category as possible. The 10 categories were Farm Animals, Zoo Animals, Vegetables, Fruits, Drinks, Colours, Sports, Pets, Tools and Transport. These were each repeated to give a total of 20 trials which were presented one at a time in a pseudo-randomised order. Once again, the overt condition proceeded in the same way, but with participants generating words as soon as the stimulus was presented.

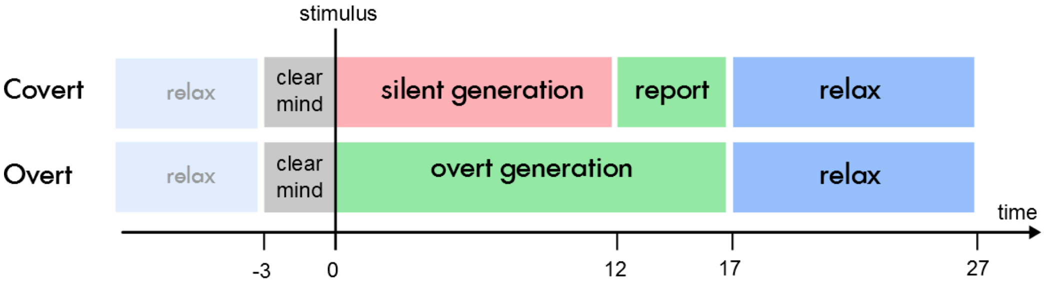


Figure 5.1: Scheme for trial timings of phonological and semantic fluency tasks.

Data Analysis

Blood flow changes were analysed using dopOSCCI, a toolbox custom built to analyse fTCD group data (Badcock et al., 2012). See Chapter 3 for further details of the data analysis steps. Epochs with values less than 60% or greater than 120% of the average CBFV were excluded from analyses. Epochs were segmented from -8 to 22s relative to stimulus presentation. All data points were baseline corrected by subtracting the CBFV during a period of inactivity -8 to -4s prior to stimulus onset. The period of interest (POI) was set from 4 to 14 seconds post stimulus onset. To ensure that blood flow for the baseline period was always calculated from resting level, the first trial of the block was not included in analyses. This resulted in 19 analysed trials per block. Laterality Indices (LIs) were calculated for each participant separately, for each of the four conditions.

5.3 Results

Data quality

In order to investigate whether overt speech led to more artefacts during recording, we analysed the number of epochs remaining for each participant after artifact rejection. A repeated measures ANOVA revealed a significant effect of production type on the number of epochs accepted ($F(1, 25) = 6.8$, $MSE = 6.67$, $p = .015$, $\eta_p^2 = .215$)) with a fewer number of epochs accepted in the overt than covert conditions (mean across fluency tasks: 14.4 (overt) versus 15.8 (covert).There was no main effect of language task ($F<1$), and no significant interaction ($F< 1$).

Participants with fewer than eight usable epochs in any condition (based on artifact rejection parameters described in section 5.2) were excluded from further analyses. Four participants were excluded on this basis. Half of these exclusions were due to artefacts in overt conditions and half due to artefacts in covert conditions. Therefore 22 participants were included in the rest of the analyses.

In order to assess the reliability of the fTCD data we conducted split half reliability analyses. Odd and even epochs were correlated for the semantic overt (r = .61, p = .003) and semantic covert condition (r = .42, p = .05). However, although the trend was in the same direction, the relationship did not reach significance for the phonological covert (r = .38, p = .08) or phonological overt (r = .32, p = .14) conditions.

Behavioural

Table 5.1 shows the average number of words produced for each trial in each condition. A repeated measures ANOVA revealed a main effect of production type (F(1, 21) = 217.6, MSE = 1.60, $p < .001$, $\eta_p^2 = .91$), with more words produced during the overt than covert task. This is expected, given the difference in response time windows between conditions.

A main effect of language task was also observed (F(1, 21) = 12.3, MSE = .98, $p < .001$, $\eta_p^2 = .3$, with more words produced during the semantic than phonological task (mean 7.4 versus 6.7 words per trial). The interaction was non significant (F<1).

Condition	Mean (SD)	Range
Phonological Covert	4.6 (.9)	3 - 8
Semantic Covert	5.3 (1.0)	4 - 8
Phonological Overt	8.5 (1.9)	5 - 13
Semantic Overt	9.3 (2.3)	3 - 13

Table 5.1: Mean number of words produced per trial in each condition

fTCD Laterality Indices

In all conditions, group averaged LIs were positive. In addition, one-sample t-tests showed that each of the four conditions were significantly different to zero and can be considered left lateralised at a group level (See Table 5.2 and Figure 5.2). Table 5.2 shows the number of participants who showed low laterality (not significantly different to zero) or were right lateralised (negative LI, significantly different to zero) in each condition. This variability is also displayed in Figure 5.2. Six participants had a negative LI in one or more of the four conditions. Detailed visual inspection of individual trials from all six participants did not show more artefacts or signal noise for them than for other participants. Section 5.4 discusses these participants in more detail.

			Categories		
Production	Task	LI (SD)	# left	# right	# low
Covert	Phonological	3.6 (1.6)	23 (88.4%)	0	3 (11.5%)
	Semantic	3.3 (1.5)	23 (88.5%)	0	3 (11.5%)
Overt	Phonological	3.2 (2.4)	20 (76.9%)	1 (3.9%)	5 (19.2%)
	Semantic	2.7 (2.2)	22 (84.6%)	1 (3.9%)	3 (11.5%)

Table 5.2: Descriptives of Laterality Indices and number of participants categorized as left, right, or low lateralised

A repeated measures ANOVA showed no differences in LI strength between conditions. The main effects of production type [F (1, 21) = .48, MSE = 6.37, $p > .1$, η_p^2 =.022] and language task [F (1, 21) = 2.85, MSE = 1.52, $p > .1$, η_p^2 = .092] as well as the interaction [F < 1,η_p^2 =.028] were not significant.

Correlations

Given the difference in the response time-window between overt and covert trials, correlations between the number of words generated and LI during each condition were examined separately. For covert generation there was no significant correlation between LI and the number of words produced in the phonological (r = -.08, p>.1) or in the semantic condition (r = -.11, $p >$ .1). However, there was a significant correlation between strength of LI and the number of words produced in the overt phonological condition (r = .64, p = .001), yet the correlation between words produced and LI in the overt semantic condition just failed to reach significance (r = .40, p = .06). See Figure 5.3.

In order to avoid distortion of the correlations from participants that demonstrated 'atypical' language lateralisation (Cai, Van der Haegen, & Brysbaert, 2013; Illingworth and Bishop, 2009; Whitehouse and Bishop, 2008), participants that had LI values lower than 0, and therefore a right hemisphere bias, in any of the conditions were excluded from the analyses. After excluding these four participants a similar pattern of relationships was observed. There was no significant correlation between the LI and the number of words produced for the covert phonological condition (r = -.08, $p >$ .1) whilst semantic covert now reached significance (r = .51, p = .05). For

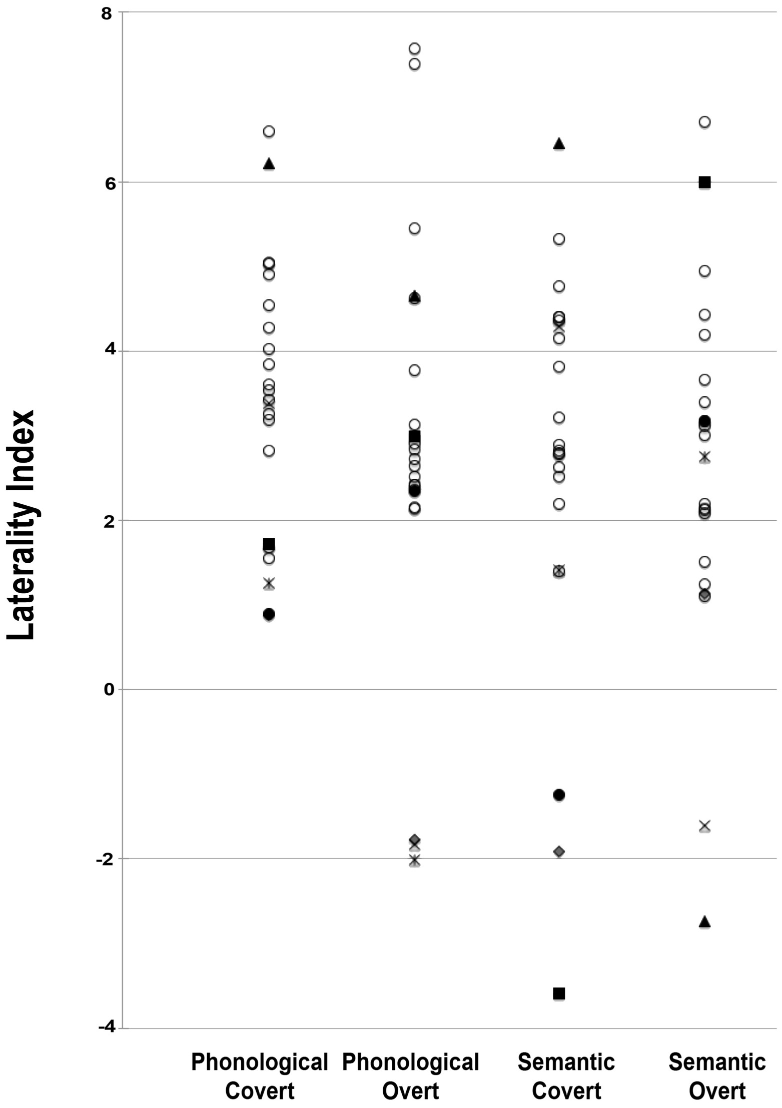


Figure 5.2: LI scatterplots for each condition. The LIs for atypical individuals in any of the four conditions are shape coded. Each shape consistently represents a participant across all conditions.

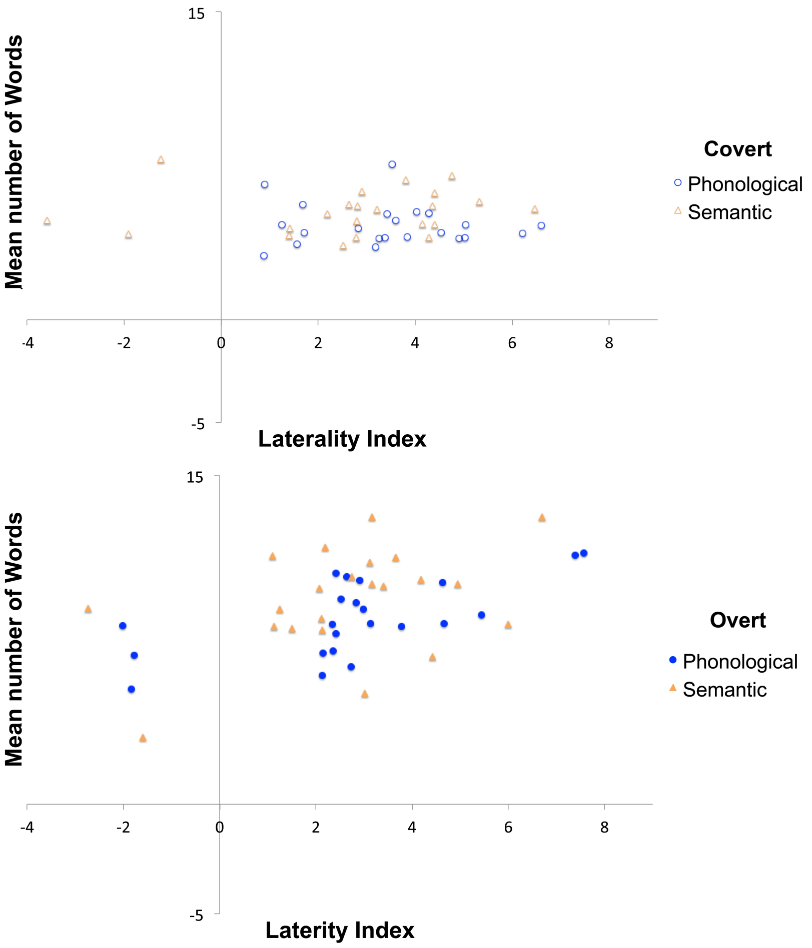


Figure 5.3: The relationship between number of words and laterality indices in covert (top panel) and overt (bottom panel) conditions

the overt conditions, there was a positive correlation between the LI and the number of words produced in the phonological condition ($r = .61$, $p = .01$) but not in the semantic condition ($r = .23$, $p > .1$).

Correlations between the mean LI for each of the four conditions showed that LIs for the language tasks (phonological and semantic) were correlated for the covert ($r = .77$, $p<.001$) and the overt ($r = .43$, $p = .05$) tasks.

5.4 Discussion

We examined lateralisation of processing across two fluency tasks using fTCD. Our design allowed us to examine the influence of overt versus covert speech production and phonological versus semantic processing on the strength of the TCD signal. These two factors have been confounded in many previous studies, which have often used production tasks to examine phonological processing and comprehension tasks to examine semantic processing.

The mean LI for all four conditions was positive, reflecting left lateralisation of the task at a group level. In addition, the majority of individual participants were categorised as left lateralised in each condition. The strength of LI was not influenced by the type of production or task. Nor was there an interaction between the two factors. Nevertheless, these null findings, in combination with additional correlational analyses, lead us to some important conclusions regarding the usefulness and sensitivity of TCD as a research tool.

Covert versus overt generation

A greater overall number of epochs were rejected from the overt than the covert conditions. However, importantly, when applying an inclusion criteria of eight or more usable epochs in each condition, the same number of participants were rejected from overt and covert conditions. This suggests, at least with the period of interest that we selected in these analyses, that sufficient trials of good quality data can be collected when overt speech is required. In addition, we found that covert and overt word generation did not differ in terms of strength of LI and a similar number of participants were categorized as left lateralised during each mode of production (80% in both covert and overt conditions). Thus, our findings contribute to the increasing body of studies that have validated the use of overt speech production tasks to measure language lateralisation using fTCD.

Our findings further previous studies by directly contrasting overt and covert speech production during the performance of the same language task.

fMRI studies have demonstrated that although there is extensive activation of bilateral motor regions during overt speech production (e.g. Price, 2012; Riecker et al., 2005), nonetheless prefrontal cortex activation is typically left lateralised (Riecker et al., 2005; Terumitsu et al., 2006). Our finding of no difference in strength of LI between overt and covert conditions supports the suggestion that the blood velocity changes, as measured by fTCD, are driven predominantly by pre-motor processes.

Also in line with previous studies, we found no correlation between number of words generated in the report phase of the covert trials and the strength of LI, measured during the covert generation period (Badcock, Nye, & Bishop, 2012; Knecht et al., 2001; Stroobant et al., 2009). The lack of correlation between these non-contemporaneous measures is most likely due to a ceiling effect on the number of items that can be reported within the short time window. We argue this based on one of our novel findings from the current study: that of a positive correlation between the number of words generated in the phonological overt trials and the strength of LI. Accounting for this relationship in terms of greater primary motor demands alone seems unlikely, given that there are no overall differences in LI between overt and covert trials. Rather it is more likely that this relationship reflects the increasing demands on pre-motor cortex as more words are generated. The role of language domain in this pattern will now be considered.

Phonological versus semantic processing

The overall strength of LI did not differ between phonological and semantic word generation. This lack of difference in LI could be related to the fact that here phonological and semantic processing were tested using production tasks. Previous fTCD studies have typically confounded the use of receptive versus production tasks with linguistic domain. Our null finding emphasises the fact that task requirements should be considered when contrasting tasks across language domains. Even though there were no significant differences in LIs between phonological and semantic tasks, as with the overt/covert speech contrast, correlations suggested subtle differences between the two language domains, despite very similar task requirements. In accordance with previous behavioural studies, participants produced more words during the semantic than phonological fluency task (Crowe, 1998; Hurks et al., 2006; Monsch et al., 1994). However, the correlation between number of words produced and strength of LI was only significant in the phonological and not the semantic condition. One possible interpretation of this is that phonological search is more dependent on pre-motor processes, measured by fTCD, than semantic search.

Atypical lateralisation

There are two main possible reasons for apparent switching of lateralisation between conditions in six of the participants. The first possibility is that one or more of the measurements was unreliable. In two participants, the LIs were not significantly lateralised, therefore variability or inconsistency in their lateralisation throughout the task is a likely cause. In the four remaining cases where participants were categorised as significantly lateralised in opposite directions, measurement error is unlikely (given also that probe placement and testing sessions were not flagged as cause for concern in terms of data quality). It is possible that during overt production the participant recruits different strategies to complete the task, for example additional non-linguistic processes such as task monitoring (they may be more aware of not wanting to repeat items if aloud). Alternatively, more right-lateralised linguistic processes such as varying prosody or intonation during overt production might also lead to this pattern.

In cases where mixed/crossed laterality is observed across different language tasks, we do not currently have good estimates of an individual's reliability other than the artefact rejection procedures described previously. Split-half reliability will not help interpret the data from these individuals, because split-half reliability is calculated for the whole task, using LIs calculated from average odd versus average even cerebral blood flow changes. To calculate an individual's odd-even reliability would require applying the peak latency retrospectively to individual epochs, regardless of where in the epoch the maximum difference fell. Future considerations of sensible estimates of individual reliability, perhaps without the need for applying LI calculations, would be valuable.

Summary

In summary, we found no differences in strength of LI between overt and covert word generation measured using fTCD. This suggests that during the current test conditions, the fTCD signal was not greatly influenced by motor processes, but was most likely driven by pre-motor activity as well as linguistic and cognitive processes. Our data demonstrate that *overt* word generation can be successfully used to assess language lateralisation using fTCD. We have shown that accurate measurement of the behavioral response allows correlational analyses that may provide a more complete picture of fTCD signal change than simply considering effects of task manipulations in the absence of individual differences in behaviour.

Chapter 6

The effect of task demands on lateralisation

This study has been published elsewhere: Payne, H., Gutierrez-Sigut, E., Subik, J., Woll, B., & MacSweeney, M. (2015). Stimulus rate increases lateralisation in linguistic and non-linguistic tasks measured by functional transcranial Doppler sonography. Neuropsychologia, 72, 59-69.

6.1 Introduction

To date, the primary experimental tasks used with fTCD to investigate language lateralisation have involved internally generated words. For example, with adults, verbal fluency tasks have been used as in Deppe et al. (2000) and Knecht, Deppe, Ebner, et al. (1998). With children, sentence generation has been used, in the form of picture or video description (Lohmann et al., 2005; Bishop et al., 2009; Haag et al., 2010; Groen et al., 2012; Chilosi et al., 2014). These studies converge with findings from other neuroimaging modalities indicating a robust leftward asymmetry in functional responses in language production. In order to maximise the contribution of fTCD to the field, and to further our understanding of developmental changes in language lateralisation it would be beneficial to take a multidimensional approach to language (as per Bishop, 2013) by examining language lateralisation across a range of different language skills and not only during generation of novel material.

During free generation tasks such as verbal fluency, participants are required to think of or articulate as many words as possible; leading to considerable inter- and intra-individual variability in the amount of subvocally generated or overtly articulated words. We speculate that this variability contributes to individual differences in the degree of lateralisation that is measured. Data from Chapter 5, which investigated lateralisation during overt and covert fluency in adults, suggests this may be the case. Strength of lateralisation was positively correlated with the number of words produced; suggesting a relationship between the signal measured using fTCD and the premotor requirements of the task.

Our primary question in the current study was whether language lateralisation could be robustly measured using fTCD during a metalinguistic judgement task, which permits a level of control of the amount of articulatory planning required. To achieve this we used a written word rhyme judgement task, which does not require mental generation of novel items, but, we reasoned, still sufficiently engages articulatory planning processes. During rhyme judgement of orthographically dissimilar word pairs, participants must sub-vocally rehearse items in order to correctly complete the task. The choice of a rhyme judgement task was also motivated by fMRI studies reporting peaks in activation during rhyme judgement in left posterior mid and inferior prefrontal gyri (Booth et al., 2002; Kareken, Lowe, & Chen, 2000; Lurito, Kareken, Lowe, Chen, & Mathews, 2000; Paulesu et al., 1993; Xu et al., 2001). These are regions perfused by the middle cerebral artery (MCA), from which measurements are made using fTCD.

A second aim of the study was to examine how ‘linguistic’ and ‘non-linguistic’ tasks affect the fTCD signal within participants. Previous studies have also examined this, with the aim of testing the nature of the relationship between hemispheric specialisation across cognitive domains. It is interesting that these studies used the standard word generation task as the ‘linguistic’ task and either a visual memory (Lust et al., 2011; Whitehouse & Bishop, 2009), spatial orientation (Dorst et al., 2008) or a line bisection task (Flöel et al., 2005; Badzakova-Trajkov et al., 2010; Rosch et al., 2012) as the ‘non-linguistic’ task. Whilst this approach has made important contributions to the field, it presupposes that the tasks being used are equally representative exemplars of a whole cognitive domain i.e. verbal or visuo-spatial (here we use linguistic and non-linguistic for consistency). An alternative view is that these linguistic and non-linguistic tasks have very different processing and output demands. For example, differences in the format of visual stimuli (e.g. videos versus single letters) may influence lateralisation of neural activity to a greater extent than the domain being targeted (linguistic or non-linguistic).

Here, we examine the variability of hemispheric lateralisation for linguistic and non-linguistic processing, using paced judgement tasks which are well matched in terms of task demands: rhyme judgement in response to written word pairs and line similarity judgement in response to visual line arrays. Again, the choice of non-linguistic task was informed by the fMRI literature.

Kareken et al. (2000) asked participants to make same/different judgements to line arrays in addition to rhyme judgements to orthographically dissimilar rhyme pairs. They reported greater left than right hemisphere activation for the rhyme task. In the line judgement task, they reported strongly right lateralised activation over a large proportion of the posterior parietal lobe, and a distinct area in the right posterior middle temporal gyrus, an area supplied by the MCA.

One benefit of using externally paced judgement tasks is that it allows the direct manipulation of task demands via the number of stimuli presented. The final aim of the study was to characterise the influence of task demands on language lateralisation. Though 'task demands' can refer to a variety of different factors, in the current study we address one specific element, that of pace, by increasing the number of judgements to be made during the active period. We predict that increasing the pace of judgements required will lead to increased strength of lateralisation. During the rhyme judgement task, two factors are hypothesized to drive this increase – the greater number of words to subvocally articulate (placing higher demands on premotor processes) and the increased cognitive effort of completing the task at a faster pace.

Previous studies that have examined the relationship between the number of words articulated and strength of LI have typically reported low or non-significant correlations (e.g. Knecht et al., 2000). However, in these studies the amount produced has been inferred from the overt report period following covert generation. In contrast, we have shown that the amount of material generated and strength of LI do correlate positively when concurrent measures are taken during an overt word generation task (Gutierrez-Sigut, Daws, et al., 2015).

Studies that have manipulated cognitive effort have done so via the familiarity of the stimulus, with no control over the output. For example, Dräger and colleagues conducted covert word retrieval tasks with fMRI (Dräger et al., 2004) and fTCD (Dräger & Knecht, 2002). Difficulty was manipulated by presenting word stems of high and low frequency and instructing participants to covertly retrieve legal words using the target stems. There were no differences in the strength of lateralisation between high and low frequency stimuli, either in the fMRI or fTCD data. Using a similar approach, Badcock, Nye, & Bishop (2012) manipulated task difficulty using letters of greater or lesser frequency in a covert word generation task. They reported no differences in lateralisation between difficulty levels. Here task difficulty was categorised into low, medium, and high productivity letters, based on the average number of reported words after the active period. As suggested above however, this method is a somewhat indirect measure of amount produced during the covert period, and therefore also of difficulty.

Here we predict that an increase in the rate of presentation will lead to an increase in the strength of left lateralisation during the rhyme judgement task, due to the combined factors of a greater number of words to subvocally rehearse and increased task difficulty. By testing the effect of pace on a non-linguistic task, we go some way to tease apart these factors. A finding of stronger lateralisation in fast paced conditions for both rhyme and line tasks implies task difficulty associated with increased pace, rather than articulatory planning demands being the sole driver of the strength of lateralisation.

In summary, in Experiment 1 we tested whether left and right lateralisation can be established using fTCD during rhyme and line array judgement tasks which were well matched in their demands. In Experiment 2 we sought to determine the effect of pace on lateralisation for linguistic and non-linguistic tasks, by manipulating the number of stimuli presented during a trial.

6.2 Experiment 1

6.2.1 Method

Participants

A total of 38 right-handed participants were recruited for Experiment 1. All participants were monolingual native speakers of British English. No participants reported a history of neurological disorders or language related problems. Participants were all right handed as assessed by an abridged version of the Edinburgh Handedness Inventory (Oldfield, 1971). To screen for reading difficulties, which are associated with impaired metalinguistic abilities (Wimmer et al., 1994), reading comprehension was assessed using the Kirklees Reading Assessment (Vernon-Warden revised, Hedderly, 1993).

Data from several participants were excluded because of inability to find a signal or poor signal quality (6 cases), low reading comprehension scores (greater than 2 SD below the group average; 2 cases), and/or low accuracy on the experimental tasks (scores lower than 2 SD below the group mean (<83% on rhyme or <81% on line; 2 cases). Therefore data from 28 (11 male) participants were included in the study. The average age of participants was 26.2 years (SD = 6.4; range: 18.60 – 49.56). The average reading score was 34.66 (SD = 3.48; range 27 – 40; maximum possible score = 42), which corresponds to a mean reading level categorised as ‘adult’ on the test used (range: 16 years - >23yrs). Of the 28 participants, 21 were students at UCL and 7 were from the local community. These participants did not differ in

Rhyming	Non-rhyming
cry–high	bed–knee
fate–weight	bomb–foam
toes–blows	broad–wood

Table 6.1: Examples of rhyme judgement stimuli

age (t(7.17) = 1.6, p = .15) or reading score (t(8.53) = .25, p = .80 (analyses adjusted for unequal variances using Welch-Satterthwaite adjusted t-tests).

Stimuli

Rhyme judgement stimuli were 180 words presented in 90 word pairs (based on those in MacSweeney, Goswami, & Neville, 2013). Half of the word pairs rhymed and half did not (see Table 6.1 for examples). All words were monosyllables and had a single coda. To ensure that the rhyme decision could not be made on the basis of spelling similarity (orthography) of the items in a pair, the orthographic similarity of word pairs was measured using the metric of Davis (2010; http://www.pc.rhul.ac.uk/staff/c.davis/Utilities/MatchCalc). This metric takes into account letter position to estimate the overall orthographic similarity between two words: 0 indicates no overlap and 1 indicates identical letter strings. The mean overlap values were: rhyming word pairs = .34 (SD = .13), non-rhyming word pairs = .33 (SD = .13). There was no significant difference between word sets (t(88) = 0.65, p = .94, cohen's d = 0.01). On average, the rhyming and non-rhyming sets were also matched on number of letters, number of phonemes, frequency (Francis & Kucera, 1982), and, where data were available from the MRC database (Coltheart, 1981) on number of orthographic neighbours, familiarity, concreteness and imageability (all p's > .1).

Line judgement stimuli were 180 line sets presented in 90 pairs, one item above the other (see Figure 6.1). Line sets comprised a series of 3 to 6 vertical and angled lines. The number of lines in each array was matched to the number of letters in the rhyming words. Half of the line array pairs were identical and half were dissimilar by one or two line orientations. Line sets were created from text characters in the same point size as letters. Behavioural piloting showed comparable accuracy and reaction times for word and line stimuli.

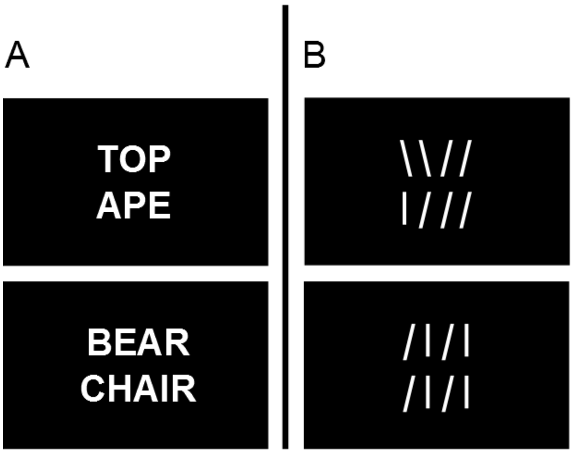


Figure 6.1: Stimuli for rhyme judgement (A) and line judgement (B)

Procedure

Participants performed both rhyme and line judgement tasks. The order of the tasks was counterbalanced across participants. Trials began with a three second "clear mind" period, during which participants were instructed to focus on the black of the screen. This was followed by the presentation of five successive stimulus pairs (either words or lines). Participants had to judge whether word pairs rhymed or line arrays were the same or different. Each active phase lasted for 17.5 seconds. After the active phase there was a 10 second *relax* period in which participants were instructed to imagine a visual scene. We have previously used this duration of relax period to allow normalisation of the blood flow to baseline (Gutierrez-Sigut, Daws, et al., 2015). The whole test cycle for each trial was 30.5 seconds and there were 18 trials for each condition (see Figure 6.2). The rhyme and line judgement tasks were performed in separate blocks, each lasting 9 minutes, 9 seconds.

Button press **yes** (rhyme/matching lines) and **no** (non-rhyme/non-matching lines) responses were made with the index fingers of each hand. Participants were instructed to keep their index fingers in a comfortable position over the keys to minimise movement. The button indicating match or mismatch was counterbalanced across participants but was kept consistent for the participant across tasks. The keys 'Z' and 'M', as found on a typical QWERTY keyboard, were used to record responses. Accuracy and reaction time data were recorded for each item. Both **yes** and **no** trials were presented within each epoch. However, since fTCD is measuring a haemodynamic signal, it has relatively poor temporal resolution and therefore it is currently not possible to disambiguate blood flow responses to rhyme versus non-rhyme, or

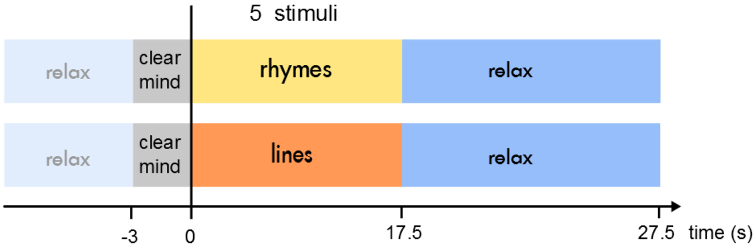


Figure 6.2: Scheme for trial timings in Experiment 1.

line match versus line mismatch, trials in the fTCD signal.

Data analysis

Data were analysed using a custom toolbox for MATLAB, dopOSCCI (Badcock, Holt, Holden, & Bishop, 2012). Artefact rejection thresholds were set such that epochs containing blood flow velocities less than 70% or greater than 130% of the average velocity for that individual were rejected. As is the current standard for fTCD analysis, the maximum left-right difference allowed was set to 20% after normalization (where the mean blood flow velocity for the total sample is adjusted to 100) to further protect from the possibility of inaccurate signals contributing to averages.

Blood flow velocity changes were analysed on a trial-by-trial basis from -6 to 23.5s post initial stimulus presentation. The sample points measured from each artery were corrected to a pre-stimulus baseline period from − 6 to 0 seconds, to protect against differences across trials in the low frequency components of cerebral blood flow. A period of at least 10s of recording was made before the start of the first trial to allow a baseline for the first trial. Participants fixated on the screen for this time.

To calculate Laterality Indices (LIs), periods of interest (POIs) were set from 6 – 23.5 seconds to allow for a lag in the blood flow speed response post stimulus. Within this window the maximum difference in blood flow between left and right was identified. LIs for each individual are given by the mean difference between left and right over a 2s interval around this peak. This is the current standard method for analysing fTCD data (see Badcock et al., 2012; Deppe, Ringelstein, & Knecht, 2004).

	Accuracy (%)	Response Time (s)
Task	Mean (SD)	Mean (SD)
Rhyme	96.2 (2.9)	1.26 (.24)
Line	96.7 (2.4)	1.45 (.26)

Table 6.2: Mean accuracy and reaction times for Experiment 1.

6.2.2 Results

Behavioural data

Table 6.2 shows accuracy and reaction time data for the rhyme and line judgement tasks. Paired t-tests showed no significant difference in accuracy between the tasks (t(27) = .78, p = .44, cohen's d_z = 0.15), however reaction times during the line judgement task were significantly longer than during rhyme judgement (t(27) = 4.21, $p < .001$, cohen's d_z = 0.80).

fTCD data

After artefact rejection there were a comparable number of trials for rhyme and line tasks (t(27) = .35, p = .7, cohen's d_z = .06. The mean average number of trials were rhyme = 17.1 (SD = 1.1), line = 17.0 (SD 1.1). All participants had at least 14 acceptable trials (min = 14, max = 18). To assess reliability, we conducted split-half correlations between LIs from odd and even trials. The rhyme task showed good split half reliability (r = .55, p = .002). The line task was less consistent, showing a moderate correlation approaching significance (r = .34, p = .06).

Group mean and median LIs for the rhyme and line judgement tasks are shown in Table 6.3. Rhyme and line tasks showed group level left and right lateralisation respectively in 1 sample t-tests (rhyme: t (27) = 2.48, p = .02 cohen's d_z = 0.46; line: t (27) = 4.44, p = < .001, cohen's d_z = 0.84). The majority of fTCD studies categorise individuals into 'left', 'right' and 'low' (or 'bilateral') laterality based on the extent and direction of their lateralisation index. An individual's standard error is used to determine whether they are significantly different from zero, which indicates equal blood flow change in left and right MCAs. The categorisation of participants in this way is also shown in Table 6.3.

We tested whether the strength of lateralisation was significantly different for the two tasks with a t-test on the rhyme LIs with reversed sign for the line LIs. This was non-significant (t(27) = 1.55, p = .13, cohen's d_z = 0.29)

			Categories		
Task	LI (SD)	Median	# left	# right	# low
Rhyme	.84 (1.80)	1.3	10 (36%)	4 (14%)	14 (50%)
Line	-1.64 (1.96)	-2.1	2 (7%)	14 (50%)	12 (43%)

Table 6.3: Descriptives of Laterality Indices for rhyme and line tasks in Experiment 1.

implying comparable strength of lateralisation in each task. However, there was no evidence for a correlation between strength of lateralisation on the rhyme and line judgement tasks ($r = .06$, $p = .77$).

6.2.3 Summary of Experiment 1

In Experiment 1, 28 right-handed participants showed group level left hemisphere lateralisation, as measured using fTCD, when performing a metalinguistic task that does not require overt or covert word generation. Furthermore, right hemisphere lateralisation was also established for a non-linguistic task, which was matched to the linguistic (rhyme) condition in task requirements. This suggests that fTCD is indeed sensitive to ‘verbal’ and ‘non-verbal’ processing, above and beyond the cognitive requirements of completing a match/mismatch decision.

We note that the group mean LI of 0.84 during the rhyme judgement is lower than those LIs reported in previous studies of word generation, for example: 2.7 (Stroobant et al., 2009), 1.69 (Bishop et al., 2009), 2.11 (Somers et al., 2011), 3.19 (Krach & Hartje, 2006), 3.94 (Dorst et al., 2008), and 2.41 (Badcock, Nye, & Bishop, 2012). In addition, considering the data categorically, we find a lower percentage of participants categorised as significantly left lateralised (36%) than previously reported, for example: 82% (Bishop et al., 2009), and 85% (Flöel et al., 2005). The proportion of participants categorised as right lateralised for the line judgement task was also low (50%) compared to previous studies of right-handed adults: for example, 75% (Whitehouse & Bishop, 2009) and 72% (Dorst et al., 2008). Given our previously reported association between strength of lateralisation and number of words generated (Gutierrez-Sigut et al., 2015), we reasoned that making more rhyme judgements in the same period could boost premotor activity and result in higher LIs measured using fTCD.

To test the hypothesis that an increase in pace would lead to an increase in strength of left hemisphere dominance, we contrasted performance on slow and fast paced rhyme judgement tasks in a within subjects design. We predicted that an increase in the rate of presentation would lead to an increase in the strength of left lateralisation during the rhyme judgement task. We hypothesized this to be due to both the increase in the amount of material to be sub-vocally rehearsed and the increase in task difficulty resulting in greater effort. These factors can be teased apart to some extent by testing the effect of pace on a non-linguistic task.

6.3 Experiment 2

6.3.1 Method

Participants

Eighteen of the participants who performed Experiment 1, also performed fast paced versions of the judgement tasks. However, to enable the data from Experiment 1 and Experiment 2 to be contrasted directly, steps were taken to avoid practice and order effects. All participants who had already taken part in Experiment 1 were invited back to take part in Experiment 2. Nine participants (6 male) responded and subsequently performed the fast paced version of the tasks (Experiment 2). A further 9 cases were first recruited to perform Experiment 2 and returned at a later date to perform Experiment 1.

The mean age of these participants was 26.9 years (SD = 7.1). Performance of the fast and slow paced tasks was counterbalanced and each participant (except one) performed the two levels of pace in separate sessions. All participants were right-handed and the mean average reading score (Kirklees Reading Assessment, Vernon-Warden revised, Hedderly, 1993) was 34.5 (SD = 4.09), which corresponds to a reading level categorised as ‘adult’.

Stimuli & Procedure

Stimuli for the fast paced versions of rhyme and line judgement tasks were the same as for Experiment 1 (see 6.2.1 above) but each pair was presented twice throughout the session, in a pseudo-randomised order. Trials proceeded in the same way as in Experiment 1, with the exception of the number of items presented in the active period. Ten stimuli, each displayed for 2.1s, were presented in each epoch of the fast paced version. This is in contrast to the presentation of five stimulus pairs for 3.5s each in Experiment 1 (See Figure 6.3). Therefore, the active period for the fast paced condition was 21s, compared to 17.5s in the slow paced version. The longer period was

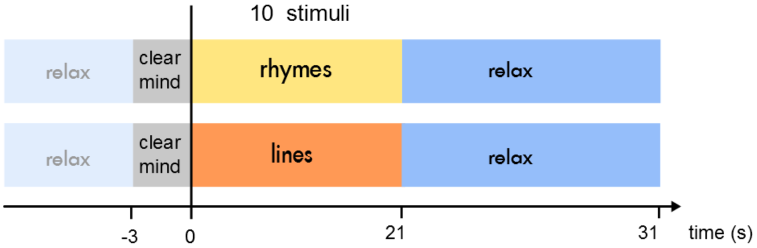


Figure 6.3: Scheme for trial timings in Experiment 2.

necessary to allow all of the stimuli to be presented twice at the fast presentation rate, but maintaining the same number of trials as in Experiment 1. Faster stimulus presentation was not possible since piloting established that presenting the line stimuli for less than 2.1s would have led to a considerably higher error rate.

Data analysis

Artefact rejection thresholds and baseline correction parameters were the same as for Experiment 1 (see 6.2.1). It could be argued that a more appropriate length of epoch for the fast paced condition is -6 to 27.5 seconds, to account for the longer stimulus presentation period. The analyses were rerun with this longer epoch length and this did not affect the outcomes reported here. It seems therefore likely that the marginally longer presentation period did not affect the physiological responses to the stimuli in a way which would bias left-right blood flow responses. As in Experiment 1, epochs were analysed from -6s to 23.5s post initial stimulus. Periods of interest (POIs) were set from 6 – 23.5 seconds[1]. Data were analysed using IBM SPSS 21 using the GLM Repeated Measures procedure, to control for non-independency of the LIs. We used a 2 x 2 full-factorial design with pace (fast vs slow) and task (rhyme vs line) as within-subject factors.

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[1] Despite the marginally longer active period in the fast paced conditions, latencies of the maximum L-R difference were comparable for averaged slow (11.4s) and fast (11.5s) tasks. To ensure this wasn't an artefact of the short POI, analyses were repeated with a longer POI (6 – 20s) and still peak latencies were comparable for slow (13.5s) and fast (13.6s) conditions on average. These comparable peak latencies suggest that the marginally longer presentation period did not affect the physiological responses to the stimuli in a way which would bias left-right blood flow responses to the stimuli. Therefore the same POI for both paces was used.

		Accuracy (%)	Response Time (s)
Task	Speed	Mean (SD)	Mean (SD)
Rhyme	Slow	97.4 (2.3)	1.2 (.26)
	Fast	95.4 (3.3)	.98 (.14)
Line	Slow	97.1 (2.5)	1.42 (.27)
	Fast	92.9 (3.3)	1.13 (.20)

Table 6.4: Descriptive statistics of behavioural responses for Experiment 2

6.3.2 Results

Behavioural data

Mean accuracy and reaction time data for the four conditions are given in Table 6.4. Data from 2 participants were lost due to technical problems during recording. Therefore data from 16 participants are reported. A 2 (fast versus slow) x 2 (rhyme versus line) ANOVA on the accuracy data showed a main effect of task (F(15) = 8.76, p = .01, MSE = 3.71), this was due to a higher level of accuracy on the rhyme task than the line task. There was also a significant main effect of pace (F(15) = 16.97, p = .001, MSE = 9.08) indicating higher accuracy in the slow compared to fast condition. There was also a significant interaction between task and pace (F(15) = 5.13, p = .04, MSE = 4.12). The interaction was due to the fact that the faster pace of presentation led to a greater drop in performance in the line condition (t(15) = 4.92, p = <.001 cohen's d_z = 0.31), than in the rhyme condition (t(15) = 2.06, p = .06, cohen's d_z = 0.13).

The same analysis of the reaction time data showed a main effect of task (F(15) = 13.79, p = .002, MSE = .039), indicating longer reaction times to line judgements than rhyme judgements and the expected main effect of pace (F(15) = 36.03, p < .001, MSE .03) indicating faster reaction times to the fast paced than slow paced stimulus presentation. This is expected given the fast paced stimuli were displayed for a shorter amount of time. The interaction was not significant (F(15) = .86, p = .38, MSE = 0.02).

fTCD data

Trial rejection rates due to artefacts were low. There were no differences in the number of accepted epochs between rhyme and line tasks in either slow or fast versions of the task (slow: t(17) = .26, p = .7, cohen's d_z = .06; fast: t(17) = .25, p = .8, cohen's d_z = 0.19). All participants had at least 14

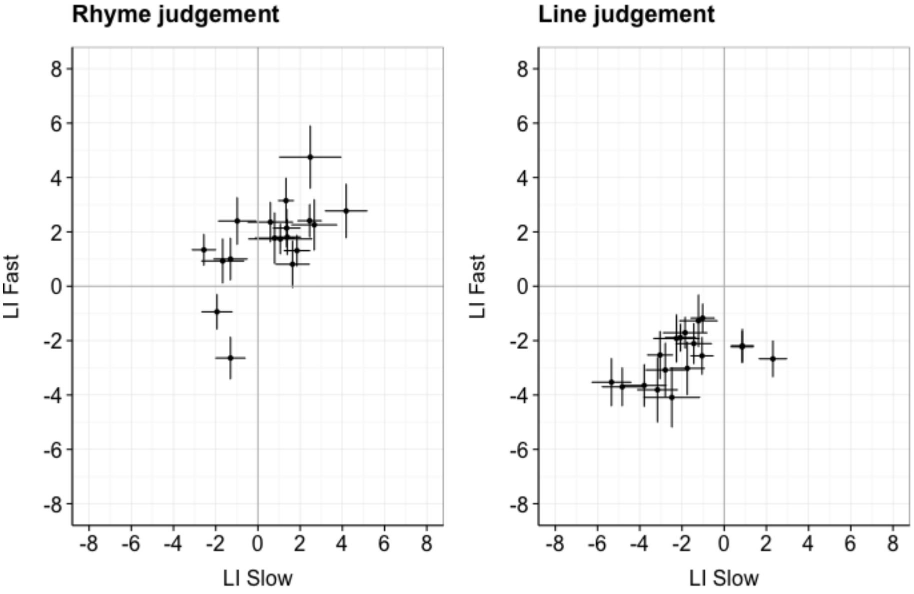

Figure 6.4: Relationship between LIs at different stimulus presentation speeds. Bars indicate standard errors. Positive LIs indicate left-lateralisation, negative LIs denote right-lateralisation.

accepted trials (slow: min = 14, max = 18; fast: min = 16, max = 18). Split half reliabilities for slow and fast rhyme judgement conditions were good (r = .63, p = .005 and r = .67, p = .002). Split half correlations for slow and fast line judgement revealed lower consistency (r = .15, p = .55 and r = .24, p = .33).

To test the consistency between fast and slow speeds, we tested the correlation between LI at each speed, and this was significant for both rhyme (r = .60, p = .008) and line (r = .52, p = .028) tasks. This relationship is shown in Figure 6.4.

Group mean and median LIs for the rhyme and line judgement tasks are shown in Table 6.5. Whilst rhyme judgement was significantly left lateralised during the fast paced presentation (t(17) = 4.4, p < .001, cohen's d_z = 1.0) lateralisation was not significant during the slow paced task at the group level (t(17) = 1.5, p = .15, cohen's d_z = 0.35). Significant right hemisphere lateralisation was found for both the slow and the fast paced line conditions (slow: t(17) = 4.1, p = .001 cohen's d_z = 1.0; fast t(17) = 12.5, p < .001, cohen's d_z = 2.9). Mean blood flow plots are shown in Figure 6.6. Figure 6.7 plots the distribution of individual LIs for each of the four conditions.

Correlations revealed no evidence for a relationship between the strength of lateralisation in the rhyme and line tasks when performed at the slow pace

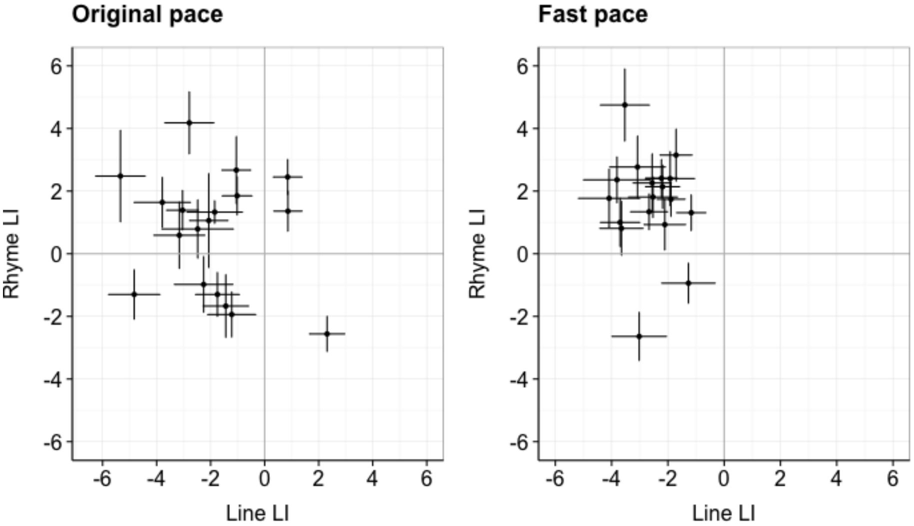

Figure 6.5: Lateralisation Indices in rhyme and line tasks. Bars indicate standard errors. Positive LIs indicate left-lateralisation, negative LIs denote right-lateralisation.

(r = -.10, p = .70) nor at the fast pace (r = -.14, p = .58). For illustrative purposes, these relationships are plotted in Figure 6.5.

As in Experiment 1, we used the reversed values for line judgement LIs in order to assess the effect of pace on the strength of lateralisation. Using absolute values would obscure the fact that some participants showed left lateralised (positive) LIs during line judgement. A 2 x 2 repeated measures ANOVA revealed a main effect of task (F(1,17) = 7.07, p = .017, MSE = 3.11) with line conditions more strongly lateralised than rhyme, and a main effect of pace (F(1,17) = 9.35, p = .007, MSE = 1.38) with stronger lateralisation in the faster conditions. The interaction was not significant (F(1,17)= .21, p = .66, MSE = 1.26.).

6.3.3 Summary of Experiment 2

In Experiment 2, we tested the effect of pace on blood flow lateralisation during linguistic and non-linguistic judgements. An increase in the number of judgements to be made in the active period significantly affected behavioural performance on rhyme and line judgement in both accuracy and reaction times. Increased pace negatively affected response accuracy on the line judgement task, to a greater extent than for rhyme judgement. The strength of lateralisation in both rhyme and line judgement tasks was affected by increased pace, with stronger left and right lateralisation in fast

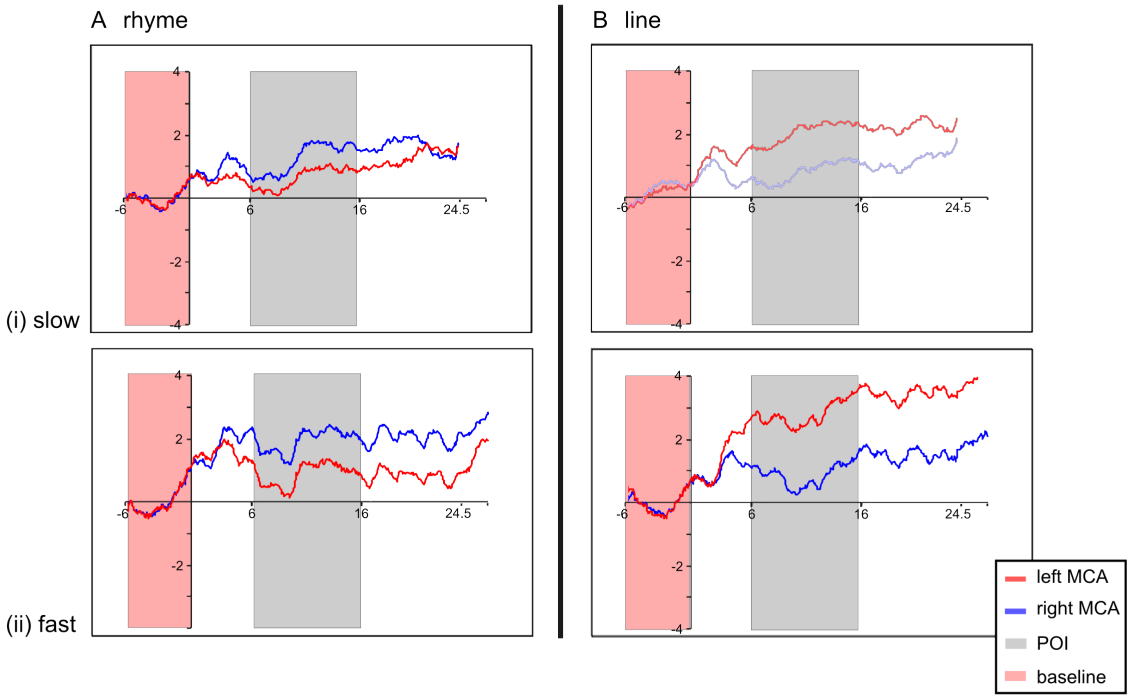

Figure 6.6: Average blood flow change during each condition

				Categories		
Task	Speed	LI (SD)	Median	# left	# right	# low
Rhyme	Slow	.67 (1.88)	1.19	6 (34%)	2 (11%)	10 (55%)
	Fast	1.60 (1.58)	1.79	12 (66%)	1 (6%)	5 (28%)
Line	Slow	-1.90 (1.93)	-1.96	1 (6%)	8 (44%)	9 (50%)
	Fast	-2.62 (.89)	-2.55	0	17 (94%)	1 (6%)

Table 6.5: The left side of the table shows descriptive statistics of Lateralisation Indices (LIs) for each condition in Experiment 2. The right side of the table indicates the percentage of individuals who were categorised as left, right, or low lateralised.

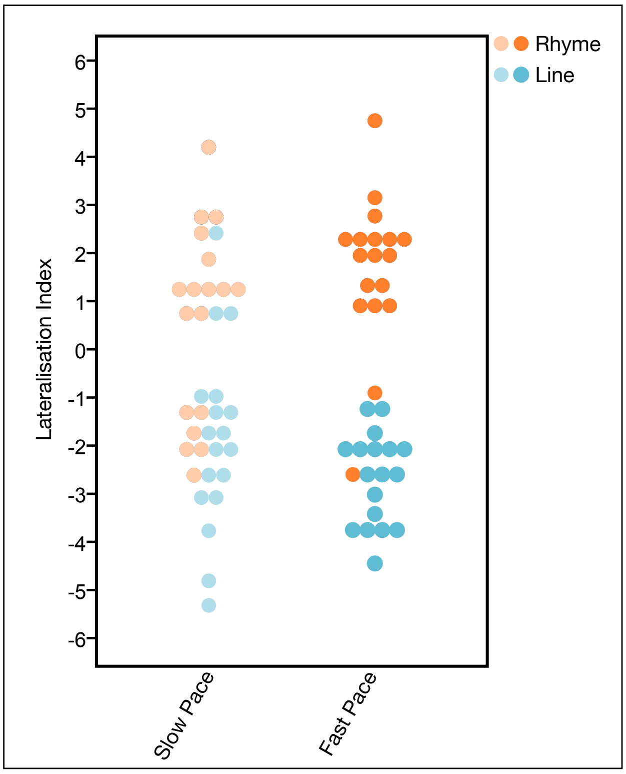

Figure 6.7: The spread of LIs for individuals performing each of the tasks

paced rhyme judgement and line judgement respectively. This was coupled with the observation that in the fast paced conditions, fewer participants were in the 'low' lateralised category, for both tasks.

6.4 Discussion

The two experiments reported here were designed to address methodological questions about the role of task demands, specifically stimulus presentation rate, on hemispheric lateralisation measured using fTCD. We demonstrated that lateralisation can be robustly established using two novel fTCD tasks: a language task that does not require generation of novel items, and a non-linguistic line array judgement task, which was well matched to the linguistic task in stimulus format and output requirements. By manipulating the number of stimuli presented during a trial, we also demonstrated a clear effect of task demands on lateralisation for both the linguistic and non-linguistic tasks. We will now discuss each of these findings in turn.

Linguistic and non-linguistic judgement tasks

Several previously published fTCD studies with adults have used tasks other than free word and sentence generation to assess the sensitivity of the fTCD technique to measure language lateralisation. For example, Badcock et al. (2012), asked participants to passively listen to a short story accompanied by pictures, the final word of which was replaced with a pure tone. It was expected that participants would implicitly generate the word to complete the sentence. In a separate task, participants were asked to listen to a definition of an object and name the object during the active period. Stroobant et al. (2009) asked participants to generate grammatically correct sentences from jumbled words, to read a fixed number of words from a text and to make self-paced semantic decisions between three visually presented words. In these studies, the language tasks led to left hemisphere lateralisation at the group level. However, in each study the average laterality indices reported were low compared to those recorded during word generation from the same participants. Furthermore, the proportions of individuals showing robust left lateralisation were low.

In the current study we used rhyme judgement as an alternative to word generation. Participants made button press responses to indicate whether two written word pairs rhymed. Rhyme judgement, we reasoned, does not require mental generation of new items, but still sufficiently engages articulatory planning processes. This task has been reliably shown to be left lateralised in the majority of right-handed participants as measured by the BOLD response in a number of fMRI studies (Kareken et al., 2000; Lurito et al., 2000; Pugh et al., 1996). The data from Experiment 1 showed that fTCD can indeed reliably measure changes in blood flow speed associated with a non-generation task and is sufficiently sensitive to measure the left lateralised cognitive demands of rhyme judgement, despite differences between BOLD and CBFV/rCBF (Mechelli et al., 2000).

fTCD has also been used to examine lateralisation during non-linguistic tasks such as: visual memory (Groen et al., 2011), mental rotation (Serrati et al., 2000), figure assembly, cube comparison and selecting an identical figure from an array (Bulla-Hellwig et al., 1996; Hartje et al., 1994). Whilst results from these studies have been mixed, and some showed low or no lateralised responses (Hartje et al., 1994), more recent line bisection and visual memory tasks have shown replicable and reliable right lateralisation (Rosch et al., 2012; Whitehouse & Bishop, 2009). In the current study we used line array judgement in an attempt to closely match the task demands of the rhyme judgement task. This close matching of the linguistic and non-linguistic tasks allows us to address the relationship between lateralisation for linguistic and non-linguistic skills within participants. Previous fTCD studies that have addressed this issue have not matched linguistic and non-linguistic conditions for task requirements (e.g. Dorst et al., 2008).

In the current study participants made button press responses to indicate whether two sets of lines were oriented in exactly the same way or whether two words rhymed. We demonstrated, as predicted, significant left hemisphere lateralisation during rhyme judgement and right hemisphere lateralisation during line judgement. We did not observe any significant correlations between the strength of lateralisation during performance of the linguistic and non-linguistic tasks. This is not surprising given that we did not recruit left handers (who are more likely to show right lateralisation for language than right handers) and therefore could not investigate this relationship at the population level as other studies have done (Badzakova-Trajkov et al., 2010; Whitehouse & Bishop, 2009; Cai et al., 2013).

The effect of pace of stimulus presentation on strength of laterality index

In Experiment 1, using a slow stimulus presentation rate, we found lower LI values than are typically reported in studies requiring word generation, and fewer participants than expected showing significantly lateralised blood flow. This pattern of 'weak' lateralisation was also observed during the line judgement task. Previous studies that have used language tasks other than word or sentence generation have attributed low lateralisation to increased right hemisphere involvement (Buchinger et al., 2000; Stroobant, Van Boxstael, & Vingerhoets, 2011), arguing for the recruitment of distributed higher cognitive processes such as theory of mind or inference during story comprehension. Stroobant et al., (2011) also suggest that less lateralised responses during listening to stories may be due to reduced motoric demands in contrast to generation tasks. Similary, Badcock, Nye, & Bishop (2012) attributed lower lateralisation in their receptive task to inconsistent or weaker implicit production when participants are expected to label a missing word.

With regard to non-linguistic tasks, it has been argued that strong right hemisphere lateralisation is most likely to be found during tasks that combine visual attention and visuomotor manipulation and tasks that do not include both factors are likely to show weak effects (Vingerhoets & Stroobant, 1999). In Experiment 2, we tested the hypothesis that previous linguistic and non-linguistic tasks that have shown weak lateralisation may simply not have been sufficiently demanding to drive detectable hemispheric lateralisation. Participants made (blocked) rhyme or line judgements during fast or slow presentation rates of stimulus pairs. Faster presentation, and therefore more judgements to be made within the same time window, led to higher LIs than during the slow condition. This effect of pace held for both the rhyme and line judgement tasks since there was a main effect of pace and no interaction with task type. At the individual level, twice as many participants were categorised as significantly left-lateralised for the rhyme task and right lateralised for the line task during fast presentation compared to slow presentation speeds.

It is important to emphasise that the slow and the fast paced conditions had the same stimuli and the same task requirements. It seems plausible therefore, that previous linguistic (but 'non-generation') tasks that have been used in the literature (e.g. reading aloud or sentence completion) were not taxing enough, or did not stimulate a sufficient degree of articulatory rehearsal in order to drive detectable left hemisphere lateralisation. For example, reading high frequency words (Stroobant & Vingerhoets, 2000) requires little phonological processing demands and articulating a single item (Badcock, Nye, & Bishop, 2012) requires negligible articulatory planning or rehearsal. Similarly, non-linguistic paradigms that have not found significant lateralisation (e.g. cube comparison and figure assembly: Bulla-Hellwig et al., 1996; Hartje et al., 1994; Serrati et al., 2000), have required single responses within trials of approximately 15 seconds duration. These tasks may not require sufficient effort to drive detectable right hemisphere lateralisation. Our results suggest that it is not necessarily the type of task that determines the extent of lateralisation, but the effort required to complete it.

Although in the current study we found a convincing effect of increased pace, we note that the proportion of participants categorised as left lateralised during the fast rhyme task (66%), and the mean LI (1.6) were both relatively low compared to previous 'gold standard' word generation studies. There are a number of possible reasons for this. First, using fMRI it has been established that word generation leads to activation over a large portion of the left hemisphere in contrast to rhyme judgement, which shows more focal inferior frontal cortex activity (Lurito et al., 2000). Since fTCD measures only relative differences in blood flow speed between the hemispheres, it may be that lateralised activity in more extensive regions leads to stronger LIs than in more focal regions. Second, whether a participant is categorised as significantly lateralised (using a one sample t-test) depends on the number of epochs measured and the consistency of that individual's LIs over all the epochs. Some of our conditions had lower split-half reliability than has been reported in studies of word generation (e.g. Gutierrez-Sigut et al., 2015), which may have contributed to fewer participants being categorised as significantly lateralised. It is possible that consistency across trials, and hence split-half reliability, may be improved in future studies by extending the relaxation period or increasing the number of trials.

Despite weaker lateralisation during rhyme judgement in contrast to previous studies of word generation, we argue that rhyme judgement could be a valuable clinical assessment tool, since the best surgery outcomes are likely to come from the use of a battery of language tasks (Gaillard et al., 2004; Ramsey et al., 2001). Moreover, if we wish to better understand which characteristics drive the fTCD signal, externally paced tasks allow a much greater degree of experimental control, including control of number of words produced, than word or sentence generation.

Based on the findings from the non-linguistic task, and the effect of the pace manipulation on behavioural performance, we speculate that task difficulty is a driving factor in the increase in lateralised blood flow, in addition to the amount of articulatory rehearsal. If the effect of pace was related to an increase in premotor activity alone, due to greater articulatory planning, then we would expect the influence of pace on the strength of LI to be evident only in the rhyme condition. However, faster pace of judgements led to increased LIs in both the linguistic and non-linguistic conditions. We therefore suggest that task difficulty does indeed play a role in lateralisation of blood flow, as measured by fTCD in the middle cerebral arteries, above and beyond articulatory rehearsal.

It is interesting to note that a previous fTCD study which manipulated task difficulty of a non-linguistic task, reported an influence of task difficulty on behaviour but not on strength of LI (Rosch et al., 2012). Participants were there required to perform a line bisection task and task difficulty was manipulated in two ways: stimulus duration and distance of stimulus from the midline. That these manipulations of 'task difficulty' did not influence LI but our manipulation of pace of stimulus presentation did, is perhaps not surprising. The increased effort required to solve more complex tasks versus that required for faster paced tasks would likely be mediated by different processes. Future studies with direct contrasts of such manipulations are needed to address this issue.

Although the BOLD signal and CBFV may not relate to pace in the same way (Rees et al., 1997) we can at least speculate about the areas that might drive the greater degree of hemispheric lateralisation during speeded rhyming from studies using other neuroimaging modalities. Price et al. (1996), using PET found a main effect of stimulus presentation rate during overt and covert word reading tasks in visual, motor and language related areas including left dorsolateral prefrontal cortex. Similarly, Sherman et al. (2011), using fMRI, reported that increased presentation rate, from 15 words per minute to 60 words per minute in a covert generation task, increased strength of activation in left inferior frontal gyrus, and anterior part of the left superior temporal gyrus (Shergill et al., 2002). These areas lie within the perfusion territory of the MCA and therefore increased involvement of these areas is likely to affect the TCD signal.

Summary

We have demonstrated that a metalinguistic judgement task, which does not involve the overt or covert generation of novel words or sentences, can be used to assess hemispheric lateralisation of language using fTCD. We also demonstrated that a non-linguistic task, with similar task demands as rhyme judgement - line array judgement, can also be used to assess right hemisphere lateralisation.

Importantly, we demonstrated significantly greater hemispheric lateralisation when rhyme and line judgements are presented at a fast compared to a slow pace. Whilst it is tempting to attribute the stronger left hemisphere lateralisation during faster rhyme judgements to increased premotor demands alone, the finding that right hemisphere lateralisation for line judgements was also stronger for fast compared to slow paced presentation rate, suggests that general 'task difficulty' also plays a role in influencing the strength of laterality index. Thus we suggest that fTCD is sensitive to increased premotor demands and also to task difficulty, which may or may not be driven by a spatially distinct area within the territory of the MCAs. Future studies are needed that explicitly disambiguate the influence of these factors, for example by using fixed pace linguistic judgements of varying difficulty. In addition, manipulating the variables of pace and task difficulty separately in a non-linguistic task such as line judgement may shed light on the conflicting pattern of results between the current results and previous fTCD studies of task difficulty in spatial tasks (Rosch et al., 2012).

Chapter 7

The effect of phonological demands on lateralisation

7.1 Introduction

In Chapter 2.1, it was noted the assessment of language lateralisation can be affected by 'situational' factors such as task demands. Few studies have examined task-related fluctuations in lateralisation of the fTCD signal. Such fluctuations present a potential confound when addressing questions of whether lateralisation develops with age and learning. Chapter 6 described the results of an experiment which tested the effect of one dimension of task demands (pace) on the lateralisation measure obtained from fTCD. A significant effect of pace was found for a linguistic (rhyme) task, as well as a non-linguistic (line) judgement task. We suggested that the more pronounced lateralisation found in the fast-paced rhyme judgement task could relate to the increased premotor demands of a higher volume of judgements presented, due to the greater number of items to subvocally articulate. However, the finding of increased lateralisation for both linguistic and non-linguistic tasks renders this explanation somewhat unsatisfactory. Another possibility is that participants' increased effort exerted in response to the more difficult fast paced tasks could be a causal factor affecting lateralisation. To further our understanding of the parameters which affect cerebral blood flow lateralisation, this possibility should be tested empirically.

The previous chapter also noted that task difficulty can be defined in several ways. The large number of ways to manipulate difficulty explains, in part, the mixed findings of task difficulty effects in both the fMRI (see Gilbert et al. (2012) for a discussion) and fTCD literatures (Rosch et al., 2012; Badcock et al., 2012). In the judgement task used in Chapter 6, task difficulty was manipulated via the general cognitive effect of pace. Another way to address this issue is to isolate a domain of language processing and use psycholinguistic theory to inform a prediction about tasks which tax that domain to a greater or lesser extent.

In the current study, we chose to manipulate the presence or absence of phonological demands. Models of single word reading tend to make a distinction between a fast 'lexical' route and a slower 'sublexical' route which requires the phonological recoding of orthography to access the word (Coltheart et al., 2001; Seidenberg & McClelland, 1989; Plaut et al., 1996). In the case of skilled adult readers, single word naming likely involves a lexical route. When, however, the reader is required to manipulate the orthographic material by some phonological (for example, syllable counting) or semantic process (for example, providing an antonym), this will call upon additional processing requirements. In the case of phonological tasks, many will require the reader to phonologically encode the word in order to manipulate its phonological structure. In sum, there is likely to be either a qualitative or quantitative difference in processing when phonological search is required, such as the types of phonological search processes involved in generating novel rhymes.

Rhyme generation has been adopted in a small number of studies to test the effect of different phonological demands on word retrieval. In a group of 19 adults, Krach & Hartje (2006) contrasted word and rhyme generation. Using fTCD, the authors measured significantly greater left lateralisation for rhyme generation than standard word fluency (generate as many words as possible beginning with target letters). The group later provided supporting evidence and more detail about spatial resolution by using fMRI in a similar design (Kircher et al., 2011). The authors contrasted lexical word fluency, semantic fluency, and rhyme generation. They found that generating rhymes leads to a more extensive left-lateralised activity, driven by greater activity in the left inferior parietal lobule (Brodmann area 40) during rhyme production (Kircher et al., 2011).

However, in these tasks participants were asked to produce words freely in the active period, leading to statistically significant differences in the number of items produced in the rhyme and word generation conditions (Krach & Hartje, 2006: lexical > rhyme; Kircher et al., 2011: semantic > lexical > rhyme). Differences in the amount produced complicates the interpretation of differences found in lateralisation. On the one hand, more production implies an easier task which might be expected to relate to lower lateralisation (assuming a positive association between task demands and strength of lateralisation – see Chapter 2.1). On the other hand, more production could imply more articulatory planning and execution and lead to increases in the strength of lateralisation and make any differences in lateralisation between conditions artificially reduced. The relative weighting of these factors may affect the extent of the difference observed between generation conditions, and furthermore may not be consistent across participants. The issue of suitable task contrasts is further complicated by the different stimuli for each type of generation task: initial phonemes for the word generation versus whole pseudowords rhyme generation. It is plausible that differences in blood flow increases could be attributed to the different demands of processing the target stimuli.

In the current study, we test the effect on the fTCD measure of lateralisation of task difficulty. Here we use one set of stimuli in two tasks: single word reading (Reading) and rhyme generation (Rhyming). These tasks manipulate the phonological processing demands yet result in similar articulatory output. With relative control over the amount of articulatory planning, we can begin to tease apart contributing factors to variation in the fTCD signal by manipulating phonological search demands. It is predicted that a simple single word reading task (using high frequency words) will elicit lower and less consistent left lateralisation than a rhyme generation task which requires higher levels of phonological processing.

7.2 Method

Participants

In total twenty-six right-handed participants were recruited for the study. All were native speakers of English, who reported no history of disorders of language or literacy. Handedness was screened using an abridged version of the Edinburgh Handedness Inventory (Oldfield, 1971) . Seven participants were excluded. This was due to poor signal quality (3 cases), data loss mid-recording (2 cases) or inability to perform the rhyme generation task (2 cases – rhyming accuracy $>$ 2 SD below the group mean). Therefore 19 adults (6 male) were included in the final sample. The average age of participants was 23.8 years (SD = 6.29; range = 18 - 41 years). Reading comprehension was assessed using the Kirklees Reading Assessment (Vernon-Warden revised, Hedderly, 1993). The mean reading score was 31.6 (SD = 5.4, min = 23.0, max = 40.0) which corresponds to an adult reading level on this test.

Materials

Reading and Rhyming conditions used the same 180 words. Stimuli were the same set as used in Chapter 6, based on those in MacSweeney, Goswami &

Neville (2013). See Appendix 13 for the word list. All words were monosyllabic with a single coda. For both conditions, words were presented one at a time in a pseudo-randomized order that was unique for each person. The order of Reading and Rhyming conditions was counter-balanced across participants.

Procedure

Both conditions proceeded in the same format. Trials began with a 4s 'clear mind' period, followed by blocks of 10 stimuli words displayed for 1.6s each. The rate of presentation was based on piloting which indicated that this was sufficient time to generate a rhyme but without long pauses between items. After this active phase there was a 20 second relax period before the beginning of the next trial (See Figure 7.1). For both Reading and Rhyming there were 18 trials of 10 words each.

In the *Reading task*, participants were instructed to read the word aloud. In the *Rhyming task*, participants were instead asked to generate aloud a rhyming legal English word. Responses were audio recorded for offline transcribing and scoring. For the Rhyming task, all English words were accepted, as were repetitions and proper nouns. Participants were given 2 practice trials and were required to produce accurate answers for at least 85% of the target words to proceed. In 2 cases, participants did the practice a second time to reach this level of competence.

Data analysis

Epochs were set from -6 to 34s. Baseline correction was performed from – 6 to 0s (the trigger). Periods of interest (POIs) were set from 10 – 25s. A period of 5-10s of recording was made before the start of the first trial to allow a baseline for the first trial.

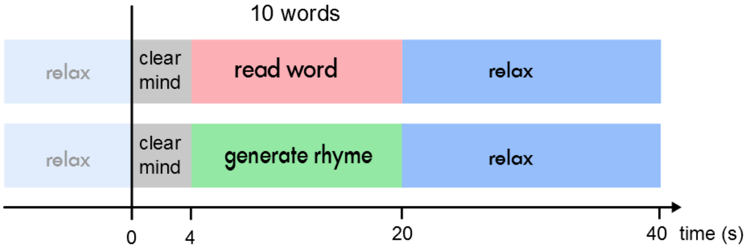

Figure 7.1: Timing of trials for the Reading and Rhyming tasks

7.3 Results

Reliability of fTCD data

All participants had 13 or more suitable trials after epoch rejection. The average number of epochs accepted did not differ between conditions (t(18) = 1.3, $p > 1$, Reading = 17.6, SD = .60, Rhyming = 17.2, SD = 1.4).

Split-half correlations failed to reach significance for the Reading task (r = .43, p = .06) and showed a significant positive correlation for the Rhyming task (r = .92, p < .001). These correlations indicate consistent LI values across the 18 epochs for the Rhyming condition. Lateralisation throughout the Reading condition was less consistent.

Behavioural

As expected, accuracy in the Reading condition was near ceiling due to the age appropriate reading level of the group (mean % words correct = 99.8, SD = .34). For Rhyming, the average percentage of correctly generated rhymes was 75.1% (SD = 9.5). The percentage of responses which contained an utterance (correct or incorrect) was 86.2% (SD = 9.5). Errors were, in the main, phonological (for example, "tone" to rhyme with "foam" - a half rhyme) or orthographic (for example, "head" to rhyme with "bead"). Only a small proportion (approximately 3%) were unrelated or vocalisations such as "umm". Given the high overall performance rate, and the inability to remove single stimuli from analyses, all fTCD trials were included in the analyses.

fTCD Laterality Indices

Table 7.1 and Figure 7.2 show the LIs for the Reading and Rhyming tasks. The table also indicates the number of participants who showed individual significant lateralisation in either direction. The "low" group are those who did not differ significantly from 0 in either direction.

At the group level, the Reading task was not significantly left-lateralised (t(18) = .19, p = .9). Rhyming was significantly left-lateralised (t(18) = 3.32, p = .004). The mean LI for Rhyming was significantly greater (more left-lateralised) than Reading (t(18) = 2.81, p = .01).

The latency of the peak difference in blood flow within the POI was comparable between tasks (t(18) = .51, p = .62. Peak Reading = 17.1s (SD = 5.2), peak Rhyming = 17.9s (4.7).

			Categories		
Task	Mean LI (SD)	Median LI	# left	# right	# low
Reading	.11 (2.60)	.33	7(37%)	5(26%)	7(37%)
Rhyming	2.30 (3.02)	3.13	15(79%)	4(21%)	0

Table 7.1: Descriptives of Laterality Indices and number of participants for each category of lateralisation

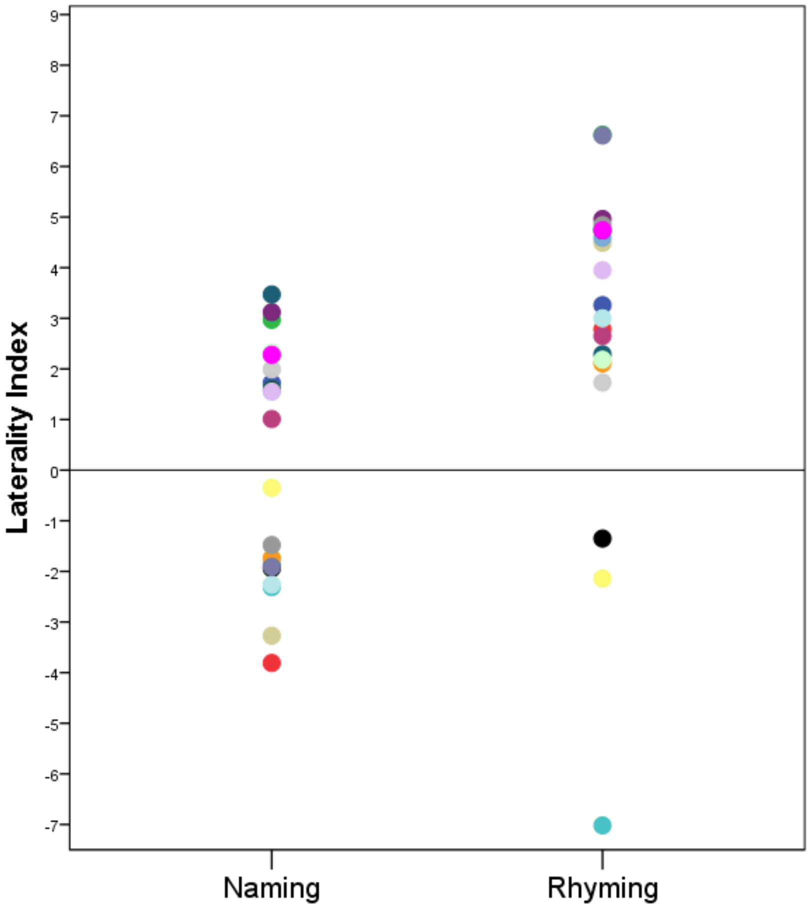

Figure 7.2: Plot of individual LIs in each condition, Naming (referred to in text as Reading), and Rhyming. Colours represent participants across conditions.

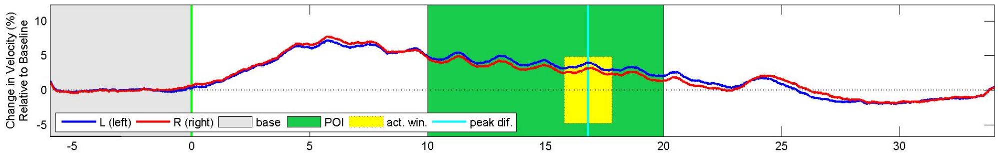

Figure 7.3: Group averaged CBFV changes for the Reading task.

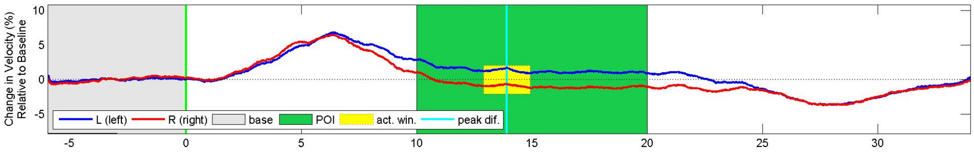

Figure 7.4: Group averaged CBFV changes for the Rhyming task

Correlations

Performance on the rhyming task was positively correlated with offline reading performance ($r = .48$, $p = .04$). We tested the association between strength of lateralisation and measures of online and offline task proficiency. The percentage of rhymes uttered (whether correct or incorrect) positively correlated with the strength of left lateralisation in the rhyming task ($r = .49$, $p = .03$), shown in Figure 7.5. There was no significant association between strength of lateralisation in the two tasks ($r = .28$, $p = .25$).

7.4 Discussion

The current study sought to test the sensitivity of fTCD to manipulations of task demands. We tested the hypothesis that the fTCD signal is sensitive to CBVF changes related to the lexical-phonological demands of the task. In our design, we used the same stimuli for both conditions. Participants were required to generate ten successive words in each trial, either to read a word aloud or to generate a rhyming word. Therefore, the design also allowed for control over the amount of subvocally generated items.

Reading words aloud did not result in significant lateralisation at the group level. This finding agrees with fMRI studies which have contrasted reading words aloud with rest (Graves et al., 2010; Turkeltaub et al., 2002; Fiez & Petersen, 1998). In contrast, generating a novel rhyme to the same word stimuli resulted in significant left lateralisation at the group level. The

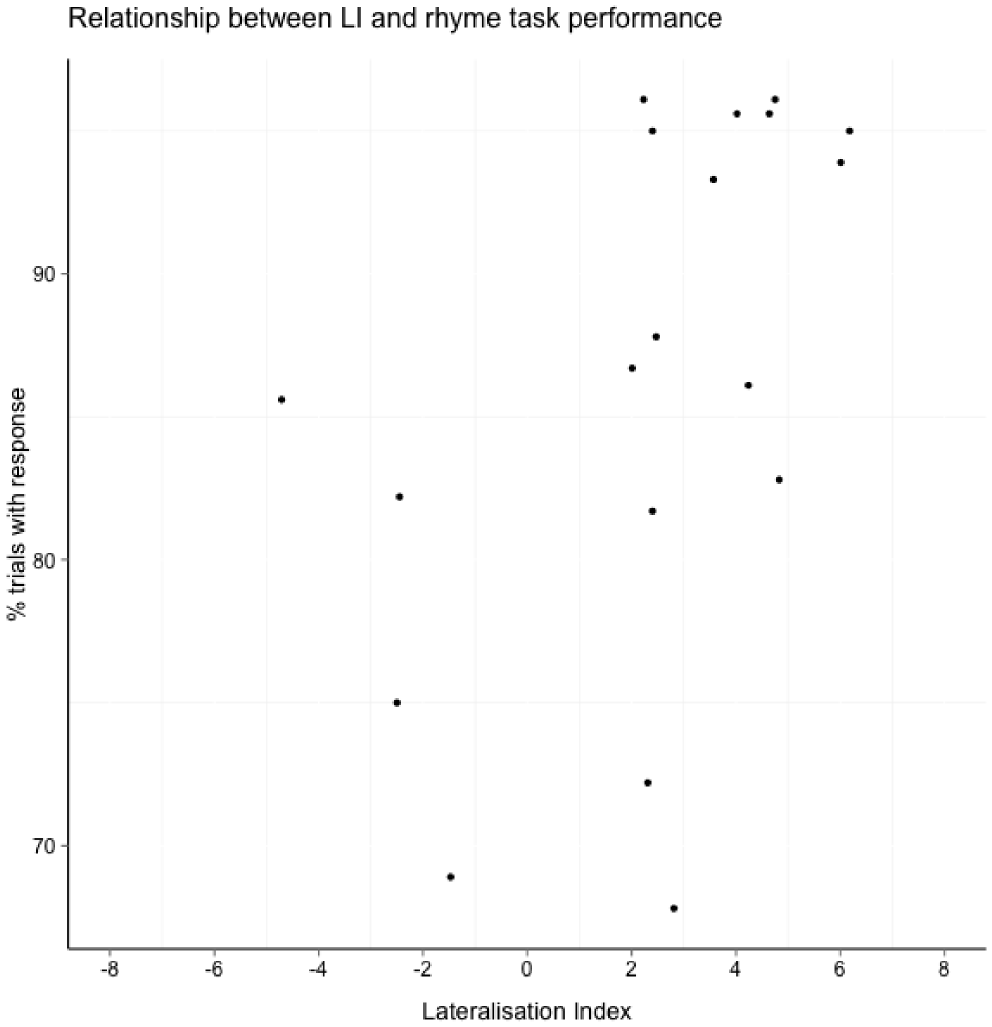

Figure 7.5: Relationship between strength of LI and amount of trials containing an utterance.

results demonstrate that despite the two conditions having the same number of stimuli and the same requirements for speech production, the greater difficulty of the rhyme task than the reading task, led to stronger left lateralisation.

In this study, task difficulty was increased in terms of the phonological demands of the task, which during rhyme generation are much greater than for reading a word. However, it is of note that task difficulty also affected lateralisation in a non-linguistic task in Chapter 6, which could be taken as evidence that increased effort results in greater blood flow. The current results could reflect simply increased 'cognitive effort' of generating rhymes. This question could be addressed using a similar contrast in a non-linguistic paradigm, by presenting consistent visual stimuli and manipulating only the demands of the task, e.g. presenting matching pairs versus mismatching pairs in independent blocks.

In summary, this study has demonstrated that manipulating only the psycholinguistic demands of the task induces measurable changes in lateralisation using fTCD. This novel task offers a way to measure lateralisation of language production minimising variability of articulatory output between participants.

Chapter 8

Summary of Chapters 5 - 7

In Chapters 5 to 7, we assessed lateralisation in adults during the standard phonological generation task, semantic generation, rhyme judgement, line orientation judgement, rhyme generation and single word naming. Observing good split-half reliability in these novel tasks indicates that fTCD paradigms can be adapted for use with children and special populations, tested in Part III of this thesis. Moving away from purely generation-based tasks affords a more comprehensive and multidimensional approach to the assessment of lateralisation of language processing, as well as the possibility of creating engaging and age-appropriate tasks.

Particularly important was the finding of reliable and concordant LIs during overt production in adults. There are several arguments in favour of using overt tasks in fTCD studies with children. First, overt word generation does not require many of the additional cognitive processes that are involved in a covert generation task with a later response period, such as response selection, short term memory and evaluation of acceptable responses for reporting (see e.g., Badcock et al., 2012). Second, an accurate measure of the behavioural response can be established that ensures task compliance. Third, the behavioural response is measured at the same time as the physiological response used to calculate the LIs, allowing relationships between the two measures to be explored. While other fTCD studies have used overt production with children (Lohmann et al. 2005; Bishop et al., 2009, Haag et al., 2010; Stroobant et al., 2011; Groen et al., 2012), it had not yet been established whether the additional articulatory demands of overt production could affect either the strength of lateralisation or the quality of the signal. We are now able to elicit overt responses from children assuming negligible systematic effects of articulation on the fTCD signal.

The correlation between the number of words produced during word generation (Chapter 5) informs our decision to take online measures during expressive language tasks with children in the form of the number of words produced (Chapters 9 and 10). Including the measure of number of words produced by children in future studies allows a potential contributing factor to variability in LIs to be quantified, regardless of whether the more strongly lateralised responses in Chapter 5 reflected additional articulatory demands or increased effort/engagement with the task.

The finding of an effect of pace during judgement tasks in Chapter 6 informed our decision to include a study with children in which the pace of presentation and output demands of the task are fixed (Chapter 11). To maximise the chance of measuring robust lateralisation during language production in children we adopted a fast pace of presentation rather than single items (cf. Badcock et al., 2016, preprint[1]; Stroobant et al., 2009).

Ethical approval for the developmental studies in Chapters 9 - 11 was granted by the UCL Research Ethics Committee (ID:3612/004). Parents gave written informed consent and were aware they could withdraw their child at any time. At each testing session, children gave verbal assent to take part in the study.

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[1] from https://doi.org/10.7287/peerj.preprints.1939v2

Chapter 9

The development of lateralisation in hearing children

9.1 Introduction

Chapter 2.1 outlined evidence that language processing engages left lateralised neural systems in the majority of adults. Individual variability in the direction and extent of lateralisation observed in adults can, in part, be attributed to demographic, anatomical, and task-related factors (Tzourio-Mazoyer et al., 2017; Josse & Tzourio-Mazoyer, 2004). However, the role of development and the characterisation of how the adult system emerges is likely to shed further light on whether developmental factors contribute to variability in hemispheric dominance for language. Put another way, at present it is unclear whether lateralised processing is a precursor or a consequence of language development (Bishop, 2013).

The development of lateralisation

Chapter 2.2 described previous studies that have tested lateralisation of language processing in children and its possible developmental trajectory. Studies have shown left-lateralisation in response to passive auditory speech perception tasks with babies (e.g. Dehaene-Lambertz et al., 2002, 2006; Pena et al., 2003) as well as to comprehension of spoken language in older children (Szaflarski et al, 2012). Left lateralisation has also been reported in response to other domains of language with older children, for example verbal fluency (Holland et al., 2001; Gaillard et al., 2003; Szaflarski et al., 2006), vowel identification (Everts et al., 2009; Lidzba et al., 2011) and semantic lexical decision (Everts et al., 2009). Correlations with age have been reported (Holland et al., 2001; Lidzba et al., 2011), suggesting more focal and stronger left-lateralisation with increasing age. The only longitudinal fMRI study also found an increase in the strength of lateralisation with age (Szaflarski et al., 2012). Chapter 2.2 includes further discussion of these studies.

In accordance with fMRI and fNIRS studies, existing fTCD studies also report reliable left lateralisation in young children and school-aged children using expressive language tasks such as picture description (Lohmann et al 2005; Stroobant et al., 2011 but cf. Haag et al., 2010), phonological fluency (Haag et al., 2010) and animation description (Bishop et al., 2009; Groen et al., 2012). Groen et al (2012) used fTCD to address the question of changes in lateralisation with age in a large group of 6 - 16 year olds. They found that age was not a significant predictor of the extent or direction of lateralisation. Despite no significant effect of age, they reported higher standardised vocabulary scores in children who were left-lateralised than in those who showed weak or right lateralisation. They suggest that established left-lateralisation relates not to absolute skill level, but to higher levels of skill for a child's age.

However, previous fTCD studies suffer from some of the same limitations as fMRI studies of older children. In particular, Groen et al (2012) was cross-sectional in design and demonstrated large individual variability in strength of hemispheric dominance. Thus it is possible that potential developmental effects of age on lateralisation may have been underestimated.

The relationship between strength of lateralisation and language proficiency

To assess whether greater (stronger) left lateralisation is associated with cognitive advantage, studies have tested the relationships between lateralisation and online task proficiency, as well as offline measures of academic attainment or language ability.

Most fMRI studies of child language have used covert or passive paradigms which reduce the need for movement associated with articulation. As a result, potential correlations between the extent or direction of laterality and online task performance cannot be directly tested. Studies using other techniques, such as fTCD and fNIRS, which have been able to assess online task proficiency suggest there is no relationship between task performance and the strength of lateralisation (Stroobant et al., 2011; Groen et al., 2012; Paquette et al., 2015).

Offline measures of language proficiency have shown mixed relationships with the strength of lateralisation: higher verbal IQ has been associated with more bilateral activity (Lidzba et al., 2011), advanced cognitive abilities have been reported in those with greater degrees of left-lateralised language processing (Everts et al., 2009). Other studies have found no relationship between offline measures of proficiency and lateralisation (Holland et al., 2001; Wood et al., 2004; Gaillard et al., 2003; Groen et al., 2012 - though splitting the group into categories of left- right- and low- lateralised, there were significant differences in vocabulary between left-lateralised and non-left-lateralised children).

The effect of literacy on lateralisation of spoken language

One potential reason for the mixed results in terms of developmental effects on lateralisation are differences in literacy knowledge between children within and between studies. Behavioural studies have shown that learning to read affects skills which support language such as phonological short term memory (Nation & Hulme, 2011). Learning to read is also associated with changes to the neural correlates of processing spoken language (Raichle, 2009). Correlates of learning to read have been examined in non-literate adults compared to literate peers, suggesting that left lateralised temporoparietal and occipito-temporal regions show greater activation in those who are able to read (Carreiras et al., 2009; Castro-Caldas et al., 1998; Dehaene et al., 2010; Li et al., 2004).

Developmental changes in lateralisation for spoken language may therefore be related to the level or rate of literacy acquisition of the children included in the study. A study by Monzalvo & Ghislaine (2013) provides evidence for the effect of learning to read on the neural bases of spoken language. A difference in the extent of left-lateralised responses to spoken language was reported between the most advanced 6-year-old readers compared to their pre-reading peers. Examining changes in lateralisation before the acquisition of literacy would reduce this possible confound.

The current study

Here we assess individual variability of functional lateralisation and its relationship to language and literacy abilities in the preschool years, a period during which much of the foundations of language skill are laid (Herschensohn (2007), pp 27-64). In recruiting children at 3 years old, we are more likely to find a larger spread of scores in behavioural language measures. Importantly however, these will not be influenced by variability in literacy knowledge. We will capitalise on the variability in language abilities by examining the relationship between age, proficiency, and lateralisation of language processing. By assessing lateralisation of language production in the same young children at two time points early in their development (the preschool year and the first year of school), this study provides the first preliminary data of potential longitudinal changes in lateralisation measured using fTCD.

We test the hypothesis that, in line with longitudinal fMRI data of expressive language development (Szaflarski, Altaye, et al., 2012), left-lateralisation will increase in strength between the ages of 3 years (Time 1) and 4 years (Time 2). If significant changes in lateralisation are observed, we will also test whether the extent of change in lateralisation relates to increases in measures of language and literacy. If changes in lateralisation are driven by increased proficiency, the greatest changes should be observed in those children who make the most pronounced gains in language ability from Time 1 (T1) to Time 2 (T2).

To address questions about potential advantages of increased lateralisation, we test whether the strength or direction of lateralisation relates to online or offline measures of proficiency at each time point, in correlational analyses. These are considered as exploratory analyses.

9.2 Method

General design and procedure

Children were tested twice, twelve months apart (mean age 3 years 9 months at T1, 4 years 8 months at T2). At each time point, testing took place over two or three sessions on separate days. At T1, fTCD testing was done in a separate room at the child's preschool. Cognitive and language testing took place either at preschool or at the child's home. At T2, children were enrolled at five different schools around the Bristol area. Children were tested for all measures in separate rooms at their respective schools. Given the very small sample size, school was not entered as a factor in analyses.

Participants

Twenty-one children were recruited from a single preschool. For three of the children, it was not possible to acquire good quality fTCD data at either session so their data were not included in later analyses. In total, 18 children (5 boys) took part at both time points. The average age at Time 1 was 3;9 (years;months). Ages ranged from 3;2 to 4;3. The average age at Time 2 was 4;9 (range: 4;3 - 5;4). All children were monolingual native English speakers. None had any reported developmental disorders. During the course of testing, it became apparent that one child had a history of otitis media with effusion ('glue ear') which had resolved. Given that her language and literacy were age-appropriate, she was included in all analyses. All children had non-verbal IQ within the normal range, as assessed by the British Ability Scales, 3rd edition (BAS-III; Elliot & Smith, 2012) *Pattern Construction* task (mean standard score = 60.6, min = 33, max = 80).

Materials

Language and literacy

Expressive vocabulary was assessed at both time points with the *Naming Vocabulary* subtest of the BAS-III (Elliot & Smith, 2012). Receptive language was assessed with the *Verbal Comprehension* of the BAS-III (Elliot & Smith, 2012). Standard scores are reported.

Rapid Automatized Naming (RAN) was assessed at both time points using the *Naming Speed* (picture) subtest of the Phonological Assessment Battery (Frederickson et al., 1997). The test comprises five highly nameable objects presented ten times each in a random order to produce a sheet of 50 pictures. The total time from initial articulation is counted until the child has named all the pictures.

Knowledge of letters was assessed using a single measure at T1 and two measures at T2. At both time points simple letter sound knowledge was assessed by testing the number of letters of the alphabet known, presented in a random order. No standardised measures of letter knowledge are available for preschool-aged children therefore raw scores are reported. At T2 we also the *Letter Sound Knowledge* subtest of the York Assessment of Reading Comprehension Early Reading (YARC; Hulme et al., 2009) in order to obtain a standardised measure of letter knowledge where possible. At time 2 only, the *Early Word Recognition* subtest of the YARC was included as the children had begun literacy training. Standard scores are reported for both these measures at time 2.

Handedness

Handedness was assessed using two measures of hand preference: a card reaching task and observations of tool use. For the card reaching task (Bishop et al., 1996), twenty-one cards depicting highly nameable objects were placed at seven evenly spaced locations in a semi-circle in front of the child. The locations were 40cm away from the child at approximately 30 degree intervals. In a random order, which was the same for every child, the experimenter asked the child to reach for a given card and place it in a pile in front of them. Children were instructed to place their hands in their lap between each card. The experimenter marked which hand was used to reach (right (R), left (L), or both (B)) for each card. As per Bishop et al (2014), the dependent variable was a Card Laterality Quotient (Card LQ), calculated by subtracting 0.50 from the proportion of reaches made with the right hand. This results in scores ranging from +0.50 for participants reaching exclusively with the right hand, 0 for those who do not show a preference, to −0.50 for those reaching exclusively with their left hand.

For observations of tool use, children were asked to use four objects in turn. Children were instructed to place their hands on their lap while the experimenter put the item/s on the table in front of them. First a pencil was placed in the middle of a piece of paper and children were asked to draw a picture. Some of them wanted to show writing their name so this was also allowed. The other objects were scissors, pouring from a jug into a glass (the latter placed behind the jug to avoid bias), and picking up a glass. The experimenter marked whether the child used right, left, or both hands for each item. An Objects Laterality Quotient (Object LQ), was calculated for each child, given by

$$LQ = \frac{(R - L)}{(R + L + B)} \times 100 \tag{9.1}$$

fTCD

Changes in cerebral blood flow velocity (CBFV) were recorded during an Animation Description task developed in Bishop et al. (2009) which has been used with 4 year old children through to adults (Bishop et al., 2009; Groen et al., 2013, 2012). Laterality Indices measured for this task show good reliability within and across testing sessions (Bishop et al., 2009). For the animation description task, the child was asked to watch a cartoon of a penguin in a series of clips (maximum 30 clips, dependent on the child's compliance). The cartoon has environmental sounds and some unintelligible vocalisations but it is generally silent. Figure 9.1 shows trial timings. A period of silent watching (12s) was followed by a prompt for the child to describe the events of the animation (10s) after which the child was instructed to sit quietly for a rest period of 16 seconds. After the rest period, the experimenter checked the child was ready to proceed to the next clip to ensure maintained attention.

Data analysis

Data analysis for the developmental fTCD data proceeded in much the same way as the adult studies with some small adjustments. Unusually high or

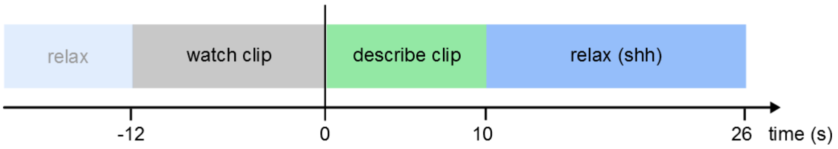

Figure 9.1: Scheme of animation description task

low blood flow speeds were defined as ±50% of the average speed as opposed to ±40% for adults. This less conservative approach was taken to maximise the number of trials for this low age group, but was deemed to be acceptable given good split-half reliability (see below).

A further change was the addition of a function to save trials that had minimal signal dropout (`https://github.com/heathermarypea/dopStep`). This functionality was developed with Dr Nick Badcock during an ESRC Overseas Institutional Visit to MacQuarie University during my PhD. The function checks how many sample points are outside the activation limit set (in this case, ±50%). If it was less than a pre-specified amount, e.g. 1% of total sample points, the extreme values are replaced with with an interpolated value (based on values 1.5s before and after the extreme value) at evenly spaced intervals. This procedure is only applied to reserve epochs where very few sample points show extreme values. Epochs were set from -12 to 26s, baseline correction was applied using the average left-right difference from -10 to 0, and the period of interest was set between 4 and 18s. As before, LIs are calculated from the average difference in a 2s window around the peak left-right difference.

9.3 Results

Behavioural data

For reference, descriptive statistics for all behavioural measures are in Table 9.1. Standardised scores are age adjusted, therefore predictably there were no significant changes in standard scores over the year (all p's >.1). For the unstandardised measure of letter knowledge (number of letter sounds known), there was a significant increase in letters known (t(17) = 7.3, p <.001, d_z = 1.91, see Table 9.1). In terms of online task performance, the average number of words produced during the active period increased significantly (t(14) = 5.2, p <.001, d_z = 1.36). Performance on the rapid naming task

	Time 1		Time 2	
	M(SD)	min-max	M(SD)	min-max
Age (years)	3.8 (0.3)	3.2 - 4.3	4.8 (0.3)	4.2 - 5.3
Comprehension (SS)	59.2(8.1)	48 - 74	63.0 (6.0)	49 - 72
Vocabulary (SS)	62.0 (8.3)	43 - 80	63.9 (12.6)	38 - 80
RAN (sec)	89.3 (23.1)	60.6 - 123.6	66.4 (18.0)	40.0 - 101.0
Letters known	11 (8)	3 - 25	23 (4)	10 - 26
Object LQ	73.4 (30.9)	0.0 - 100.00	80.9 (33.7)	-25.0 - 100.0
Card LQ	.15 (.20)	-2.1 - .5	.12 (.17)	-.18 - .45
Words/trial	7.0 (2.7)	1.8 - 13.2	12.4 (3.4)	7.1 - 19.9

Table 9.1: Behavioural descriptive statistics for all children (n = 18). SS = standard score; RAN = rapid automatised naming; LQ = laterality quotient

also improved significantly, with children performing the task more quickly at T2 (t(15) = 4.2, p = .001, d_z = 1.06. There were no significant changes in handedness according to either measure, at the group level (p's > .1)

fTCD data quality

Three children were excluded from analysis from T1, as they had fewer than 9 acceptable trials. In two cases this was due to epochs being rejected at data analysis and visual inspection of their recordings suggested a poorer quality signal. In one case the child did not complete sufficient trials at testing. The average number of trials accepted at T1 was 13.7 (SD = 3.2, min = 9, max = 23). The average number of trials accepted at T2 was 16.7 (SD = 3.2, min = 10, max = 25).

Split-half reliability was estimated by correlating the LIs for odd and even trials for each participant. These showed moderate and significant correlations suggesting consistency in lateralisation through the task. For T1 (n = 15); r = 0.56, p = .03 and for T2 (n = 18); r = 0.56, p = .02. Standard errors of LIs provide another way of quantifying variability in the extent of lateralisation across trials. Standard errors were significantly lower at T2 than T1 (t(14) = 2.1, p = .05).

Effects of age on lateralisation

We tested the hypothesis that strength of lateralisation will increase in strength from T1 to T2. Group averaged plots for changes in cerebral blood

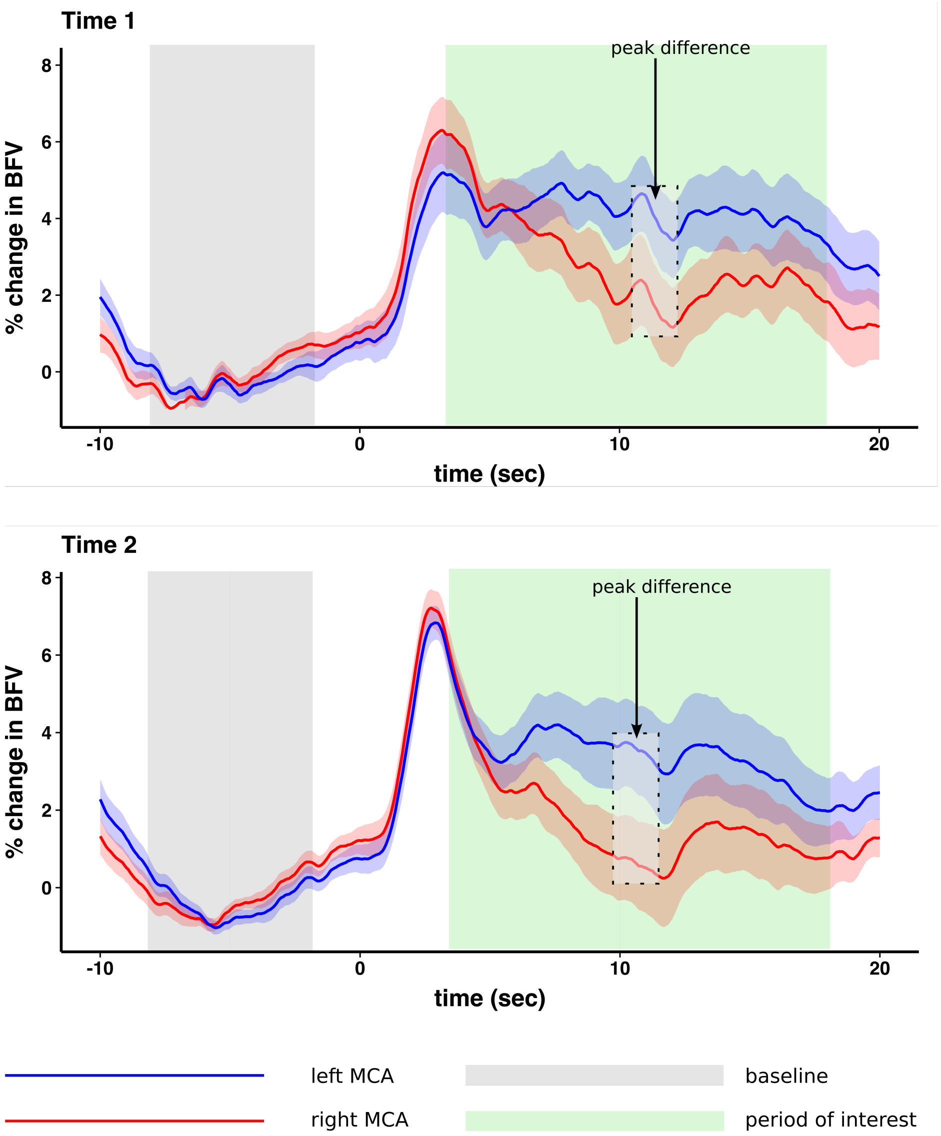

Figure 9.2: Group averaged changes in CBFV during Animation Description at each time point. Shaded areas show the standard error at each sample point.

flow during the task are shown for each time point in Figure 9.2. For these plots, all children who had sufficient epochs were included (n = 15 at T1, n = 18 at T2). Table 9.2 shows descriptive statistics for LIs for children who had useable data at each time point. The peak difference indicated in the plots is for illustrative purposes only — the group mean LI for the group is calculated from the distribution of LIs of children based on their own peak difference (which may correspond to different peak latencies). Descriptives for the average peak latencies are also shown in Table 9.2.

To test the effect of age on lateralisation, only children with fTCD data at both time points were included (n = 15). Paired t-tests revealed no significant change in strength of LIs from T1 to T2 (t(14) = .48, *p* = .64). Given that the LIs were somewhat non-normally distributed, as shown in histogram plots in Figure 9.3, we also tested the effect of time using a non-parametric t-test based on differences in the median LI values. This was also non-significant (Wilcoxon signed ranks test: Z = 1.19, *p* = .23, ns, T1 median = 3.2, T2 median = 3.8). In terms of consistency in the strength of lateralisation, LIs at T1 and T2 showed a moderate association which approached significance (r = .47, *p* = .07). This relationship is shown in Figure 9.4.

Time	Age	LI	Peak Sec	Categories		
		M(SD)		# left	# right	# low
1	3.8 (.30)	2.2 (3.5)	10.6 (3.9)	11 (73%)	3 (20%)	1 (7%)
2	4.8 (.30)	2.6 (2.9)	9.9 (2.8)	11 (73%)	2 (13.5%)	2 (13.5%)

Table 9.2: Descriptives of Laterality Indices and categories

Concurrent correlations

There were a number of significant correlations between behavioural measures taken at the same time point. Correlations between t1 measures are shown in Table 9.3 and between t2 measures in table 9.4.

Correlations with language proficiency

We had aimed to test whether the extent of change in lateralisation relates to increases in measures of language and literacy. However, given that no change in lateralisation was observed between T1 and T2, the variance in LIs was not sufficient to correlate with the variability of behavioural gains.

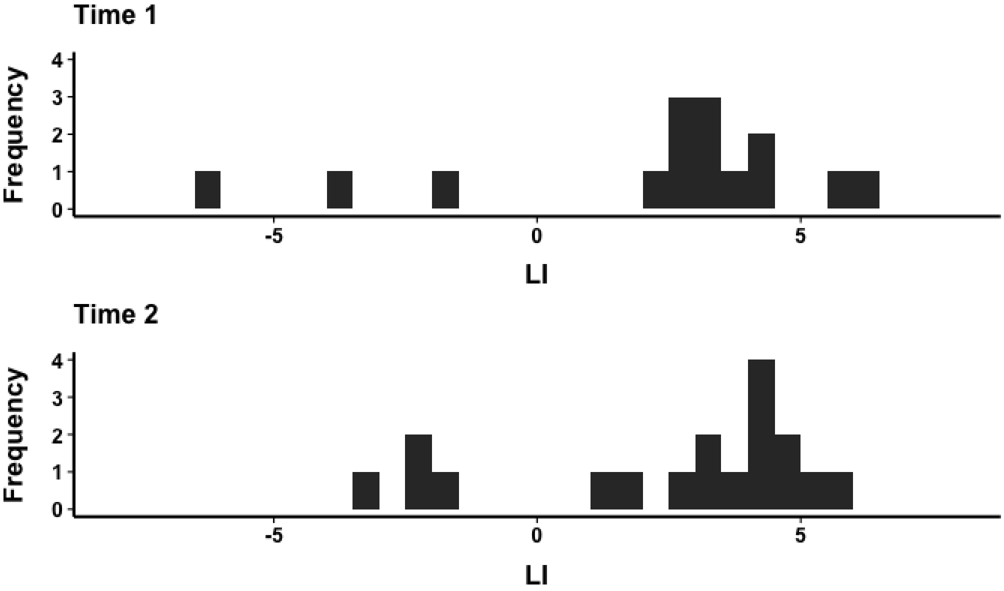

Figure 9.3: Distribution of LIs at each time point. Positive values indicate left lateralisation; negative values indicate right lateralisation. Error bars indicate the standard error of the child's LI.

To address questions about potential advantages of increased lateralisation, we tested whether the strength or direction of lateralisation relates to online or offline measures of proficiency at each time point. In terms of concurrent relationships between physiological and behavioural measures, at Time 1 there were no significant correlations between strength of lateralisation and proficiency (either in offline measures or in the online measure of number of words generated: r values between -.2 and .2, all p's >.1). The same was true at Time 2, though the relationship with the number of words generated approached significance (r = .46, p = .053).

Correlations between strength of lateralisation at T1 and language measures at T2 were also explored. The only correlation that reached significance was the strength of LI at T1 showed a positive correlation with letter-sound knowledge at T2 (r = .58, p = .02). This correlation held when letter knowledge at Time 1 was entered in a partial correlation (r = .63, p = .02). However, this would not survive correction for multiple comparisons. As indicated in the Introduction, these were exploratory analyses and therefore are interpreted with caution. Furthermore, as depicted in Figure 9.5, the significant correlation appears to be driven by one right lateralised participant with low letter knowledge.

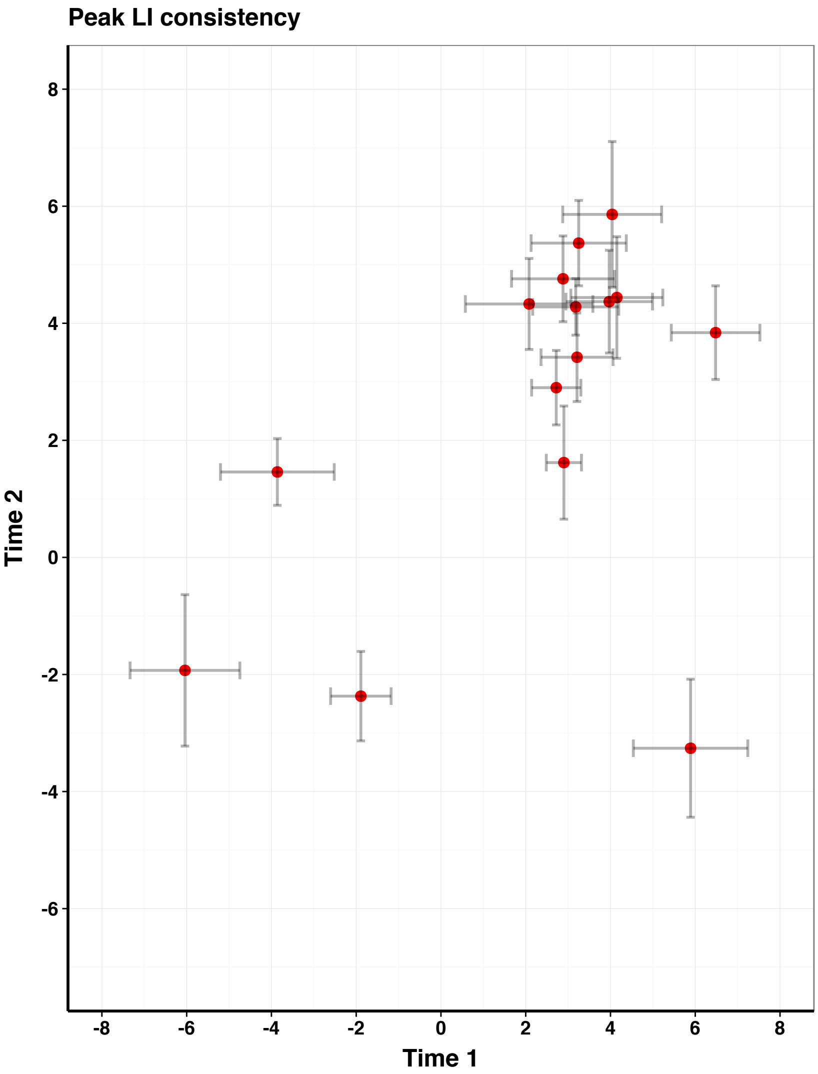

Figure 9.4: LIs with standard errors for each time point

	1	2	3	4	5
1. RAN					
2. Comprehension	-0.38				
3. Vocabulary	-0.65**	0.37			
4. Letter knowledge	-0.60*	0.60**	0.72***		
5. Card LQ	-0.38	0.10	0.37	0.24	
6. Words/trial	-0.07	0.06	-0.10	-0.26	-0.36

Table 9.3: Correlations between behavioural measures at Time 1.

	1	2	3	4	5	6
1. RAN						
2. Comprehension	-0.42					
3. Vocabulary	-0.32	0.60**				
4. Letter knowledge	-0.70**	0.32	0.50*			
5. Card LQ	-0.41	-0.36	0.01	0.49*		
6. Word reading	-0.08	0.20	0.46	0.56*	0.17	
7. Words/trial	-0.14	0.18	0.08	-0.15	0.00	-0.19

Table 9.4: Correlations between behavioural measures at Time 2.

Secondary analysis

In a minority of cases there were several potential points within the period of interest that could have been maxima (see Figure 9.7). A slight difference in normalisation process or heart cycle integration could lead a different maximum to be identified and therefore a different LI to be calculated. I therefore chose to recalculate the LIs based on the entire active period to allow the entire difference between left and right to be taken into account. This issue is explored further in the General Discussion. Figure 9.7 demonstrates the differences in approach. This alternative approach is appealing when considering potential correlations between lateralisation and behaviour, as the right-left difference in CBFV for the entire period is a more conservative way of estimating laterality and may prove to be more robust in some cases (see Part 12). Figure 9.6 shows how the two participants who appear to change lateralisation from T1 to T2 are deemed as more consistent (low lateralised) at both time points using the more conservative analysis. Given the novelty of the method and simplicity of the LI calculated here, we propose that the extent of lateralisation across the whole period of language production is a more suitable measurement to minimise apparent changes in laterality which may be artefactual.

Reanalysis in this way did not drastically change the overall results,

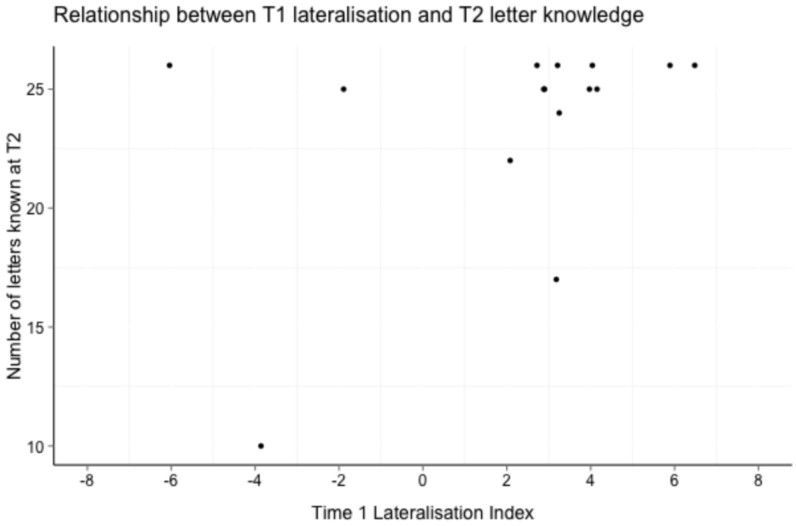

Figure 9.5: Strength of lateralisation and number of letters known at T2.

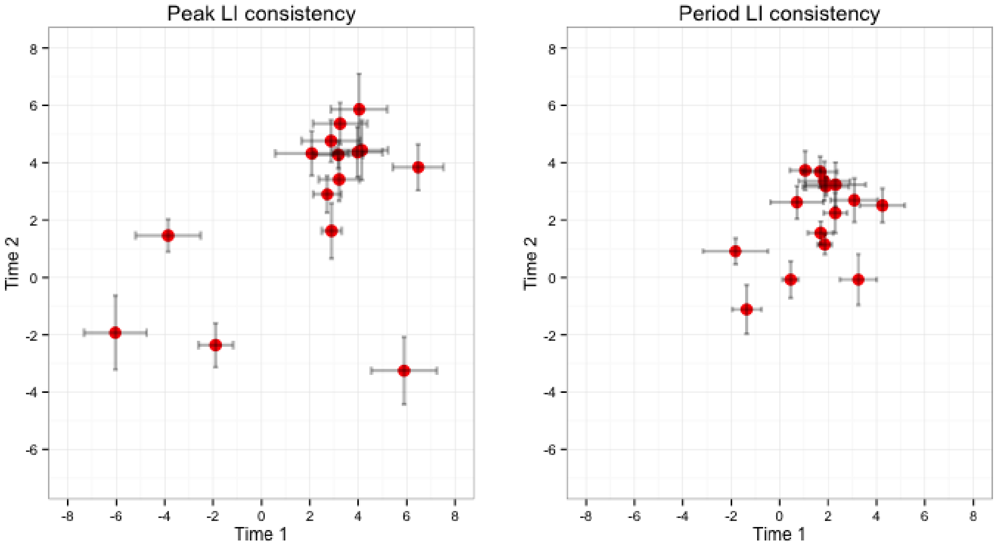

Figure 9.6: Reproducibility of LIs from Time 1 (x axes) to Time 2 (y axes) for each analysis type.

however the LIs were now more normally distributed as reflected in a non-significant Shapiro-Wilk test of normality (T1 statistic = .94, df = 15, p = .33; T2 statistic = .91, df = 15, p = .15). The split-half reliability was still good (T1, r = .52, p = .04; T2, r = .64, p = .005). Standard error estimates of LIs were significantly lower for both T1 (t(14) = 3.8, p = .002) and T2 (t(17) = 5.6, $p < .001$). Concurrent correlations with behaviour were unchanged (all p's > .1, ns). Two correlations between measures at different time points now reached significance. The first was a positive correlation between strength of lateralisation at T1 and letter knowledge (standard score) at T2: r = .66, p = .007). The second was a positive relationship between strength of lateralisation at T1 and gains in vocabulary knowledge raw score (r = .55, p = .03).

9.4 Discussion

There is currently no consensus on whether hemispheric lateralisation for language processing increases with age. Previous studies have either used cross-sectional designs to test correlations with age or have not accounted for differences in task performance over time. The current study combined the increased predictive power of testing longitudinally, as opposed to a cross-sectional design, with precise measurement of online task performance. In doing so, we hoped to answer two questions about language lateralisation in young children using fTCD. First we tested whether the strength of lateralisation increases over the preschool year (3 years to 4 years). Second we tested whether there was a relationship between strength of hemispheric lateralisation and language proficiency.

Hemispheric lateralisation for language production at 3 and 4 years old

Previous studies of hemispheric lateralisation using fTCD have tested children aged 4 and older, that is - after they have started school (Bishop et al 2009, 2014; Groen et al., 2012) or included a range of ages with only one child aged under 4 (Lohmann et al., 2005). In the current study, we tested children in the preschool year, who had not yet started formal literacy training. During an expressive language production task we found significant group-level left lateralisation. The extent and distribution of lateralisation was comparable to other studies adopting the same task protocols (see Table 9.5). Contrary to our predictions we did not observe any group level increases in the strength of lateralisation between testing points at 3 and 4 years.

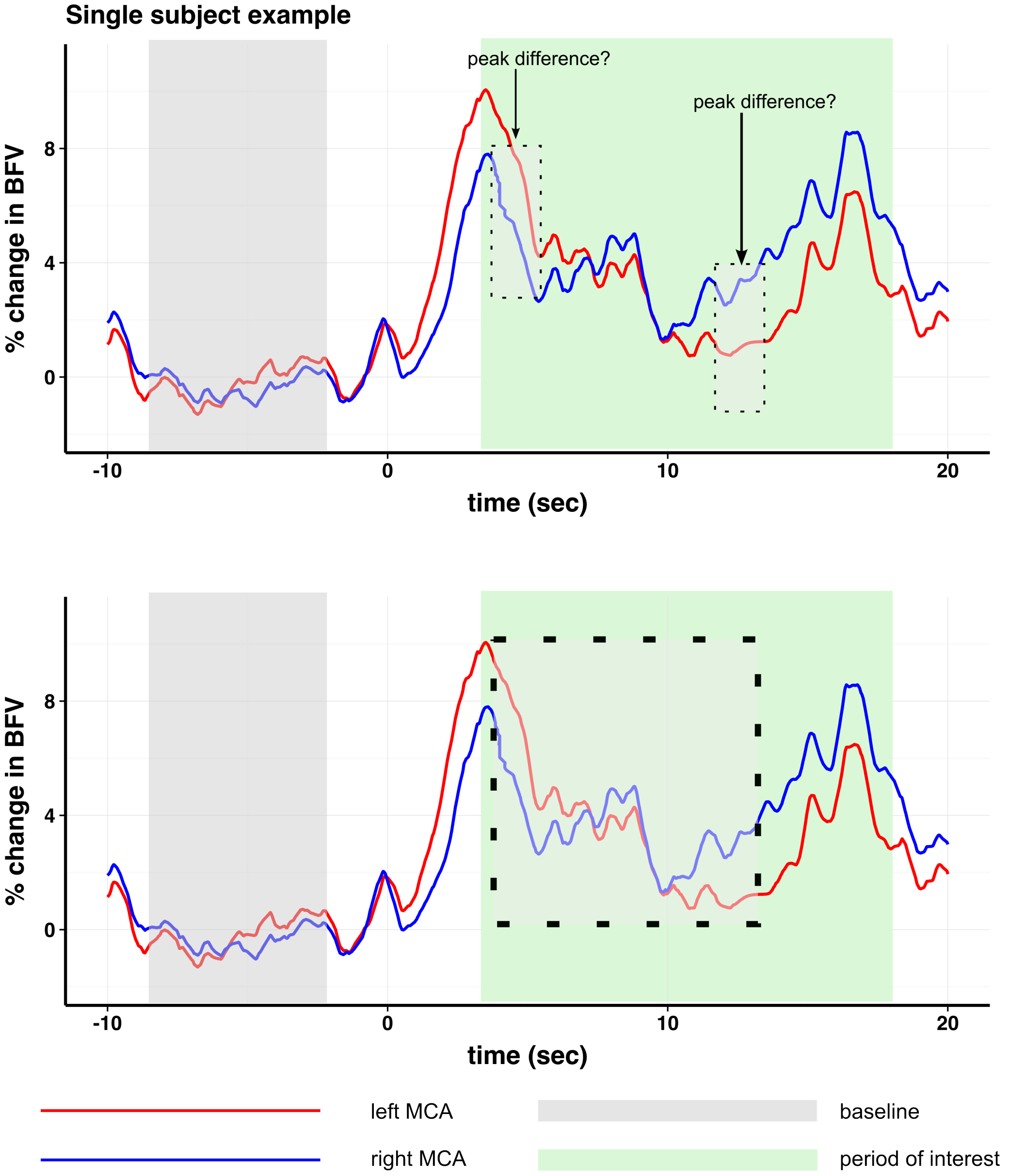

Figure 9.7: For illustrative purposes: calculating the LI from maximum differences versus whole period.

Author (year)	Age	LI	Categories		
	Mean (SD)		% left	% right	% low
Bishop et al., (2009)	4.1 (0.6)	1.9 (3.8)	62	19	19
Groen et al., (2012)	10.7 (2.5-estimated)	2.1 (3.2)	80	15	5
Chilosi et al., (2014)	8.5 (3.0)	1.7 (0.9)	70	20	10
Current study T1	3.8 (0.3)	2.2 (3.5)	73	20	7
Current study T2	4.8 (0.3)	2.6 (2.9)	73	13.5	13.5

Table 9.5: Comparison with previous studies using the animation description task with typically developing children

This finding fits with a recent cross-sectional study of lateralisation during language production in a study using fNIRS (Paquette et al., 2015). Here children in the youngest of the three groups (3-6 years old) showed significantly left-lateralised haemoglobin concentration changes across frontal channels. Despite better performance in the fluency task in older groups, there were no differences in the extent of lateralised responses between groups. Older participants showed stronger activation overall, but this was not specific to either hemisphere. There was some evidence however that the number of words generated correlated with haemoglobin concentration in left frontal channels, ($r = .30$, $p = .06$), raising the possibility that differences in performance could drive lateralisation in young children, obscuring any potential group differences due to other factors such as age. Our data support this pattern. At T2, there was a trend towards higher (more left-lateralised) LIs in children who produce more during the active period.

The relationship between lateralisation and language proficiency

Aside from testing the relationship with the amount of speech output during the task, we also sought to examine whether a child's level of language proficiency relates to differences in lateralisation. Lateralisation can be treated either categorically or as varying in strength. We considered each of these possibilities in turn in relation to the current study.

At each time point, there were no significant differences in standardised scores of language level for children categorised as left-lateralised versus low or right lateralised. There was also no evidence for concurrent associations between strength of lateralisation (considered as a continuous variable) and offline measures of language and literacy.

Across testing points however, we found evidence of relationships between lateralisation and language proficiency. Stronger lateralisation at T1 was associated with better letter knowledge at T2. With a larger sample size, it would be possible to test a regression model predicting early reading scores from letter knowledge and lateralisation, but the numbers here are too small for this to be meaningful. A question arises as to why, in the presence of a correlation across time points, we did not observe any concurrent relationship between strength of lateralisation and letter knowledge at T2. It is possible that the smaller variability in letter knowledge at T2 (all the children knew at least 16 letter sounds) made testing correlations between other variables and letter knowledge at T2 less sensitive. A significant Levene's test of homogeniety of variance between letter scores at T1 and T2 provides some support for this suggestion (W(1,34) = 11.5, p = .002).

Future considerations

This study has limitations in its ability to sufficiently test longitudinal changes in lateralisation, most clearly in its longevity and sample size. Testing developmental trajectories (or any repeated measures design) benefits from a greater number of sample points in time to allow a mixed effects model to be estimated. A double baseline design could have increased the validity, allowing better interpretation of our null result. The current study, with only two testing points was therefore somewhat limited in its ability to examine developmental change. In terms of sample size, we acknowledge that testing a group this size is likely to be insufficiently powered to detect small effects over time. Weiss-Croft & Baldeweg (2015) reviewed the literature addressing potential developmental changes in the strength of lateralisation and concluded the few reliable effects of age had small effect sizes (estimated using coefficient of determination, R^2). In the current study, a post-hoc power calculation indicated that a sample size of 15 would be only sufficiently powered (80%) to detect an effect size of greater than Cohen's d = 0.7 (corresponding to a large effect size). To detect a medium effect size, as has been reported in previous studies of developmental changes in lateralisation, an estimated sample size of 51 would be needed. As a proof of concept however, in testing very young children using fTCD and the Animation Description task (Bishop et al., 2009), this study provides important preliminary data.

Another consideration with the data collected here is the difference in epochs attempted at Time 1 and Time 2 by some of the participants. It is therefore possible that one or other testing session involved noisier and have less reliable data. Some evidence for this is the significant difference in SEMs at T1 and T2. Relying on split-half reliability as a measure of data quality may not sufficiently screen out children with non-optimal placing of probes (for a further discussion of this, see Part 12).

In the current study we assessed lateralisation of a storytelling task which tests many subcomponent of language and extralinguistic skills. Activity during speech production is assessed relative to the control period during which the children watched the video clip in silence. While pilot data has suggested children do not show lateralisation during video watching (Bishop et al., 2009), individual variability in activity during passive video watching has not been tested empirically, to our knowledge. Therefore, it is possible that age-related changes in lateralisation during the video watching could obscure any changes in the active period.

Having data from several tasks to compare trajectories may help to alleviate some of these concerns. For example, a simple syllable repetition task at a constant pace would provide a comparison between lateralisation associated with articulatory planning and execution and that which relates to higher order narrative construction skills.

Summary

This study replicates findings of left-lateralisation of narrative production in young children using fTCD. As such, it contributes to ensuring the validity of this technique in developmental science. The novel aspects of our findings raise two important points. The first relates to claims that lateralisation strengthens through development. Here we saw that despite large gains in performance on behavioural measures, strength of lateralisation was not significantly changed. The second point is preliminary evidence for a relationship between the establishment of robust left-lateralisation during a spoken language production task at age 3 showing a relationship with letter knowledge a year later. If this finding holds in a larger sample, it suggests that the organisation of the neural systems supporting spoken language in early childhood may exert some influence on future literacy attainment. Alternatively both skills could be underpinned by common, early specified skills such as sensitivity to the phonological structure of connected speech.

Closer analysis of the task and baseline demands in terms of their impact on lateralisation will help to strengthen the interpretations we can draw from these data. This small study is limited in its ability to generalise to a wider population, given its limited power. However, as a first step in validating longitudinal testing using fTCD, this study lays some of the groundwork for testing whether left lateralisation during language processing (in this case, expressive language production) is a cause or consequence of the development of language proficiency.

Chapter 10

Language lateralisation in children born deaf

10.1 Introduction

The developmental study described in Chapter 9 focused on typically developing children for whom there is relatively little variability in language input. In contrast, children born severely or profoundly deaf have hugely diverse backgrounds in terms of their exposure to language. One main source of variability is the language environment of the child, specifically in terms of the modality of language used at home; speech, sign, or both. A second main source of variability is whether they receive an amplification device such as a hearing-aid or cochlear implant which may or may not provide some access to auditory speech. Therefore, studying lateralisation during language processing in deaf children provides a unique perspective on the potential relationship between exposure to language and lateralisation.

Directly assessing functional hemispheric asymmetries using brain imaging has been difficult in this population, given that cochlear implants have until recently been contraindicated with fMRI and remain so except where there is clinical need. To date, only one study has directly investigated functional hemispheric asymmetries in *children* born profoundly deaf, using fTCD which is safe for cochlear implants and permits greater freedom of movement than other imaging modalities. Chilosi et al. (2014) tested children who had received cochlear implants, with the aim of testing the effects of auditory input on language lateralisation. The authors reported that deaf children with cochlear implants (CI) showed typical left hemisphere lateralisation of cerebral blood flow during a speech production task. The cochlear implanted group were not significantly more or less lateralised than age-matched hearing controls. The authors claimed that 'neurodevelopmental plasticity after CI seems to be influenced by stimulus-driven experience,' arguing for a critical role of the auditory input received from the CI. However, deaf children, with or without implants, access language through visual speech and, in some cases, a signed language: both of which have been shown to be robustly left lateralised in deaf adults (see MacSweeney et al., 2008). Attributing left lateralisation of speech production in deaf adolescents with CI to increased auditory input may be premature, especially without either a control group of deaf children without CIs or a pre- and post-implant assessment of lateralisation.

Variability in language experience

The signed and spoken language input experienced by individuals born deaf is extremely variable. A small proportion of deaf children, those born to Deaf[1] parents, may learn a signed language as their first language and consequently show similar milestones in language development (Morgan & Woll, 2002). However, approximately 95% of deaf individuals are born to hearing parents, who may or may not learn a sign language. Therefore, the majority of deaf children are unlikely to be exposed to a full grammatical sign language from birth (Mitchell & Karchmer, 2004). As well as atypical experience of language input due to differences in exposure to sign language, there is also large variability in terms of deaf individual's experience of spoken language. On one hand, variability in exposure to visual speech is minimal, because all deaf children grow up in predominantly hearing/speaking societies. On the other hand, access to auditory speech varies greatly depending on the type of (if any) amplification device used by the child, as well as the age at which they receive the amplification. The typical clinical picture in the UK is that a high proportion of deaf children will have a cochlear implant, and many will have bilateral cochlear implants before they turn 3 years old. It is estimated that approximately 70% of eligible 0-3 year olds will receive mono- or bi-lateral implants (Raine, 2013). Given that most profoundly deaf children are now fitted with cochlear implants, many deaf children will have some access to speech sounds. Although children with cochlear implants make huge gains in spoken language and literacy (Geers & Nicholas, 2013), it is nonetheless the case that they still have impoverished access to spoken English compared to typically hearing children, and the amount of useful speech information gained through an implant varies widely.

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[1] Capitalised 'Deaf' is used here to describe individuals who self-identify as members of the Deaf community and who primarily use sign language.

For these reasons, deaf children have extremely variable language exposure in their early years and develop signed and spoken languages to varying degrees of proficiency (Marschark et al., 2009). The current study capitalises on the variability of language experience in young deaf children to investigate whether atypical experience of speech impacts on language lateralisation. The effect of atypical language experience on lateralisation cannot be considered without also acknowledging that language exposure will be confounded with proficiency. That is, earlier exposure to a richer source of language input is associated with age-appropriate language development in deaf children, whether for sign language acquisition (Mayberry et al., 2011) or spoken language acquisition in those children with cochlear implants (Tomblin et al., 2005). Therefore, in the current study, we will collect a range of offline language measures in addition to information about the language background of the children. We will assume that children with good language skills, regardless of modality, have had rich language input in that modality, though we acknowledge that proficiency may also relate to other extraneous, non-linguistic factors, for example, attention, working memory or socio-economic status.

Assessing language lateralisation in deaf children

The role of reduced or atypical language experience in the development of lateralisation has been of theoretical interest for some time (e.g. Gottleib et al., 1964). To answer questions about lateralisation for visual language in the absence of auditory input, developmental studies have tended to focus on manual asymmetry as a proxy for language lateralisation. Early studies of handedness prevalence reported greater incidence of left-handendess (Bonvillian et al., 1982; Conrad, 1979; Myklebust, 1960) or low/mixed handedness (Mandal et al., 1999; Gibson & Bryden, 1984). Alongside evidence from dual-task (Marcotte & Morere, 1990) and tactile field preference paradigms (Gibson & Bryden, 1984), the higher incidence of mixed or left-handedness was interpreted as evidence that impoverished access to language within a critical period could lead to atypical cerebral lateralisation (Mandal et al., 1999).

There are two main issues with these findings and their interpretation, meaning we cannot readily conclude that deaf children show atypical language lateralisation. The first is that the prevalence of atypical handedness in deaf people does not appear to differ from hearing people, when suitable measures of handedness are adopted (Papadatou-Pastou & Sáfár, 2016). The second issue is that there is no simple link between handedness and cerebral lateralisation. The lack of association is reported for functional asymmetry

(Cochet, 2016; Somers et al., 2015; B. Mazoyer et al., 2014; Groen et al., 2013), as well as structural asymmetry (Guadalupe et al., 2014). Any relationships between handedness and language lateralisation seem to depend on the strength of intrahemispheric connectivity (Joliot et al., 2016).

Studies more directly assessing the neural bases of language processing in individuals born deaf have all taken place with adults. Furthermore, they have specifically focused on the small population of deaf native signers, proficient in one or more language modality. These studies have shown that, in adulthood, deaf individuals show typical left-lateralised neural responses during the production and comprehension of signed languages (MacSweeney, Capek, et al., 2008; Braun et al., 2001; Corina et al., 2003; Emmorey et al., 2003; McGuire et al., 1997) and for processing visual speech (speechreading) (Capek et al., 2008). However, these studies have not included the range of proficiency typically observed in those with heterogeneous language backgrounds, and cannot answer questions about the role of input in the development of lateralisation.

The current study

In the current study, we assess lateralisation of blood flow during language production in a heterogeneous sample of children born profoundly deaf. In line with studies of deaf adults, we predict left lateralisation at the group level for language production in deaf children. By including a representative sample of deaf children, including those with and without CI, and those who use a signed language, we are also able to test exploratory hypotheses about both language experience and language proficiency.

If left-lateralisation of language production relates to auditory speech input, we should observe greater left-lateralised responses for those with cochlear implants than those without. Rather, we predict that left lateralisation for language is driven by language proficiency in any language modality. That is, we predict no difference between those with CI and those without and furthermore that strength of LI correlates positively with language proficiency measured by vocabulary (in sign or speech).

10.2 Method

General design and procedure

Testing took place over two or three sessions on separate days. Children were tested in separate rooms at their respective schools. In some cases, the child had a learning support assistant to accompany them. In the majority of testing sessions where BSL was required, a research assistant, fluent in BSL and with experience of administering cognitive assessments, accompanied the experimenter. In four of the sessions the experimenter gave the instructions herself, in BSL or Sign Supported English (SSE).

Participants

Thirty severely and profoundly deaf children were recruited from UK mainstream schools (1), hearing support units (17), and specialist deaf schools (12). It was not possible to record fTCD data for six of these children due to initial signal-finding difficulties (4 children), interference with the placement of probes from glasses (1 child), or inability to attempt a sufficient number of trials (1 child). Therefore, data were collected from 24 children (14 male). The average age of the sample was (7;10, min = 5;0, max = 11;5). All children had normal non-verbal IQ as assessed by the British Ability Scales, 3rd edition (BAS-III; Elliot & Smith., 2011) *Pattern Construction* task (mean standard score = 48.9, min = 34, max = 66). Further inclusion criteria were applied later in the analysis (see Results) therefore demographics for the final sample are given in the Results section.

Materials

Language and literacy

Language proficiency was assessed across four domains – reading accuracy, speechreading, and BSL comprehension and vocabulary knowledge. Reading accuracy and speechreading were included to estimate the child's level of receptive language proficiency in English. BSL comprehension was included to assess receptive proficiency in BSL. Vocabulary knowledge was included as a best attempt to capture a general level of language ability, regardless of the modality of the output. Reading was measured using the Single Word and/or Early Word Reading subtests of the York Assessment of Reading Comprehension (YARC, Hulme et al.,2009). Single word reading was attempted only if the child could complete the majority of the Early Word Reading subtest, so as not to demotivate the child for the later tasks.

Speechreading accuracy was assessed using the Test of Child Speechreading, Single Word and Sentences subtests (ToCS, Kyle et al., 2013). In this computerised task, children are presented with a single item or sentence spoken by one of two models. The child is asked to point to the corresponding picture for the object or sentence. Distractor items shared visual properties with the target (visemes), either for the initial, vowel or final segment. This task has been standardized with 86 deaf children (Kyle et al., 2013) and used in several studies of language and literacy in separate cohorts of hearing children and those with language impairments (e.g. Knowland et al., 2016).

BSL was assessed using the British Sign Language Receptive Test (Herman et al., 1999). In this task, children watch a series of clips in BSL, and are asked to select a corresponding picture from four options. The sentences test the child's comprehension of BSL word order, placement, and classifiers (handshapes to denote particular properties of nouns). Prior to testing, children are asked to produce signs in response to pictures of all nouns that appear in the clips, which acts a screen for sufficient vocabulary knowledge to complete the task. Children who could produce fewer than 50% of the signs did not continue with the test. This information was corroborated with teacher report of language preferences. In our sample, those children who did not successfully complete the vocabulary screen were all deemed to have little or no exposure to BSL in teacher report.

Vocabulary knowledge was estimated using the Naming Vocabulary subtest of the British Ability Scales (BAS-III; Elliot & Smith, 2012). Given that standard scores for these scales are normed for hearing children, we report only raw scores. For word reading and vocabulary knowledge, points were awarded in a cumulative manner, such that if the child knew the item in either English or BSL they would be awarded a point. Some children provided both but this was not reflected in their scores.

Handedness

Handedness was assessed using the two measures of hand preference that were used in Chapter 9: a card reaching task (Bishop et al., 1996) and observations of tool use. For the card reaching task (Bishop et al., 1996), twenty-one cards depicting highly nameable objects were placed at seven evenly spaced locations in a semi-circle in front of the child. The locations were 40cm away from the child at approximately 30 degree intervals. In a random order, which was the same for every child, the experimenter asked the child to reach for a given card and place it in a pile in front of them. Children were instructed to place their hands in their lap between each card. The experimenter marked which hand is used to reach (right (R), left (L), or both (B)) for each card. A laterality quotient (LQ), was calculated for each child, given by

$$LQ = \frac{(R - L)}{(R + L + B)} \times 100 \tag{10.1}$$

The second handedness measure was a simple tool-use inventory, following Annett (1970). Items included were pencil, scissors, pouring from a jug to a cup and drinking from a cup. Children were instructed to place their hands on their lap while the experimenter put the item/s on the table in front of them. First a pencil was placed in the middle of a piece of paper and children were asked to draw a picture. The other objects were scissors, pouring from a jug into a glass (the latter placed behind the jug to avoid bias), and picking up a glass. The experimenter marked whether the child used right, left, or both hands for each item.

fTCD

Changes in cerebral blood flow velocity (CBFV) were recorded during the same Animation Description task described in Chapter 9. The task, developed in Bishop et al. (2009), has been used with 4-10 year olds (Bishop et al., 2009; Groen et al., 2012; 2013), and was also used in the study of school-aged children with cochlear implants described above (Chilosi et al., 2014). Laterality Indices measured for this task show good reliability within and across testing sessions (Bishop et al., 2009).

During the task, the child was asked to watch a cartoon of a penguin in a series of clips (maximum 30 clips, dependent on the child's compliance). A period of silent watching (12s) is followed by a prompt for the child to describe the events of the animation (10s) after which the child is instructed to sit quietly for a rest period of 16 seconds. After the rest period, the experimenter checks the child was ready to proceed to the next clip to ensure maintained attention.

Children were not prompted to use a specific language, but children who communicated predominantly in BSL were given the instructions in BSL. The child is then instructed to sit quietly for a rest period of 16 seconds. To ensure the best possible fTCD recording, we commissioned a custom-made child-friendly elastic headset to allow for minimum interference with cochlear implant magnets and hearing aids. Responses were recorded using a digital video camera and tripod, and where appropriate, a digital dictaphone as a backup.

fTCD data analysis

The data were analysed in much the same way as those in Chapter 5, with the same minor adjustments from the adult pipeline as in Chapter 9. The CBFV envelope was epoched from -12 to 26s around the onset of the active report period ("What happened there?"). Baseline correction was applied to sample points between -10 and -2s pre-trigger. Normalisation for each channel was done on an epoch-by-epoch basis and activation that was +/- 40% of this normed data was considered to be unacceptably high or low. Trials with more than 5% activation outside of this range were rejected. Trials with less than 5% were corrected as before (see Chapter 9). Lateralisation Indices were calculated in the typical way for the peak difference between left and right channels within a period of interest which ran from 4 – 18s.

Task performance analysis

Videos of behavioural responses were coded using ELAN transcription software (http://tla.mpi.nl/tools/tla-tools/elan; Max Planck Institute for Psycholinguistics, The Language Archive, Nijmegen, The Netherlands). This allows time-aligned annotations for multiple tiers of description. For example, a child's utterances can be marked using a separate tier for each hand and another for speech. Here, onsets and offsets of the following actions were coded for right-hand, left-hand, and speech:

- during the video presentation (which is the period against which we baseline correct)
- during the active period (where the child is asked to describe the animations)
- during the 'shh' relax period (used to allow blood flow velocity to return to near-resting levels).

Total seconds of each transcription were calculated and averaged over the number of viable epochs for that child. Merged totals of hand-movement (right plus left) and communication (any) were calculated from the transcriptions. Adjusting of the headset was also coded regardless of where in the trial it occurred (i.e. rest or active periods). Trials with any significant headset adjustment will usually be picked up by artefact rejection because the speed of the adjusted probe will be >20% than the mean blood flow of the total recording, however this was also checked manually and any trials which included periods of headset adjustment were manually removed. Manual rejection was also applied to instances where the child produced utterances during the baseline or for the majority of the 'shh' relax period. Instances of self-grooming, brief points or single short vocalisations were ignored.

10.3 Results

Demographic information for each child can be found in Table 10.1.

Child n	Gender	Age	Reaching LQ	Object LQ	Amplification	LI	Group
		y;m				M(SD)	
1	M	5;0	0.5	100	HA	6.1 (1.6)	Left
2	F	5;6	-0.1	50	HA	5.1 (4.6)	Left
3	M	6;5	-0.1	50	HA	4.2 (4.0)	Left
4	M	6;5	0.0	100	HA	2.7 (3.2)	Left
5	M	8;9	0.1	0	HA	2.8 (2.5)	Left
6	F	9;3	0.1	100	HA	2.2 (3.0)	Left
7	F	9;7	0.5	100	HA	-2.3 (1.3)	Right
8	M	10;1	0.3	100	HA	3.9 (2.5)	Left
9	F	10;8	0.2	100	HA	2.4 (3.3)	Left
10	M	11;3	0.4	50	HA	-4.9 (2.4)	Right
11	M	7;10	-	100	BAHA	4.5 (2.5)	Left
12	F	5;1	0.2	75	CI	4.3 (2.2)	Left
13	M	5;3	0.2	100	CI	5.6 (2.2)	Left
14	M	5;3	0.5	100	CI	2.5 (2.0)	Left
15	M	5;4	0.2	100	CI	3.5 (2.6)	Left
16	M	5;11	-0.4	-50	CI	3.0 (1.7)	Left
17	F	6;8	0.2	50	CI	-1.8 (1.9)	Low
18	M	7;5	-0.1	100	CI	4.7 (2.6)	Left
19	F	7;9	0.5	100	CI	2.8 (1.6)	Left
20	F	8;5	0.5	100	CI	-3.4 (4.6)	Low
21	M	8;10	0.3	100	CI	1.4 (2.5)	Low
22	M	9;10	-	50	CI	-4.8 (2.5)	Right
23	F	9;11	0.5	100	CI	3.3 (2.4)	Left
24	F	11;5	0.5	100	CI	4.7 (4.9)	Left
Mean (SD)	-	7;9	0.2 (0.2)	79 (39)	-	2.2 (3.2)	-

Table 10.1: Details about each child tested (n = 24). BAHA = bone-anchored hearing aid; CI = cochlear implant; HA = hearing-aid; LQ = laterality quotient. Italicized entries denote cases not included in group analyses.

fTCD data quality

Data from three children were identified as potentially poor quality during the first phase of data analysis (italicised in Table 10.1). In two cases this was due to a low number of trials after epoch rejection (<9) combined with non-optimal signal on visual inspection. In the other case the child had >9 epochs accepted and good recording at visual inspection but a high number of epochs rejected due to speech during the relax period (leaving only 6 trials to analyse). The following analyses of group LIs were run with and without these participants with no change to the main findings. The statistics below reflect the data from the more restricted group of 21 children (13 male). The average age of the group was 8;0 (min = 5;0, max = 11;5).

Split-half reliability for the group was good (r = .91, $p < .001$), indicating consistency in lateralisation through the recording. The average number of suitable trials was 14.4 (3.8) (min = 9, max = 22), and the average latency of the peak difference within the period of interest was 11.0 (2.8) (min = 6.4,

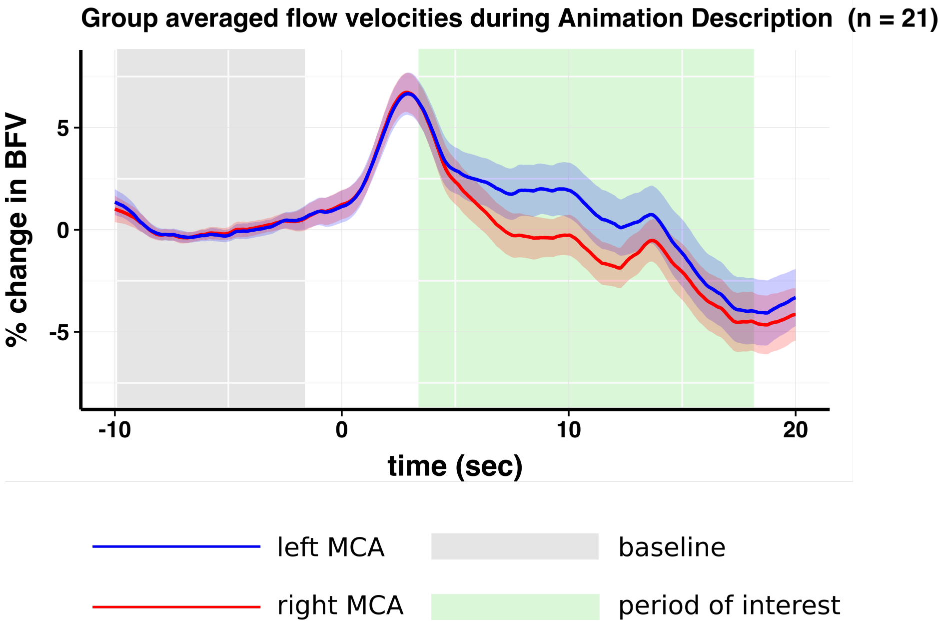

Figure 10.1: Group averaged changes in CBFV during Animation Description. Shaded areas indicate standard errors at each sample point.

LI	Peak Sec	Categories		
M(SD)		# left	# right	# low
2.5 (3.0)	11.0 (2.8)	17 (81%)	3 (14%)	1 (5%)

Table 10.2: Descriptives of Laterality Indices and categories for the full group

max = 17.7).

Whole group fTCD results

Group averaged CBFV change for all available epochs is shown in Figure 10.1. This plot shows the entire group, independent of language modality or cochlear implant status. Table 10.2 gives group level descriptive statistics for the mean LI and numbers of participants who showed significant left or right lateralisation, or no significant lateralisation (low). The mean LI for the group was significantly different from 0 ($t(20) = 3.8$, $p = .001$), indicating group level left-lateralisation.

	Cochlear Implant	Hearing Aid	Test Statistic	p
N	10	10		
Gender	6 male	7 male	$\chi^2 = .6$	.7
Age (y;m)	8;4	7;8	t = .61	.55
Vocabulary in sign/speech (M)	150	150	t < .001	> .9
Seconds of sign and/or speech (M)	7.9	7.5	t = -.39	.7

Table 10.3: Demographic and behavioural data for children with and without cochlear implants.

Effects of auditory speech experience on lateralisation

To address the question of whether increased access to auditory speech drives typical left-lateralisation for language, we broke the group down by hearing aid status. Table 10.3 shows the composition of these two groups in terms of age, gender, and vocabulary ability scores. The groups were comparable in their language proficiency (vocabulary in sign and speech) scores (t(18) = 0.0, p = .68, implanted mean = 149.8 (34.4), non-implanted mean = 149.8, (32.4). There were also no significant differences between implanted and non-implanted subgroups in the average amount of communication (either in speech or sign), t(17) = -.39, p = .70, implanted mean = 7.9 sec (2.5), non-implanted mean = 7.5 sec (2.3). Figure 10.2 shows CBFV changes over the available averaged trials for the implanted (top panel) and non-implanted (bottom panel) children. One child was not included in this analysis as they had received a Bone Anchored Hearing Aid, which does not fit easily into either CI or non-CI group.

Paired sample t-tests of the LIs for the implanted (n = 10) and non-implanted group (n = 10) revealed no significant differences in the strength of lateralisation (t(18 = -.22, p = .54: implanted mean = 2.5 (2.8), non-implanted mean = 2.2 (3.4).

Associations between lateralisation and language proficiency

Given the small proportion of children who showed atypical low or right lateralisation (4/21), we were unable to test whether typical left-lateralisation relates to proficiency (i.e. whether differences are observed between those categorised as typical versus atypical lateralisation, as per Groen et al., 2012).

An alternative option is to test whether the *strength* of lateralisation relies on the development of language in any modality. To do this, we considered absolute LIs, regardless of direction, and tested the association between

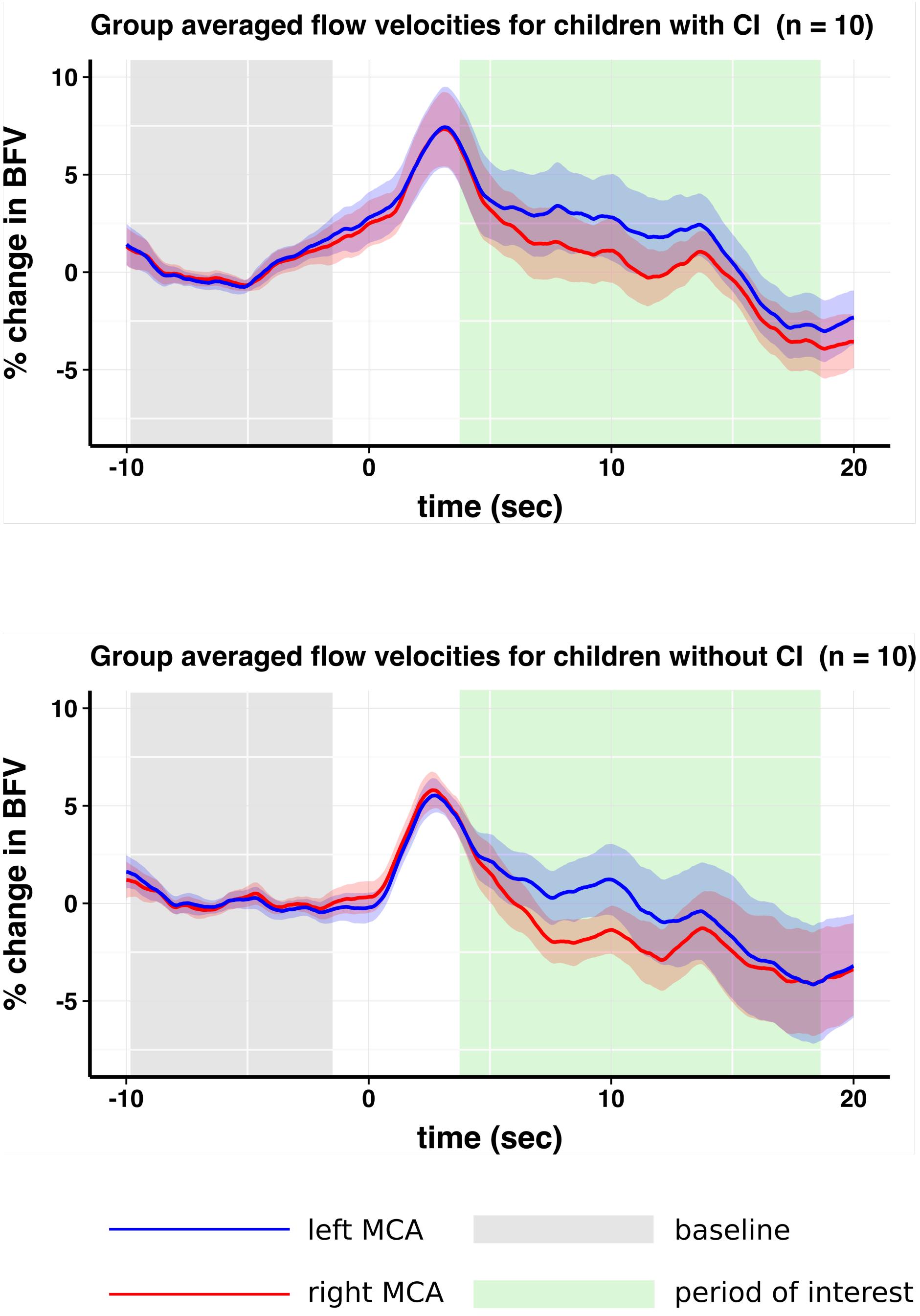

Figure 10.2: Group averaged changes in CBFV during for implanted (top) and non-implanted (bottom) children. Shaded areas indicate standard errors at each sample point.

strength of lateralisation and vocabulary. There was no evidence of an association (r = -.34, p = .13).

Language proficiency could also be estimated in the current study by measuring the amount of language produced, in sign or speech, during the active period. This measure correlated well with the offline vocabulary measure of proficiency (which credited sign and speech) (r = .70, p = .001), and with the measure of BSL comprehension which we used to estimate proficiency for sign (r = .85, p = .03). However, there was no significant relationship between the amount of communication produced by the child and their strength of lateralisation (r = -.4, p = .08).

10.4 Discussion

The current study used fTCD to assess lateralisation for language processing in a group of children born deaf. The study offers further evidence for the suitability of fTCD to assess lateralisation in children with cochlear implants (CIs). The study builds on a previous finding of left-lateralisation in a group of deaf children with CIs using the same Animation Description paradigm (Chilosi et al., 2014).

Testing the effects of auditory speech input

Specifically, this study aimed to test an alternative interpretation of the data presented by Chilosi and colleagues (2014). Using fTCD, the authors observed group level left lateralisation during speech generation in school-aged children who had received cochlear implants. The LIs of the children with cochlear implants did not differ in strength from those of a hearing comparison group. They also observed similar numbers of children categorised as left, low, or right lateralised in each group, which were also in line with other studies of hearing children using language generation tasks. The authors interpreted this as evidence for developmental plasticity, specifically related to deprivation *and subsequent re-afferation* of networks which support language processing.

An alternative interpretation of typical left-lateralised activity during language production in deaf children with cochlear implants is that they have, to varying degrees of proficiency, learned language. That is, it is not the re-afferation of auditory cortices which drives lateralisation for language production. Rather, it is the exposure to and development of structured language. To test this, we recruited a heterogeneous group of deaf children who had a range of language backgrounds and variability in their experience of auditory speech. We found that in this group, regardless of hearing aid status or mode of language production, deaf children, as a group, showed typical left-lateralisation during language production. We found no differences in the strength of lateralisation between those who had received cochlear implants and those who had not. It seems therefore premature to attribute left-lateralisation in deaf children to their implant status and therefore their access to auditory speech input.

Testing the effects of language proficiency

We predicted a role for language learning in the development of typical left-lateralisation, in the form of an association between the level of language proficiency (whether in speech or sign) and typical lateralisation for language production. No such association was observed. There are several reasons why this may be the case. First, it is possible that our measure of proficiency (vocabulary knowledge in either sign or speech) is not an accurate indicator of the child's general language level. Assessing vocabulary knowledge as age-appropriate or not in deaf children who use BSL should be done using items which have been normed on deaf native signers, rather than adapting a scale which has been developed for hearing children. Such norms are not currently available. It is possible that the age of acquisition of some of the items used in the BAS-III *Naming Vocabulary* scale is later in BSL than the analogous word in English, biasing the test to rate proficiency as higher in those with spoken language. However, it seems unlikely that this would drastically affect the correlations between proficiency and LI. The measure of vocabulary was positively correlated with other offline measures of language ability used here, including one which specifically assessed BSL development. There was also a positive correlation between vocabulary and the amount of communication that took place in the active period. This suggests that the children with higher vocabulary scores were indeed those with more advanced levels of language proficiency. Nonetheless, we were unable to adequately adjust for chronological age for the vocabulary measure, as it has not been normed on deaf children. It is also possible that other aspects of language acquisition such as the development of grammar are more strongly related to lateralisation during language production, and we did not have adequate measures to assess this in the current study.

Another issue complicating testing correlations with lateralisation is the low number of children who showed low or right lateralisation. In this study, we did not exclude left-handers (see below), but we did not actively seek to oversample left-handers in the hope of finding a sufficiently large spread of lateralisation indices (as per Whitehouse et al. (2009); Knecht et al. (2000).

The skewed distribution of LIs does not lend itself well to tests of linear association such as Pearson's product moment correlation. It is therefore preferable to either exclude those showing low or right lateralisation if they are substantially smaller in number than those with left-lateralised language, or to test correlations between absolute strength of lateralisation and the behavioural variable of interest. This is the association we tested in the current study. Testing the correlation between the strength of lateralisation and proficiency asks a different question of the data: is the degree of lateralisation related to proficiency? This subtly different question and its implications are discussed in the General Discussion (Chapter 12). In drawing conclusions from the current study, it is more accurate to say that were not able to effectively test whether proficiency in either language modality is key to driving typical adult patterns of language lateralisation.

A note on handedness

In the context of previous behavioural research into handedness in deafness as a marker for atypical cerebral lateralisation, it is of interest to note the results from three of the participants in this study who showed partial or complete left-handedness. Figure 10.3 shows the distribution of LIs from the current study, with left-handers marked in blue. One left-hander showed right lateralisation, while the other two were left-lateralised. We cannot generalise from these three cases, but we can acknowledge the similarity in distribution of handedness and language lateralisation with developmental fMRI studies (Szaflarski, Rajagopal, et al., 2012). In summary, there is currently no convincing evidence that handedness and cerebral lateralisation are more related in people born deaf than in hearing.

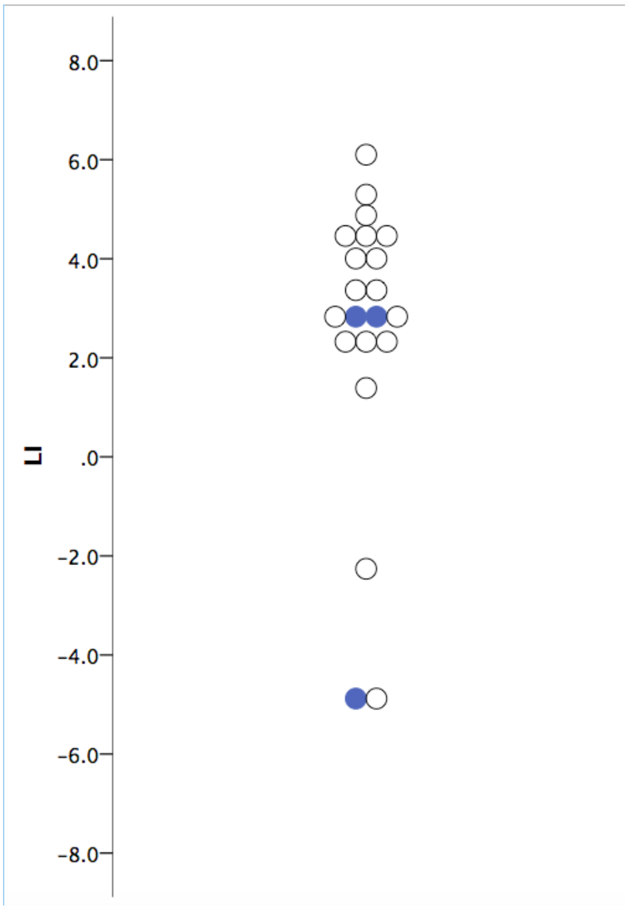

Figure 10.3: Laterality Indices for all children. Positive LIs indicate left-lateralisation, negative LIs indicate right lateralisation. Left-handed children are shown in blue.

Conclusion

This study is the first to use an imaging method to assess functional lateralisation in a representative sample of deaf children. Using fTCD permitted the measurement of online language production in children who use sign, speech, or a combination of the two. Regardless of the modality of language output and the experience of the child with auditory speech, we found that the majority of deaf children in our sample showed typical left-lateralisation. This pattern is similar to that seen in deaf adults (e.g. MacSweeney et al. (2002)).

Given the difficulties in recruiting deaf children, we decided to keep exclusion criteria to a minimum for this study. While the sample size of the whole group is similar to previous work with developmental populations (Bishop et al., 2009; Haag et al., 2010; Lohmann et al., 2005), our analysis of subgroups is likely to be underpowered. Here, we provisionally tested for differences in mean LI between CI implanted and non-implanted children and found no evidence for group differences. A recommendation would therefore be to replicate this comparison in a larger sample. Furthermore, information regarding the amount of useful speech information the child receives through their implant would be another way to assess the potential importance of speech input. Finally, examining a larger group of children learning a signed language at a range of different ages would allow us to explore differences in age of exposure to sign language on lateralisation, which appears to play a role in the neurobiology of language in deaf adults (MacSweeney, Capek, et al., 2008).

Chapter 11

Lateralisation of picture naming in hearing children

11.1 Introduction

Studies of language lateralisation in adults indicate left dominance of neural activity during a range of language tasks (Josse et al., 2006). Developmental studies, on the other hand, have tested limited aspects of language processing, often adopting tasks where online performance is not assessed. The lack of behavioural data makes interpretation of these studies difficult, especially in the context of small sample sizes which dominate the developmental cognitive neuroscience literature (Ansari & Coch, 2006).

FTCD offers a novel and simple method to address such questions, given its tolerance for overt speech responses and the ease of testing relatively large groups. A number of studies have adopted fTCD to assess lateralisation for language in children. Three studies have used a simple picture description task to assess language lateralisation in young children who may not be able to comply with the 'gold-standard' verbal fluency tasks. These have produced mixed results. Lohmann et al., (2005) and Stroobant et al., (2011) found significant group-level left lateralisation while children described animals or objects. Stroobant et al., (2011) also reported consistent direction of lateralisation over two testing points 1 month apart. Haag et al., (2010), however, reported no significant group lateralisation with only a small number of children showing left dominance whilst describing scenes from a book. The mixed results may be explained by differences in task compliance, but are difficult to interpret as there are no reported measures of online task performance.

Bishop et al. (2009) developed an animation description task as an alternative to the picture description tasks described above. The design benefited from shorter trial durations and a more engaging baseline (passively watching a video clip), rather than the silent rest baselines used in the picture description tasks. This novel Animation Description (AD) task has shown good test-retest reliability and intra-task reliability (Bishop et al., 2009; Groen et al., 2011, 2013; Bishop et al., 2014). In these studies, the authors *did* report online performance in terms of number of words produced and mean length of utterance. Neither measure related to the strength of lateralisation, suggesting that variability in lateralisation is not driven solely by differences in articulatory activity. In Chapter 9, we tested Animation Description in an independent group of school-aged children and observed good split-half task reliability and LIs comparable to those found in Bishop et al (2009; 2014) and Groen et al (2011). We found no evidence of an association between the amount of output and strength of lateralisation at the first of two testing time points, when children were 3 years old. However, a trend was observed one year later ($r = .46$, $p = .053$) with stronger left lateralisation associated with a greater number of words produced.

The Animation Description task benefits from being child friendly and engaging. However, given the wide variety of linguistic and non-linguistic processes required, it is difficult to interpret individual differences in the strength or direction of lateralisation. Animation Description relies on the child attending to and understanding the actions in the video clip, suppressing vocal responses to the clip while watching, as well as all stages from planning to execution of speech. Similarly, the earlier picture description tasks described above rely on a broad set of language skills. In these, differences in performance could be due to inability to recognise the picture, difficulties accessing additional semantic information about the picture to describe its function, or differences in sentence construction abilities, for example. None of the studies using picture description or animation description have found associations between lateralisation and offline measures of language proficiency. While it is possible that the establishment of left-lateralisation does not relate to language proficiency, it is also possible that a null result reflects the differences between the demands of the online task and those tested by standardised language measures.

We chose here to test a simple picture naming task as a way of assessing lateralisation during a task which targets fewer language subskills than free description. Using paced picture naming (also referred to as object naming in some literatures) has several benefits. First, in line with the other fTCD paradigms used with children, the task requires overt production of words. This is preferable in the case of children to ensure task compliance and measure online performance. Adopting this type of task allows the online measure of task performance to be accuracy rather than the amount of output. This provides a novel way to test the relationship between strength of lateralisation and proficiency. Second, Picture Naming as opposed to free description tasks such as Animation Description permits a higher level of control on articulatory planning and execution by presenting pictures at a fixed pace. Finally, picture naming tasks, particularly a speeded version: Rapid Automatic Naming (RAN), in behavioural research have shown good predictive power for concurrent and future literacy attainment (Lervåg & Hulme, 2009; Warmington & Hulme, 2012). Therefore, developing a task to test lateralisation of picture naming provides a first step towards a better understanding of the link between lateralisation and literacy development.

The current study aims to test a novel paced picture naming task in school aged children using fTCD, as well as related offline measures of language. Our specific aims and predictions are as follows:

- With regard to behavioural measures, we predict that measures of RAN will correlate with measures of reading fluency, following the behavioural literature on literacy development.

- We will assess reliability of the novel Picture Naming (PN) task using split-half correlations and variability in the standard errors of LIs. We predict that this constrained paced language task will show reliable group level left-lateralisation. Given that the AD task has been reliably and reasonably widely used to assess lateralisation in children, we will test whether the new task being assessed here, picture naming, shows a comparable strength of left lateralisation. Specifically, we will test for differences in the strength of lateralisation and the correlation between LIs on both language tasks.

- Of the small number of published studies in this field, many have analysed data from the same children (e.g. Groen et al., 2011; 2012, Bishop et al., 2014). We take advantage of testing a new group of children using Animation Description to test the correlation between amount of speech output and strength of lateralisation, given mixed previous results. We will also test the correlation between the online measure of task accuracy and strength of lateralisation for Picture Naming.

- Using an offline behavioural measure which is related to the online task, we hope to maximise the potential for finding a correlation between online and offline performance. Hence we predict strength of lateralisation in Picture Naming will correlate with offline measures of RAN.

11.2 Methods

General design and procedure

Participants

Twenty-eight primary school children were recruited. None of the children had diagnoses of developmental disorders of language or literacy. Five children were excluded from analysis. This was due to poor quality fTCD signal (2 cases), no audible spoken language from the child (1 case), poor accuracy on the picture naming task (greater than 2 standard deviations below the group mean: 1 case), and 1 child who was left-handed. Handedness was screened using the card reaching and object use tasks described in Chapters 9 and 10. The remaining 23 children (9 male) had a mean age of 6;9 months (range = 5;9 - 7;6).

Materials

Non-verbal measures

Non-verbal ability was estimated using the *Pattern Construction* subtest from the British Ability Scales: Third edition (BAS-3; Elliott & Smith, 2011). Scores reported here are standardised for the child's age. General speed of processing was assessed using the *Speed of Processing* subtest from BAS-3 was used. The task requires the child to complete a visual search task in the shortest time possible. Again, standardised scores are reported.

Language measures

Expressive vocabulary was assessed using the *Word Definitions* subtest of the BAS-III (Elliot & Smith, 2012). Standard scores are reported. Rapid Automatized Naming (RAN) was assessed using the *Naming Speed* (picture and alphanumeric) subtests of the Phonological Assessment Battery (Frederickson et al., 1997). The picture subtest comprises five highly nameable objects presented ten times each in a random order to produce a sheet of 50 pictures. The alphanumeric subtest followed in the same way except that the digits 1 - 9 were used. The total time from initial articulation is counted until the child has named all the pictures.

Literacy measures

Reading accuracy and fluency were assessed using subtests of the York Assessment of Reading Comprehension (YARC; Snowling, Stothard et al., 2011).

Each child started with the single word reading subtest in which they were presented with a page of words of increasing difficulty. They were asked to read as far as they could and the number of words correctly read at sight, sounded out, omitted or read incorrectly was recorded. The number of words read correctly (both at sight and sounded out) formed a score that was used to determine the difficulty of the passage they then read from the YARC passage-reading subtest. They were timed for this passage and any mistakes were recorded for frequency and type of mistake. For the beginner level passage no time was recorded as instructed in the manual. In addition, all children read a Level 1 passage to provide a comparable measure of reading fluency across all children. Children were informed that they were being timed and were encouraged to read as quickly as they could whilst reading accurately. For those children who also read a Level 1 passage in the earlier task, the fastest reading time was recorded for the reading fluency measure.

fTCD

Animation Description

Changes in cerebral blood flow velocity (CBFV) were recorded during an Animation Description task developed in Bishop et al. (2009) as described in Chapters 9 and 10.

Picture Naming

The trial timings for this task are depicted in Figure 11.1, alongside those for the Animation Description task, for comparison. Trials began with a fixation cross presented in the centre of the screen (1s). Seven individual images were then presented over 10 seconds. The child was required to name each picture as it appeared on the screen. They were reassured not to worry if they missed an item, but to carry on with the next one, so as to minimise memory demands. Following this active period, the child saw the same “shh” image used in the Animation Description task (16s). There were 98 images in total, which were presented in a random order across 14 trials. The items were chosen from a vocabulary measure used in a separate study, during which 35 typically developing children of a similar age range were asked to name a larger set of pictures. For the stimuli used here we chose the 98 most highly nameable pictures which were named correctly an average of 91% of the time (SD = 1.3%).

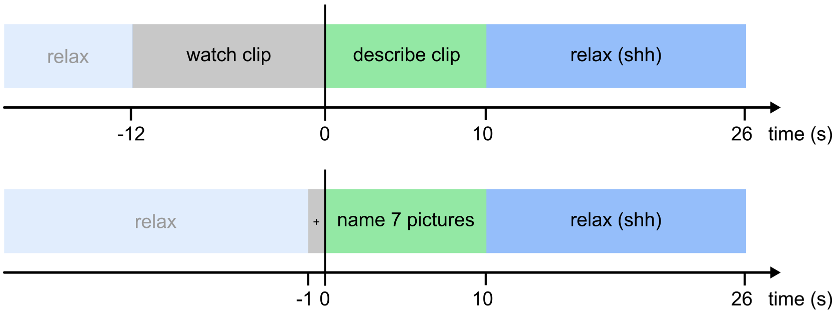

Figure 11.1: Timings for each trial of the Animation Description and Picutre Naming tasks.

Data analysis

Data analysis proceeded in much the same way as in Chapters 9 and 10. For the Animation Description task, epochs were set from -12 to 26s, and baseline correction was applied using the average left-right difference from -10 to -2s relative to the onset of the cue for the child to begin speaking. The period of interest was set between 4 and 18s. As before, LIs are calculated from the average difference in a 2s window around the peak left-right difference. For the Picture Naming task, epochs were analysed from -6 to 18s relative to the onset of the first picture. The baseline was again considered to be activity from -6 to -1s relative to onset of the first item. The period of interest in this task was set between 4 and 14s.

11.3 Results

Behavioural Results

Faster speeds for completing the Alphanumeric version of the RAN task were associated with more fluent reading: the time taken to complete the RAN task showed a negative relationship with the time taken to complete the measures of reading fluency. The relationship was significant for YARC Passage Reading Fluency (r = -.48, p = .03) and approached significance for Level 1 Reading Fluency (r = -.43, p = .06). The direction of the association was the same for Picture RAN but were non-significant (r = -.3 and -.4). Performance on Alphanumeric RAN and Picture RAN were positively correlated with one another (r = .67, p = .001). For reference, descriptive statistics for the other behavioural measures are in Table 11.1.

	M(SD)	min-max
Age (years)	6.8 (0.6)	5.7 - 7.6
Block Design (SS)	52.3 (8.5)	48 - 78
Word Definitions (SS)	62.0 (11.7)	38 - 76
Alphanumeric RAN (sec)	35.2 (9.3)	21 - 52
Picture RAN	58.7 (13.7)	37 - 89
YARC Passage Reading Fluency (total s)	106.3 (35.0)	46 - 175
Level 1 Reading Fluency (words per min)	100.0 (39.9)	42.2 - 167.0

Table 11.1: Behavioural descriptive statistics for all children (n = 23) where available. Reading Fluency measures were not taken for 3 children who were beginner readers. SS = standard score; RAN = rapid automatised naming.

fTCD Data Quality

We compared the tasks in terms of measures of data quality and reliability. The mean number of trials accepted for Animation Description was 15.0 (SD = 2.5, min = 10, max = 19). The mean number of trials accepted for Picture Naming was 13.7 (SD = .6, min = 12, max = 14). In absolute numbers of epochs, this corresponded to a significantly higher number of trials included for Animation Description than Picture Naming (t(20) = 2.3, $p = .03$). In terms of proportions, the difference was in the reverse direction, with a greater proportion of possible trials included for the Picture Naming (mean = .98, SD = .04) than Animation Description task (mean = .92, SD = .10, t(20) = 2.5, $p = .02$).

Split-half reliability for Animation Description showed acceptable reliability between LIs from odd-even trials ($r = .51$, $p = .02$). Split half reliability for Picture naming was also positive and significant ($r = .60$, $p = .004$). The SEM for LIs in each task were comparable - for Animation Description the mean SEM was .77, and for Picture Naming was .91. There was no significant difference between these values (t(20) = 1.7, $p > .1$.

Lateralisation of Picture Naming and Animation Description

Figure 11.2 shows the group averaged CBFV change during both the language tasks. Animation Description was significantly left-lateralised at the group level (t(22) = 3.5, $p = .002$), while Picture Description was not (t(20) = .56, $p > .1$). Table 11.2 shows descriptive statistics of the LIs for the two fTCD tasks.

Comparing the two tasks, Animation Description elicited significantly higher LIs than Picture Description (t(20) = 4.2, $p < .001$) indicating stronger left-lateralisation. The tasks did however concord with one another, such that the strength of LIs elicited from each task were positively correlated (r = .59, p = .005).

Task	LI	Peak Sec	Categories		
	M(SD)		# left	# right	# low
Animation Description	2.0 (2.7)	10.9 (3.0)	16 (70%)	2 (9%)	5 (21%)
Picture Naming	-.25 (1.5)	8.7 (2.8)	3 (14%)	4 (19%)	14 (67%)

Table 11.2: Descriptives of Laterality Indices for both tasks. The number (and % in parentheses) of children categorised as left, right, and low lateralised is also shown.

Correlations between fTCD and behavioural measures

For relationships with task performance we tested the correlation between strength of lateralisation and amount of speech output (for the Animation Description task) and the accuracy of naming (for the Picture Naming task). Neither of these relationships were significant (r = -.33, p = .13 and r = .21, p = .37).

In terms of relationships with offline behavioural measures, we tested whether strength of lateralisation in Picture Naming correlated with offline measures of RAN. The relationship between LI and RAN was also non-significant for both Picture RAN (r = -.31, p = .17) and Alphanumeric RAN (r = -.36, p = .11).

	M(SD)	min-max
Animation Description (words/trial)	17.4 (3.2)	11 - 23
Picture Naming accuracy (% correct)	85.3 (5.2)	76.5 - 93.0

Table 11.3: Behavioural results for Animation Description and Picture Naming tasks

Supplementary Analysis

As described in Chapter 9, there were some children whose LI was calculated from a peak which was not representative of the activity during the period of interest. For this reason, the average left-right blood flow difference was analysed for the entire period of interest as opposed to the average difference around a 2 second peak.

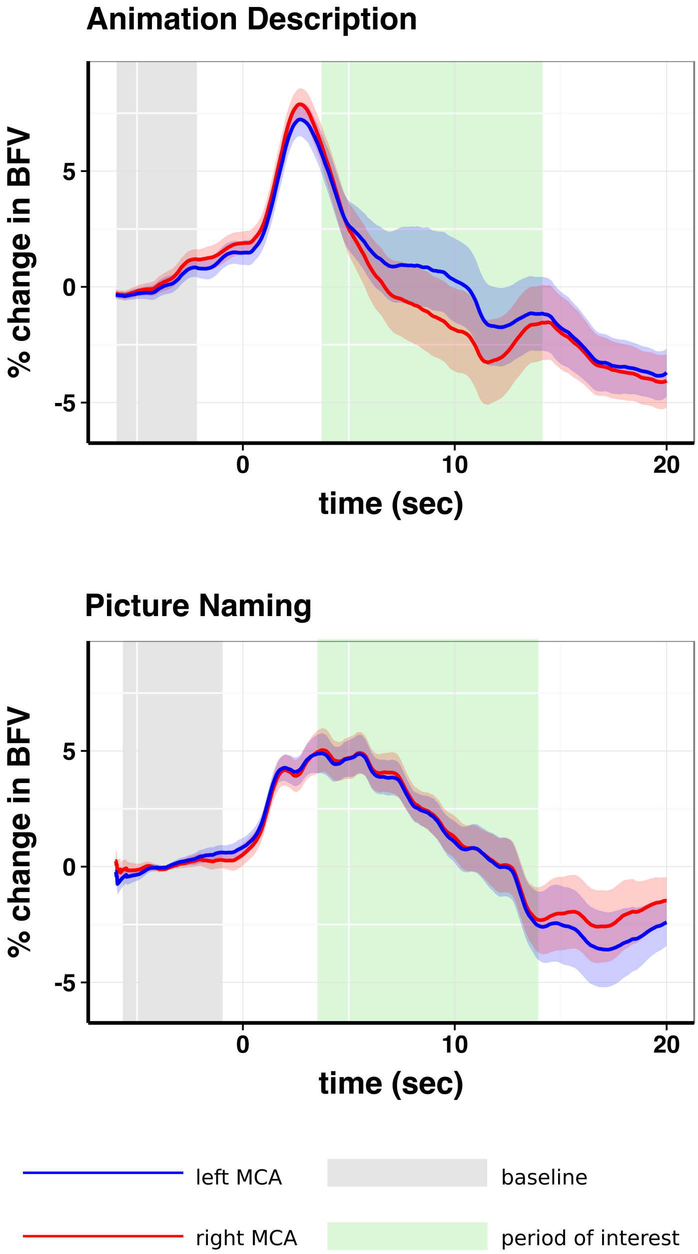

Figure 11.2: Group averaged changes in CBFV during Picture Naming and Animation Description tasks. Shaded areas indicate standard errors at each sample point.

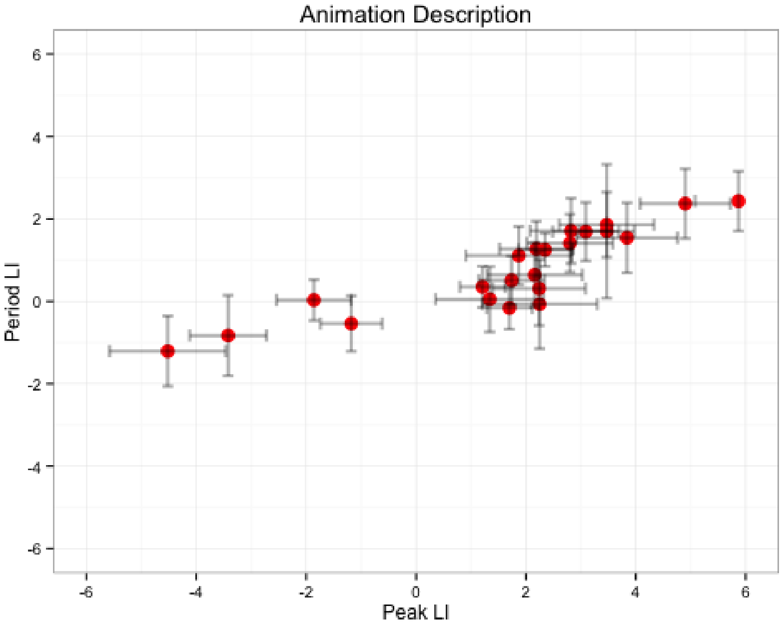

Figure 11.3: Consistency between period and peak calculations for Animation description.

The overall results in terms of group level LIs were not significantly affected. Figures 11.3 and 11.4 show the concordance between the two analysis methods (Animation description r = .89, p < .001, Picture naming r = .97,p < .001). However, using the period LI as an estimate of the strength of lateralisation, the relationship between lateralisation and offline behavioural measures now revealed a different pattern of association. The negative correlation between Alphanumeric RAN time and strength of lateralisation now reached significance (r = -.44, p = .04).

11.4 Discussion

In this study, we tested the reliability of a controlled language task designed to measure language lateralisation in children using fTCD. We also investigated the relationship between language lateralisation and online and offline language measures. Twenty-three 5-7 year-olds completed an established Animation Description task (Bishop et al., 2009) and a novel paced Picture Naming task, while changes in blood flow to each hemisphere were recorded using fTCD. In addition, they completed offline measures of reading and

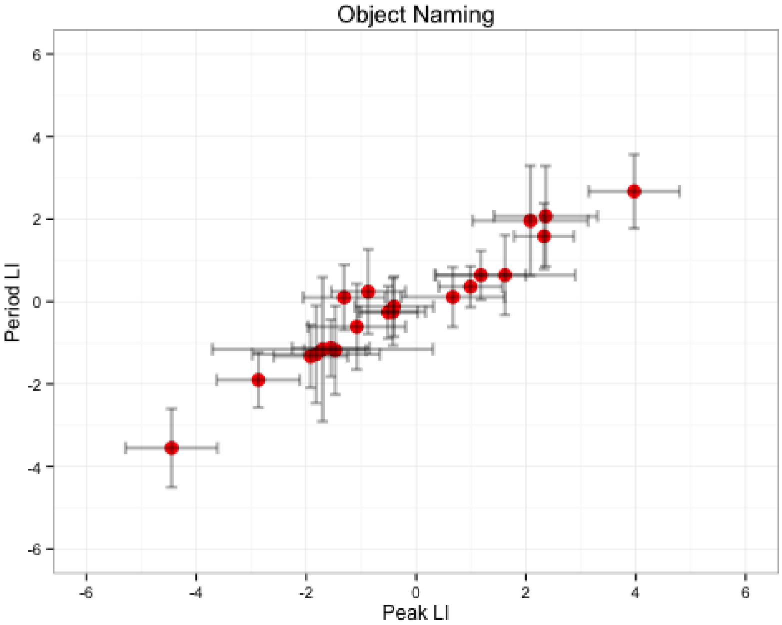

Figure 11.4: Consistency between period and peak LI calculations for Picture naming.

rapid automatised naming (RAN).

First, our findings support previous studies showing that the Animation Description task results in significant group-level left-lateralisation in young children producing speech (Bishop et al., 2009, 2014; Groen et al., 2012). As in previous studies, split-half reliabilities indicated consistent lateralisation across trials. In the novel paced Picture Naming task, group level left-lateralisation was not observed, but the task showed comparable split-half reliability and variability of LIs as Animation Description. Reflecting the lower mean LI, significant left-lateralisation was observed in 14% of children during the Picture Naming task compared to 70% of children during Animation Description.

It is possible that the lower lateralisation observed during Picture Naming because the task does not elicit sufficient lateralised activity for the sensitivity of fTCD. In an FMRI study of the reproducibility of Laterality Indices, Picture Naming was the least consistent out of a battery of expressive language tasks (Rutten et al., 2002). In general, FMRI studies report predominant activity in left hemisphere regions; the inferior frontal gyrus, middle and inferior occipital gyri and middle and inferior temporal gyri (Abrahams et al., 2003). However, the extent to which right homologous regions are involved has mixed findings in the literature (Démonet et al., 2005). MEG studies of lexical access indicate that only some subprocesses involved in picture naming may be lateralised (Munding et al., 2016), which may explain inconsistencies between studies and participants. While Picture Naming is a more constrained task than Animation Description, it nonetheless involves numerous processes including the perception of the visual stimulus, concept retrieval, access of the corresponding lexical form as well as later stages of articulation Levelt (1999); Dell & O'Seaghdha (1992). The regions involved in picture naming will therefore be critically dependent on the chosen baseline (Price et al., 2005). Differences in the spatial resolution and data analysis of fMRI and fTCD preclude the direct comparison of results between studies. FTCD studies to date, including the current study, use a very low-level baseline of rest, and hence lateralisation would be expected for fMRI tasks which show lateralisation within the perfusion terriotry of the MCA, relative to rest. For instance, inclusion of ventral occiptal cortices and fusifrom gyri in ROI analyses, or whole brain analyses in an fMRI study would lead to a different expected pattern of lateralisation to fTCD. FMRI studies with low-level baselines which do not attempt to remove activation associated with general speech production processes, show that picture naming involves the frontal operculum and inferior frontal gyri, as well as bilateral subcortical structures in the cerebellum, insula, thalamus, and cingulate gyrus (Price et al., 2005).

It is possible that in limiting the types of skills required to complete the online task, aspects of language processing that are strongly lateralised are not engaged during picture naming. However, in the context of good split-half reliability, comparable standard errors of LIs, and importantly, a positive correlation between the strength of lateralisation in relation to the established Animation Description task, it may be premature to conclude this task is not a 'good' measure of lateralisation of language processing in children. An MEG study with young children used picture naming of single items and found significant effects of hemisphere for ROIs encompassing superior temporal, supramarginal, and inferior frontal gyri (Sowman et al., 2014). In their design, the authors presented the same twenty pictures approximately 10 times and averaged the activity on an item-by-item basis. This type of analysis is not possible with the temporal resolution of haemodynamic measures. Therefore, it is likely that where significant left-lateralisation is measured using fTCD, it relies on the additive effect of responses to a number of stimuli. Therefore, increasing the number of items in our design may increase the magnitude of the LI.

Alternatively, left lateralisation for Picture Naming may relate to the establishment of the skills which support task completion, and is therefore not consistently lateralised at the group level. FMRI studies also show that stimuli-specific factors such as word frequency and length affect the extent of lateralisation (Graves et al., 2007). In children with large variability in language ability, these effects may not be consistent across participants, leading to variability in lateralisation indices. Some evidence to support this claim is that when we consider lateralisation of the whole period of interest, children with greater left-right differences were those with faster responses for offline measures of RAN. It could be argued that if a relationship exists between ability to perform the task and lateralisation, then a correlation between online task performance would also be expected. Here, there was no such relationship with picture naming accuracy. However, given that RAN is more a measure of fluency than of lexical retrieval (i.e. accuracy) this is perhaps not surprising. In the current study, we attempted to measure reaction times from stimulus to the onset of naming however background noise from the testing environment rendered this impossible. Future studies may benefit from the analysis of reaction times rather than accuracy as this more intuitively relates to fluency.

Our pattern of results is in line with an fTCD study with adults which compared three language tasks: the gold-standard Word Generation task, an auditory naming task and a passive story listening task (Badcock, Nye, & Bishop, 2012). The authors observed stronger and more consistent LIs in the Word Generation task than the other tasks which arguably involve fewer language sub-processes. They also observed positive correlations between the tasks in the strength of lateralisation, suggesting that variability in LIs for expressive tasks does "reflect meaningful differences in laterality relative to task content" rather than poor task reliability. We make a similar argument based on the current data. Animation description may indeed be the most powerful paradigm used to date to elicit hemispheric lateralisation for language that can be measured using fTCD. However, we have shown that other measures, here picture naming, should also be considered. Although less powerful in driving the fTCD signal, the fact that LIs are strongly related across tasks and that performance can be very carefully controlled make it an appealing and potentially useful tool to use in our investigations of the development of language lateralisation in children.

Chapter 12

General Discussion

The aim of this thesis was to use a novel and simple neuroimaging technique, functional transcranial Doppler sonography, to examine lateralisation of language in previously understudied populations. In doing so, it aimed to further our understanding of factors associated with variability in lateralised brain activity during language processing.

The following discussion is split into three sections. The first addresses how the studies in this thesis contribute to our understanding of the relationship between developmental factors and lateralisation of language. The second section discusses the potential impact of this body of work on the analysis of fTCD data in future studies. The final section highlights issues relating to the interpretation of fTCD data.

12.1 Developmental factors which relate to left hemisphere lateralisation for language

The main theoretical studies (in Chapters 9 – 11) tested whether lateralisation during language production is affected by various developmental factors. Maturation (age; Herve et al., 2013), exposure to language input (Zatorre & Belin, 2001; Corina et al., 1992), and skill acquisition (Plante et al., 2015; Holland et al., 2007) have all been proposed to exert an influence on the development of lateralisation. These three factors are undoubtedly interrelated. Nonetheless, the developmental studies in this thesis attempted to test whether variability in these factors relates to variability in hemispheric lateralisation during language processing. Below each of these factors is considered in turn.

12.1.1 Age

The influence of age on lateralisation for language production was investigated in this thesis in two ways. Chapter 9 tested lateralisation at two time points in hearing preschool children. This is the first study to use fTCD in a longitudinal design. The main focus of Chapter 10 was to test the effect of language input on lateralisation by recruiting a group of children born profoundly deaf. However, given the wide age range of children recruited, we were also able to test the association between strength of lateralisation and age in this group.

Chapter 9) showed that by three years of age, and before literacy acquisition, the majority of hearing children show clear left lateralisation during free generation of speech. There was no evidence for significant changes in lateralisation over one year. Similarly, there was no correlation between age and strength of LI during language production in the deaf children tested in Chapter 10.

These data at first appear to be at odds with some fMRI studies which have reported correlations with age (e.g. Everts et al., 2009; Lidzba et al., 2011; Szaflarski et al., 2012). However, these studies used covert tasks and recruited older children (6 years and older). Our findings, using overt speech production, are in line with those from other neuroimaging methods that have permitted overt responses in young children (fNIRS: Pacquette et al., 2015; MEG: Sowman et al., 2014). It is possible that the relationship with age observed in studies using covert tasks reflect age-related performance changes such as attention, effort, and changes in subvocal rehearsal strategies which could not be measured and therefore not taken into account during covert tasks.

It is also possible that lateralisation for speech production does indeed increase before three years of age, the age of the youngest children tested in this thesis. Further investigation is warranted of whether lateralisation develops between the production of first sounds and production of full grammatical sentences.

12.1.2 Language exposure

Chapter 10 tested the effect of atypical exposure to language on hemispheric lateralisation for language production. A heterogeneous group of deaf children were tested, including those with and without cochlear implants (CI). For some, their preferred language was BSL, for others it was English. The group averaged data indicated left-lateralisation, demonstrating that even children with reduced access to auditory speech can show left lateralisation during language production. When LIs were categorised there were 17 deaf children who were left lateralised (81%), 3 right (14%) and 1 low (5%). These proportions are very similar to those reported for hearing children by Groen et al., (2012) (left: 80%, right: 15%, low: 5%) and also similar to our data from hearing children of approximately the same age completing the same task (From Chapter 11 - left: 70%, right: 9%, low: 21%). In addition, there were no differences between children with and without CI in terms of lateralisation. This again suggests that access to auditory speech is not a driving factor in left lateralised language processing. These results are broadly in line with those from deaf native signing adults, who show left-lateralisation during many aspects of language processing (MacSweeney et al., 2008; Capek et al, 2008).

The conclusions above relate to development of left lateralisation categorically, regardless of strength. It is nonetheless possible that the quality and duration of language exposure relates to the *strength* of lateralisation. For example, children with access to speech sounds via an early CI or full access to BSL from their signing parents may show stronger left-lateralisation than those with later exposure. However, we had insufficient numbers of participants in this study to test differences between native (n=3) and non-native signers (n=6). To address the role of early sign language input and its effect on lateralisation, it would be necessary to recruit a far larger sample of children. Also, we only tested 10 children with CI. These children did not have a wide range of age of implantation, therefore we could not look at effects of age of cochlear implantation on lateralisation. To further address the role of auditory speech exposure on hemispheric lateralisation of language processing, a longitudinal study of children pre- and post- implant would be a useful next step.

It could be argued that 'exposure' is a rather crude measure. For example, age of sign language exposure or age of CI implantation does not account for the quality of the language input (whether sign or auditory speech). Another approach was therefore taken in this thesis to examine the influence of the heterogeneity of the deaf children in respect to language lateralisation by examining the influence of language proficiency.

12.1.3 Language proficiency

The final developmental factor of interest is language proficiency. Other studies have used second language learning to test the effect of increasing proficiency on the development of lateralisation (e.g. Plante et al., 2016). Findings suggest that familiarity with or increased expertise in language indeed results in significantly greater left-lateralisation. Whether this is analogous to first language learning however is not clear. There are likely to be influences of learning a second language that are dependent on first language acquisition.

This thesis contributes data to this issue by investigating the relationship between language proficiency and lateralisation in adults and children with different language backgrounds. These findings will be discussed below. Here it is critical to be clear what is meant by ‘proficiency’. Language abilities can be estimated from offline standardised measures and from online task performance. First we consider relationships between online measures of proficiency and lateralisation across the studies reported.

Online measures of language proficiency

The measurement of online task accuracy itself can take a number of forms. In the majority of tasks used in this thesis, the measure of online proficiency has been the number of words produced: Animation Description in Chapters 9, 10, and 11 and verbal fluency in Chapter 5). In the judgement tasks in Chapter 6, the measure of online task performance was the percentage of correct responses. In the naming tasks in Chapters 7 and 11, percentage of accurately named or read items was used. Finally, in the rhyming condition of Chapter 7, the measure of online accuracy was the percentage of trials with a) any response or b) a correctly produced rhyming word.

In the adult studies, a positive correlation between the proficiency measure and LI was observed in Chapter 5(strongest in the overt phonological fluency condition r = .64, p = .001) and in Chapter 7 between the percentage of trials with an uttered response and LI (r = .49, p = .03). In the developmental studies, a correlation between online task proficiency and LI was only observed in Chapter 9 for the number of words produced and LI at Time 2.

With regard to the correlation between number of words produced and LI in Chapter 5, it was argued that in the context of no differences between the strength of lateralisation for overt or covert speech, the correlation may reflect increased lateralisation of premotor subvocal rehearsal and search strategies. The positive correlation between online performance on the rhyme generation task and LI in Chapter 7 provides supporting evidence for this claim. When participants were asked to generate a rhyme in response to a word, a positive correlation was observed between LI and percentage of trials containing an utterance. The fact that the correlation was present when data from all attempted trials were included, and not when all correct trials were included, suggests an association between lateralisation and phonological search or planning as opposed to ability to complete the task.

In the preschool study in Chapter 9, no significant relationship between LI and the number of words produced was observed at Time 1. At Time 2 there was a trend towards a positive correlation ($r = .46$, p = .053). However, this correlation would not survive the more conservative thresholding to account for multiple comparisons. As such, this does not constitute convincing evidence for a strong relationship between the number of words produced and the strength of lateralisation in the children tested here.

Data from Chapter 7 may help to explain why we observe different patterns of association in the child and adult studies. In that study of adults, generating rhyming words from a series of single word stimuli led to stronger LIs than reading the same words aloud. It was proposed that this increase reflected a number of processes including lexical search, in this case specifically phonological lexical search. It is possible that the language output from our adult participants, in the kind of experimental studies used here, was an accurate reflection of subvocal processing related to their effort in engaging in phonological search. However, this may not be the case with the young children tested in Chapter 9: 3-4 years or Chapter 11: 6-7 years). The additional syntactic demands of a narrative task, as opposed to a lexical task, may mean that the LIs measured in these young children, may be less related to subvocal phonological search than in adults. Alternatively, they may have been effortfully searching for words without having the time in the reporting period to say them aloud. Thus, the number of words overtly produced, may not be an accurate measure of the extent of their subvocal rehearsal. In addition, in Chapter 10, many of the deaf children tested used a combination of sign and speech in their story description. Others used gestures to support their speech. It is possible that in these cases, accessing meaningful gestures or accessing signs places different types of demands on phonological access, and by extension results in regional differences in activity. This may have further contributed to the reason that we did not observe a relationship between amount of language output and strength of LI in this sample of young deaf children.

We suggest that future fTCD studies may benefit from assessing the quality rather than quantity of language output during generation tasks with children. An example would be to use measures of grammatical accuracy, such as the presence or absence of grammatical constructions which mark the developmental stages of language development. In addition, refining a task to target a particular domain of language processing, or set of language processes – such as picture naming (Chapter 11), appears to be informative when exploring the relationship between LI strength and behavioural data. Additional measures of online performance on judgment or naming tasks, such as reaction times or voice onset times, could also be useful.

Offline measures of language proficiency

We now consider relationships between offline language measures and LI. Lateralisation during picture naming (Chapter 11) by hearing children positively correlated with offline Rapid Automatised Naming (alphanumeric) performance. This suggests that the choice of measure of offline proficiency task is important. It is more likely that a relationship between LI and offline language measures will be found if the fTCD task and the offline measure tap into the same linguistic and cognitive skills. Although this seems intuitive, this is not what has been routinely tested in previous developmental fTCD studies (e.g., Lohmann et al., 2005; Haag et al., 2010; Groen et al., 2012). These studies tested relationships between lateralisation and composite scores of general language ability derived from subtests such as auditory memory, grammar knowledge, or measures of phonological awareness. Indeed, in the current studies with adults only a very cursory measure of offline language proficiency was administered – the Kirklees Reading Comprehension task (Hedderley, 1996). It is possible that choosing a measure such as phonological awareness for the rhyme judgement experiment in Chapter 6 and rhyme generation in Chapter 7 may have captured more accurately potential shared variability between proficiency and strength of lateralisation.

Previous fTCD studies with children have not found correlations with offline language measures and strength of LI (Lohmann et al., 2005; Bishop et al., 2009; Haag et al., 2010). Groen et al. (2012) took a different approach and split the group by whether they showed left lateralisation during Animation Description. Children categorised as left-lateralised had higher vocabulary scores than those categorised as low or right-lateralised. In our data, there were insufficient numbers of low or right-lateralised children in any of the studies to test such differences.

In Chapter 9, left-lateralisation in hearing children during Animation Description at Time 1 predicted letter-sound knowledge one year later. This finding would need replication in a larger sample, perhaps including those at risk of reading difficulties, to ensure a sufficiently wide spread in early literacy abilities. In addition, replication with the addition of several time points over the year to follow the trajectory learning of letter-sound knowledge more closely would be informative. For the children in our sample, many went from knowing only one or two sound-letter correspondences to knowing them all. This meant that we had no reliable measure of the rate of development of literacy.

Importantly, we did not find a positive relationship between any measures of language proficiency and strength of lateralisation in a group of children born profoundly deaf (Chapter 10). There was in fact the opposite trend –

several of the children with the lowest language levels, who produced least during the active period of the task and had the lowest offline scores, showed the highest LIs. This pattern of data was not observed in our other studies with hearing children or adults, nor has it to our knowledge been reported by others. It is possible that in these low ability deaf children the increased effort of performing the task was sufficient to drive the LI. Further research is necessary to see if this pattern (although only a trend) is found in other groups and to examine what may underlie this pattern. One possibility is that the narrative type task used is unfamiliar to deaf children, particularly those with low language ability, for whom the quality of conversation and quantity of input of mental-state terms is significantly lower than hearing children in the early years (Morgan et al., 2014).

In summary, given that the many subdomains (and extra-linguistic supporting skills) of language develop at different rates, it is perhaps not surprising that we did not demonstrate a straightforward relationship between offline language proficiency measures and online measures of language lateralisation. As well as aligning the skills tested by the fTCD task and offline language proficiency, a multidimensional approach to assessing lateralisation could also go some way to furthering our understanding of the behavioural relevance of lateralisation. Following studies of the assessment of hemispheric dominance for language in adults (Niskanen et al., 2012) and children (Wilke et al., 2006), we suggest that using a broader range of fTCD tasks tapping different aspects of language, as well as a broad range of measures of proficiency across these domains, may lead to more reliable estimates of lateralisation and language proficiency. In turn sensitivity to detecting relationships between these variables would be greater.

12.2 Analysis in future studies using fTCD

Several issues concerning the analysis of fTCD data arose during the course of the studies reported in this thesis. The issues relate to the processing steps used in the current pipeline, estimating reliability in fTCD tasks and the calculation of Laterality Indices (LIs). Here these issues are addressed in turn.

12.2.1 Processing steps in the fTCD analysis pipeline

The first methodological point concerns two of the processing steps which make up the typical analysis pipeline for fTCD data: signal normalisation and baseline correction. A clear justification for each step of data processing is vital to ensure validity and transparency for measures of brain activity used in research. The justification for normalising the blood flow speeds in fTCD is so that relative differences between CBFV change are examined. As described in Chapter 3, blood flow speed measured by TCD is scaled by the angle of insonation which is inherently unknown. Normalising the signal, so that relative units of change in speed are analysed, prevents differences in absolute speeds between left and right arteries biasing results. The key papers in the field (Knecht et al., 1996; Deppe et al., 1997, 2004; Badcock et al., 2012) suggest three ways to transform raw Doppler data to relative scales:

- Overall (whole sample) normalisation: blood flow velocity as a proportion of the entire mean for the right or left channel, expressed as percentage change. This is equivalent to standardising the whole sample to have a mean of 100.
- Epoch normalisation: Standardising each epoch to a mean of 100. This option additionally addresses the issue of signal drift or displaced probes by looking at relative signal change for each epoch at a time.
- "Deppe" epoch (baseline) normalisation: Relative speeds are calculated as a proportion of the average blood flow speed during a period of rest (the baseline). This option ensures the signals are independent of probe angle, and that the additional step of baseline correction is redundant. The justification for this method was to counteract fluctuations of the average speed across a testing session (due to slight probe movements). However, the impact of Deppe epoch normalisation versus the Knecht et al. epoch normalisation on LI calculations is unclear from the original paper, as is the potential redundancy of baseline correction (Deppe et al., 1997). Adopting this method uses a relative baseline approach rather than a subtractive one, the impact of which has not be empirically assessed.

It has not been assessed whether the differences in these processing steps impact the reliability of fTCD measures. Future studies are needed to determine the most suitable approach for the types of blocked designs used in fTCD.

12.2.2 Estimating fTCD reliability

A second analysis-related issue for consideration is that reliability in all studies in this thesis was assessed using a simple Pearson's correlation coefficient.

The correlation tests for associations between the average LIs for all odd and all even epochs. Low reliability in terms of a non-significant correlation coefficient can occur for a number of reasons. One possibility is that the magnitude of the difference in CBFV between left and right channels fluctuates through the task. Therefore, from epoch to epoch there may be non-systematic differences in LI. In these cases, poor split half reliability is a reasonable estimate of measurement credibility: lateralised blood flow is not consistently elicited. However, non-significant split-half correlations could also result from a lack of variation in LI across trials and participants. In these cases, the poor split half reliability may in fact be reliably reflecting minimal changes in lateralisation during a task.

Other reasons for poor split-half reliability that are not necessarily related to the specific task, include not returning to baseline sufficiently, probe movement, noisy data (lots of artefacts), or low numbers of epochs. Furthermore, in small group sizes the group correlation coefficient may be reduced by a small number of participants with low reliability. Future studies would do well to consider other ways to quantify intra-task reliability. It is possible that test-retest reliability may be a more informative option if lateralisation throughout the task is not consistently elicited over the same time course. Alternative methods of quantifying lateralisation may circumvent this problem by taking the time course into account (see below).

In this thesis, all tasks except phonological fluency in Chapter 5 and reading in Chapter 7 showed significant positive correlations between odd and even epochs, indicating good intratask reliability. For the reading condition, in Chapter 7, poor split-half reliability was accompanied by non-significant group level lateralisation. In the same participants, good reliability and significant left lateralisation was observed for generating rhymes in response to the same written words. Given that good reliability was measured for one of the tasks and that behavioural performance on the reading task was at ceiling, it is likely that the poor split half reliability indeed reflects low but consistent left-right CBFV differences during reading aloud. The use of regular and highly frequent words to read aloud adds to the likelihood of genuinely bilateral processing. On the other hand, the poorer reliability estimates in the phonological fluency conditions in Experiment 1 seem to be more related to fluctuations across the trial. One explanation is the changing demands during the course of the active period as people begin to generate easily and then run out of words and engage in alternate search strategies. Further investigation into the time course of the LI peak difference and its relationship to behaviour could shed some light on this.

Consistency of lateralisation across epochs is an indication that the trials are eliciting similar responses in CBFV and importantly is one indicator that the period allowed for blood flow to return to baseline is sufficient. An area for consideration however is that though baseline correction occurs on a trial-by-trial basis, it is nevertheless the case that an insufficient relax period would lead to a gradual increase in overall CBVF over time (drift). Normalisation on an epoch by epoch basis goes some way to circumvent this, but it is a factor which should be considered in studies with children for whom sharper increases and decreases in CBVF Bode & Wais (1988) may necessitate longer relaxation periods before each trial.

12.2.3 Calculation of LI

The final methodological point related to analysing future fTCD data concerns the calculation of the Laterality Index used in fTCD. Data from several of the studies highlighted the problems of using a single value to estimate differences in hemispheric blood flow velocity over time. In cases where lateralisation through the entire trial is consistent, using the peak difference has little effect on changing the extent of the LI. This is especially true where short periods of interest are selected a priori. However, in cases or tasks which show fluctuations in lateralisation, selecting the peak gives an inaccurate estimate of the extent of lateralisation compared to another task or individual, as a small shift in period of interest or trial removed can lead to a significant shift in the LI calculation – in some cases even to a change in the direction of lateralisation observed. Such non-robust LIs are not suitable measures to examine individual differences and correlations with behaviour.

To go some way to circumvent this problem, in Chapters 10 and 11, the average difference between right and left channels over the entire period of interest was used to calculate the Lateralisation Index. This provided a somewhat more conservative measure of lateralisation given that it did not select a peak difference around which to average. The consequence of this approach was a marginal increase in reliability (although see below) and significant correlations with behaviour (such as the relationship between LI and Rapid Automatised Naming in Chapter 11).

Selecting the period to calculate an LI does not fully resolve the issue of estimating robust and reliable LIs from fTCD data. Specifically, it does not address the issue of discarding time series information in the calculation of differences in CBFV (which may be informative). It also does not address the fact that peak latency calculated from the average of all the trials is used to calculate LIs for odd and even epochs for measures of reliability. This can lead to somewhat arbitrary LIs if there is a lot of variation in left-right differences through a trial.

There have been recent investigations into alternate ways of analysing fTCD data which may influence the way LIs are calculated in the future and could help to resolve questions that cannot be answered by testing for differences in group averaged LIs. One of these, developed in G. F. Meyer et al. (2014) suggests calculating a moving cross-correlation for each participant's LI. In practice this means taking the left-right difference curve of blood flow speeds and calculating an average over 5 second sections. A correlation coefficient is then calculated between each of these means for two tasks along the entire difference curve, to give a running similarity measure for each participant. In tasks with similar cognitive demands, high correlations between left-right differences should be observed. Meyer et al. demonstrate this with a proof of concept experiment. They show high correlations between LI time courses between two versions of verbal fluency - using high and low frequency letters as stimuli. Conversely, they show low correlation between the time course of LIs for a spatial task versus standard verbal fluency. Adopting this approach for a reanalysis of the rhyme line data in chapter 6 would be an interesting next step to demonstrate the validity of these two passive tasks, as well as the effect of pace. It could also be insightful for the data presented in Chapter 11 where the group averaged LI for Picture Naming was not significantly lateralised, but some individual participants did show left-lateralised responses. Calculating a cross-correlation between Animation Description and Picture Naming could be one way to test whether there is consistency in terms of lateralised responses during both tasks rather than simply a correlation between their peak LI.

12.3 Interpretation of fTCD data in future studies

This section discusses issues that arose in this thesis which may be useful to consider in the interpretation of future fTCD studies. The first concerns differentiating between strength and direction of lateralisation. The second relates to the appreciation of task related effects on lateralisation.

12.3.1 Strength or direction of lateralisation

Fair interpretation of fTCD lateralisation data relies on a clear hypothesis about strength or direction of lateralisation. It has been suggested that 'atypical' lateralisation (i.e. right dominance) may be related to delayed or atypical language development (Bishop, 2013). In order to examine direction of lateralisation from measures of brain activity it is necessary to split a continuous variable (LI) into groups. To date it has been popular in the field to categorise participants into left lateralised, right lateralised and low or bilateral groups. A very small shift in either the mean LI or standard error for that individual can result in a change of category. However, categorical variables are best reserved for discrete groups. We argue that fTCD data should not be reduced in this way, and that the continuous LI should be used to investigate effects on the strength of laterality. This is not a new idea; it has long been suggested that the use of continuous variables results in greater power (Cohen, 1983; Corballis & Lea, 1999; Maxwell & Delaney, 1993, Naggara et al., 2011; Royston, Altman, & Sauerbrei, 2006). Dichotomisation results in a loss of data, and neglects within-group variability. Using a categorisation approach, some participants may be confidently placed within a category, while data from other participants may place them on the threshold between categories. However, the category thresholds are arbitrarily defined or, more problematically, data-driven. These two cases should not be considered equivalent in terms of lateralisation, and test-retest reliability could be misleading if a change in category is reported from a .1 shift in lateralisation index. As Naggara et al., (2011) note, "what is necessary or sensible in clinical and therapeutic settings in not relevant to how research data should best be analysed".

Future studies could benefit from adopting mixed model linear regressions. This type of regression model is comparable to a repeated measures ANOVA, as by including random effects for the intercept, we are effectively accounting for individual variation in mean values for the LI in each level of the predictor. Analysing categorical data can be even more problematic when repeated measures are involved, as typical chi square tests are not valid when each participant contributes more than one count to each cell. A mixed logistic regression can bypass these problems by again allowing for random effects, allowing each participant's unique variation to be taken into account.

Examining strength of lateralisation and correlating with behaviour is an alternative way of analysing fTCD data and tests slightly different hypotheses. Doing so assumes stronger lateralisation is meaningful. This may be a problematic assumption if fTCD is being used. Stronger lateralisation could in fact be driven by right- or left-hemisphere fluctuations since the measure used is a ratio. Importantly, these may not have the same behavioural correlates and therefore strength of lateralisation could indicate different things in different individuals. Combining fTCD with a method that gives greater spatial resolution could reveal which regions are implicated in the lateralised blood flow changes measured by fTCD. For instance, it may be fruitful to use the same language production task with fTCD and fNIRS in a narrow age range of children to test whether stronger left-lateralisation measured by fTCD is associated with activity in right or left optodes to gain further insight into the regions driving changes measured by fTCD.

12.3.2 Importance of task related effects

The second point relating to interpretation of fTCD data is that an accurate interpretation of differences in LI between tasks (for example, defining one group as left-lateralised and another group as not) relies on a good understanding (and cognitive models) of the demands of the task used to elicit responses. These demands may be extra-linguistic, for example the effort required to complete the task (due to increased pace - Chapter 6) or linguistic, for example the linguistic processes involved in rhyming generation versus single word reading (Chapter 7). Considering profiles of lateralisation across different subdomains of language is likely to improve our understanding of the factors which mediate the development of lateralisation.

It has been suggested that differential lateralisation of specific components of language might relate to atypical language development (Bishop, 2013). We suggest here that manipulating task difficulty in each domain tested could help to determine variability in lateralisation related to the specific linguistic feature versus variability due to extra-linguistic task demands. Such an approach was taken by Badcock et al., (2012) but task difficulty was manipulated post-hoc, by grouping letter stimuli by the number of words produced in response to them. As well as post-hoc, the approach was also indirect, because the number of words was taken from a later report period and not measured during the active period.

Finally, the amount of articulatory planning or subvocal articulation appears to be related to strength of LI. However, this is not the only task related factor that may impact on the amount of change in CBFV. Chapter 6 demonstrated increasing right lateralisation with increasing task difficulty during a line judgment task –therefore unrelated to premotor demands. That is, we observed stronger right LIs for fast paced than slow paced visual judgements. This informed our decision in Chapter 7 to maintain a high amount of linguistic material in the active period but modulate only the pre-motor demands. In this rhyme generation task, we measured strong and robust left lateralisation. This suggests that a sufficiently taxing task, presented at a sufficiently fast rate, is needed to produce reliable measures of lateralisation using fTCD. Using tasks following these guidelines to assess different linguistic processes (which may engage different systems within the language network) may reveal clearer developmental effects on lateralisation.

12.4 Conclusion

This thesis explored cerebral lateralisation for language processing. A multidimensional view was taken of both lateralisation and language, testing whether developmental and task related factors systematically influence lateralisation. Using fTCD allowed the inclusion of preschool hearing children and deaf children: hitherto understudied populations. Data collected from these groups adds to mounting evidence against two widely held theories of lateralisation. The first is that lateralisation 'for language' increases with age. Given the insufficient data on different domains of language processing and a poor understanding of the relationship between performance and strength of lateralisation, it is premature to claim lateralisation for higher order language functions increases with age (Tzuorio-Mazoyer et al., 2016; Szaflarski et al., 2012).

The second theory is that left-lateralised auditory speech perception plays a driving role in lateralisation for higher order language processing (Tzuorio-Mazoyer et al., 2016). Here we show that children born profoundly deaf show left-hemisphere dominance during language production, whether signed or spoken. Further studies are needed to test whether language comprehension is comparably lateralised in this group.

This thesis provides support for the view that hemispheric dominance during language processing is to a degree task dependent. Therefore, online performance measures and multiple tasks are necessary for a meaningful measure of hemispheric dominance. Data collected here showed the value of using complementary online and offline behavioural tasks to explore correlations between physiological data and behaviour. Furthermore, using a constrained task such as paced picture naming might help to minimise variability in lateralisation measures which may arise from the interplay of many different regions of the language network which become more involved in higher order tasks such as narrative tasks or comprehension tasks.

To conclude, a single brain imaging technique or single task will not provide answers about the factors leading to or consequences of hemispheric lateralisation for language. Functional TCD can be used with populations for whom other imaging modalities may be inappropriate, adding a novel dimension to a multifaceted approach to language research.

Chapter 13

Appendix

.1 Words pairs for Chapter 6

Word 1	**Word 2**	**Word 1**	**Word 2**
CRY	HIGH	POT	FLY
FATE	WEIGHT	NAME	THUMB
GREW	CLUE	FINE	DAWN
BRUISE	SNOOZE	PLEAT	SHOOT
HOE	SNOW	BED	KNEE
PHONE	KNOWN	GUARD	FLAIR
GLUE	SHOE	COAL	BULL
WHITE	RIGHT	CALM	SNAIL
FRAIL	SCALE	BOMB	FOAM
BLOWN	STONE	SPEAK	FLAKE
BREAK	LAKE	SHALL	CRAWL
CHEF	DEAF	BROAD	WOOD
JAIL	WHALE	TIED	BREAD
BEER	HEAR	LOOP	POPE
TOES	BLOWS	SOON	CROWN
COT	BUY	CHOOSE	NEWS
CHIP	THROUGH	SOME	HUM
HIDE	FOOD	CONE	SEWN
SWERVE	PLEASE	MOOSE	JUICE
BEG	KEY	FIGHT	BITE
BEAD	MAID	THERE	HAIR
COAT	PUT	TRUE	FLEW
CARD	STAIR	FADE	RAID

WORK	ROAR	TRAIN	CANE
TOWED	GOOD	SHEET	MEAT
VOICE	WISE	HAIL	SALE
DART	HATE	FOUR	MORE
LOAD	SAID	LOAN	BONE
SKIN	CHAIN	MEET	EAT
COOL	TOLL	CHAIR	PEAR
PIE	SKY	TOOTH	PLOUGH
RULE	POOL	WINE	BUN
NONE	RUN	BOOTH	NO
SPOON	JUNE	SPILL	CRUEL
KITE	LIGHT	SHINE	LOSS
STUFF	TOUGH	PART	BOOT
FREE	TEA	CHIN	PRUNE
CARE	FAIR	HALF	NAIL
FLOAT	QUOTE	CLOCK	SPOKE
RARE	SWEAR	CHEAT	DATE
PEARL	GIRL	CART	LATE
SOAK	JOKE	YAWN	PLANE
SIGN	LINE	FOIL	HOLE
POOR	STORE	MESS	NOSE
ROOM	TOMB	TERM	DREAM

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