AN INVESTIGATION INTO THE INVOLVEMENT OF THE VISUAL CORTEX IN AUDITORY LANGUAGE PROCESSING AND VERBAL WORKING MEMORY IN EARLY BLIND INDIVIDUALS

by

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ABSTRACT

The visual cortex in blind individuals is functionally reorganised to support cognitive processes, including auditory language and memory. Language function is thought to arise due to input from the left fronto-temporal language network, however the pathways and brain areas involved are not established. Previous demonstrations of visual cortex involvement in verbal memory in blind individuals suggest that verbal memory performance is tied to visual cortex recruitment, however the extent of visual cortex involvement in verbal working memory is less clear. The current fMRI study compared brain activity in early blind and sighted individuals to address two main objectives; 1) to determine how linguistic information reaches the visual cortex in blind individuals via effective connections from the typical language network and, 2) to determine if increasing working memory load during an *N*-back task leads to increased visual cortex recruitment and if behavioural measurements of verbal working memory ability correlate to visual cortex activity. First, dynamic causal modelling (DCM) provided evidence for an endogenous connection from the “visual” word form area (VWFA) to the visual cortex in blind participants and this connection is positively modulated by semantic and phonological task demands. Second, increasing verbal working memory demands leads to more widespread recruitment of the visual cortex (including V1) in blind participants, however task performance on tests of verbal working memory did not differ between groups. Blind participants’ verbal working memory performance did not correlate to visual cortex recruitment. Overall, results indicate that visual cortex activity associated with semantic and phonological processing is the result of integration into the left-lateralized language network, specifically via driving input from the VWFA. As well, although the visual cortex is sensitive to verbal working memory demands in early blind individuals, this does not ultimately translate to better verbal working memory ability. Ultimately, this work provides a key piece of evidence regarding the processes that reshape the neural systems underlying cognitive functions in blind individuals and clarifies the impact of the functional reorganization of cognitive networks on cognitive ability.

LIST OF ABBREVIATIONS USED

A1 - primary auditory cortex
ARC - autocalibrating reconstruction for cartesian imaging
BMS - Bayesian model selection
BPA - Bayesian parameter averaging
CBF - cerebral blood flow
CNIB - Canadian National Institute for the Blind
DCM - dynamic causal modelling (technique) OR dynamic causal model (a single model)
EP - exceedance probability
FDR - false discovery rate
FFX - fixed effects
fMRI - functional magnetic resonance imaging
FWE - family wise error
GBF - group bayes factor
GC - granger causality
GLM - general linear model
hMT+ - human motor complex
HRF - hemodynamic response function
IFG - inferior frontal gyrus
L - left hemisphere
LCA - leber congenital amaurosis
LGN - lateral geniculate nucleus
LIFG - left inferior frontal gyrus
MNI - Montreal Neurological Institute
MOCA - Montreal Cognitive Assessment
NSERC - Natural Science and Engineering Research Council
OB - one-back
PER - perceptual
PET - positron emission tomography
PHON - phonological
SPM - statistical parametric mapping
R - right hemisphere
RFX - random effects
ROI - region of interest
ROP - retinopathy of prematurity
RP - retinitis pigmentosa
rTMS - repetitive transcranial magnetic stimulation
S1 - primary somatosensory cortex
SEM - semantic
SMA - supplementary motor area
SMC - supplementary motor cortex
STG - superior temporal gyrus
STS - superior temporal sulcus
TB - two-back

TDU - tongue display unit
TE - echo time
TR - repetition time
TMS - transcranial magnetic stimulation
V1 - primary visual cortex
V - visual cortex
VOI - volume of interest
VWFA - visual word form area
WAIS - Weschler Adult Intelligence Scale
WASI - Weschler Abbreviated Scale of Intelligence

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CHAPTER 1 - INTRODUCTION

1.1 EXECUTIVE SUMMARY

How might the human brain adapt to a marked deviation from species typical experience? Understanding the nature and extent of changes that occur as the result of atypical developmental experience can provide insight into the inherent flexibility of the brain. Such an understanding can in turn lead to a better understanding of the neural systems that underlie how humans receive, process, and interact with information from the external world. Profound sensory loss in the form of early blindness can inform our understanding of how the functional specialisation of cortical regions is impacted by the absence of visual input during development. A primary question of interest to the current investigation concerns the outcome of the neural systems that would typically subserve visual processing in blind individuals. Is the functional specialisation of the visual system constrained by inherent physiological limitations or is it able to adapt and acquire the ability to implement fundamentally different computations, including those related to cognitive functions? How does this ultimately impact the organisation of the functional networks subserving cognitive behaviour? Here, we seek to understand the nature of the involvement of visual cortical regions in cognitive processing in blind individuals, particularly language and memory, how the shift from perceptual to cognitive processing may occur and what, if any, impact this ultimately has on cognitive function and ability.

Chapter 1 of this dissertation provides a review of the literature on the impact of blindness on brain development, organisation, and function. A wide body of research suggests that, in blind individuals, the visual cortex is reorganised to process information transmitted through the remaining intact senses, including tactile and auditory information, through a process known as cross-modal plasticity (King, 2015; Kolarik et al., 2021; Kupers & Ptito, 2014). Beyond basic sensory processing, additional evidence suggests that visual regions take on unique capability to perform auditory language operations in blind individuals - evidence for visual cortex involvement has been demonstrated across a variety of auditory language tasks, including verb generation, word level semantic and phonological processing and higher-level sentence comprehension (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002; Ofan & Zohary, 2007; Bedny et al., 2011; Burton et al., 2003; Noppeney et al., 2003; Deen et al., 2015; Röder et al., 2002; Lane et al., 2015; Pant et al., 2020). This functionality is suggested to be driven by information received during development via connections from the fronto-temporal language network, which are unmasked in the absence of competing visual information. Indeed, studies investigating the possible integration of the visual cortex into existing language networks demonstrate increased functional connectivity in blind individuals between visual and language network regions (Abboud & Cohen, 2019; Bedny et al., 2011; Deen et al., 2015; Heine et al., 2015; Striem-Amit et al., 2015). However, the precise nature of the connections between the visual cortex and the typical language network remains an open question, particularly as it relates to the specifics of interregional connectivity, and how connections may change depending on linguistic task demands.

Blindness has also been shown to impact the development of the neural systems related to memory and can also impact memory ability. In particular, evidence suggests that blind individuals show superior verbal memory abilities when compared to sighted controls, and this superior ability has been directly correlated to the recruitment of the visual cortex, primarily during verbal-memory tasks that involve long-term or episodic memory retrieval or recognition (Amedi et al., 2003; Raz et al., 2005). However, how blindness impacts the function of the verbal *working* memory system is less clear as evidence regarding the superiority of blind individuals when it comes to working memory ability is mixed (Tillman & Bashaw, 1968; Smits & Mommers, 1976; Hull & Mason, 1995; Withagen et al. 2013; Swanson & Luxenberg, 2009: Dormal et al., 2016; Loiotile et al., 2020; Pigeon & Marin-Lamellet, 2015; Arcos et al., 2022; Castronovo & Delvenne, 2013; Occelli et al., 2017; Park et al., 2011; Rokem & Ahissar, 2009; Wan et al., 2010).

Motivated by gaps in the research on blind individuals involving the specifics of the integration of the visual cortex into existing language brain networks and the relationship between verbal working memory and visual cortex recruitment, this thesis addressed four primary research questions through two studies of early blind individuals; 1) how does the visual cortex interact with the typical language network during auditory language processing 2) is visual cortex activity modulated by verbal working memory demands, 3) do verbal working memory abilities differ between early blind and sighted individuals and 4) does verbal working memory ability correlate to visual cortex recruitment during verbal working memory processing. Chapter 2 provides a detailed description of the methodology used in this research.

To answer the first question, we compared brain activity in early blind and sighted controls on a task involving word-level semantic and phonological processing. Results (presented in Chapter 3) demonstrated that in both blind and sighted participants, both semantic and phonological processing activated regions within the typical language network, including regions in the left inferior frontal gyrus (LIFG) and left ventral occipito-temporal gyrus, which correspond to the functional regions Broca's area and the visual word form area (VWFA), respectively. Only blind participants demonstrated widespread visual cortex recruitment during semantic and phonological processing, including the involvement of the extrastriate cortex. We then used dynamic causal modelling (DCM) to assess how the observed activity within the visual cortex during semantic and phonological processing may be due to driving input from the LIFG and/or the VWFA. Results demonstrate a significant endogenous connection from the VWFA to the visual cortex and this connection is positively modulated by semantic and phonological task demands. This suggests that the involvement of the visual cortex in semantic and phonological processing observed in early blind individuals is due to cortico-cortical connections from the region within the typical language, specifically the VWFA.

To answer questions two, three and four, we compared brain activity between blind and sighted individuals while they performed an auditory *N*-back task with two conditions (1-back and 2-back). We also compared behavioural performance on a standardised assessment of verbal working memory, Digit Span. Results (presented in Chapter 4) indicate that Digit Span scores did not differ between blind and sighted controls, and neither did behavioural performance on the *N*-back task. Brain activity indicated that both blind and sighted participants showed similar activity within the typical fronto-parietal working memory network during both *N*-back conditions. However, only blind participants recruited the visual cortex during working memory processing and critically, recruitment increased as verbal working memory demands increased - more widespread activity was observed for the 2-back condition, including the recruitment of the primary visual cortex, V1. However, no correlation was observed between behavioural scores on the Digit Span or *N*-back tasks and visual cortex recruitment in the blind group. This suggests that memory enhancements observed previously in blind individuals may not extend to working memory ability and while visual cortex recruitment is modulated by working memory demands, recruitment does not impact behaviour.

Chapter 5 provides a general discussion of these findings. Overall, this thesis provides unique insight into the nature of neuroplastic changes that occur as the result of blindness and how these changes can impact the organisation and function of the cognitive networks related to language and memory. It provides a key piece of evidence regarding the potential mechanism for visual cortex involvement during auditory language tasks in people who are blind, specifically by demonstrating for the first time an effective modulatory connection between a region in the typical language network - the VWFA - and the visual cortex during word level semantic and phonological processing. As well, it clarifies the nature of the connection between the visual cortex involvement in verbal working memory and working memory ability in people who blind. This work has implications for our understanding of how developmental experience can fundamentally alter the neural systems underlying cognitive functions, and the extent to which the reorganisation of neural systems can impact cognitive behaviour.

1.2 IMPACT OF BLINDNESS ON BRAIN ANATOMY

What effect does visual deprivation have on the neural structures that would normally subserve visual processing in a typically developed brain? The following sections deal with a brief overview of the visual system in the non-visually deprived brain, the physical changes that can occur following vision loss in the subcortical pathways responsible for relaying visual information from the eyes to the visual processing regions in the occipital lobe and the changes that may occur in primary and visual association cortical regions. It also discusses the concurrent changes that may occur in the intact sensory systems and changes in cortico-cortical connections between the visual system and other related networks. Anatomical changes are discussed within the context of the functional changes that can co-occur in the visual system as a result of visual deprivation.

1.2.1 BRIEF OVERVIEW OF VISUAL SYSTEM

The subcortical visual pathway refers to the anatomical structures that convey information from the retina to the primary visual cortex in the brain (V1), consisting of the retina, optic nerves, optic chiasm, optic tract and the lateral geniculate nucleus (LGN) in the thalamus which ultimately projects to the visual cortex via the optic radiation (Armstrong & Cubbidge, 2019). The LGN serves as the primary route of first order information transfer from the retina to the visual cortex, while another thalamic structure, the pulvinar, receives projections from the visual cortex and serves as a higher order relay, transferring information from one visual cortical area to another (Sherman, 2020). In addition to being involved in the transmission of visual information, some regions also serve a role in multisensory integration (i.e. receive somatosensory/auditory input), including the superior colliculus in the midbrain (Gould & Nolte, 2021).

Once information reaches the visual cortex, it is processed under two main principles - hierarchical organisation and functional specialisation. Hierarchical organisation within the visual cortex refers to the progression from more general and low-level processing, which occurs in early visual areas, to the more specialised and higher-order processing of different features, which is accomplished in higher-order visual regions (Grill-Spector & Malach, 2004). The first cortical structure to receive visual information is the primary visual cortex (V1), primarily through afferent connections from the LGN. Neurons within V1 respond selectivity to spatial form (edges/contours/orientation), movement in particular directions, and depth, and this information is then built upon by subsequent regions in the visual stream that are selective for more complex types of information (Samonds & Priebe, 2020). Importantly, information is separated into two functionally specialised streams (Grill-Spector & Malach, 2004). The dorsal stream, or "where" pathway, is associated with spatial localization of visual objects (Goodale et al., 1991) and the ventral stream, or "what" pathway, is associated with visual object recognition (Mishkin et al., 1983). In general, information travels from V1 to V2 and then splits into the two streams, although V1 does project to other extrastriate (V3, V3a, V4, hMT+) visual regions as well (Dougherty & Maier, 2020; Samonds & Priebe, 2020).

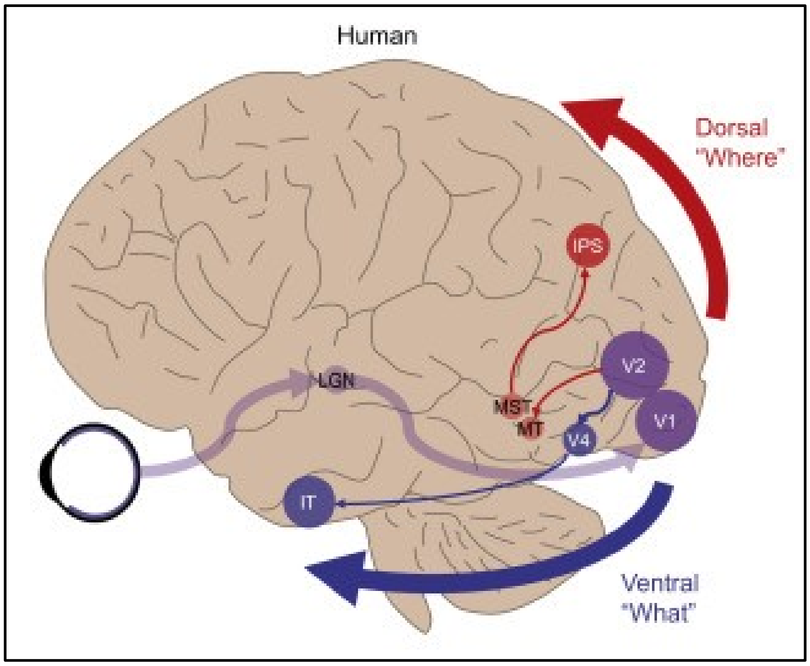

Figure 1.1: Broad overview of input and output of the primary visual cortex in the human brain, reprinted from (Samonds & Priebe, 2020)

1.2.1 ANIMAL STUDIES

Early blindness can cause physical changes in the structures that make up the visual pathway and in the visual cortex itself. For example, evidence from mice models demonstrates that a lack of visual input can lead to atrophy in subcortical visual structures including the superior colliculus (Lund & Lund, 1971; Rhoades, 1980; Smith & Bedi, 1997) and the LGN (Asanuma & Stanfield, 1990; Massé et al., 2014) as well as in cortical visual structures, including the primary and secondary visual cortex (Massé et al., 2014; Rhoades et al., 1984; Touj et al., 2020). Changes within the visual system can be accompanied by concomitant changes elsewhere in the brain - for instance, expansions within the auditory cortex (Gyllensten et al., 1966; Massé et al., 2014) and olfactory cortices (Touj et al., 2020) have been observed for dark-reared mice and anophthalmic mice. This indicates that blindness can induce large-scale structural brain plasticity in both visual and non-visual regions.

Changes in responsiveness within the visual cortex of blind animals have also been widely reported. Neurons within the visual cortex become less selective and less responsive to visual stimulation with prolonged visual deprivation (Rauschecker & Korte, 1993; Singer & Tretter, 1976; Wiesel & Hubel, 1965). At the same time, cross-modal reorganisation occurs such that cells within the visual cortex of blind animals, including cats, mice and rats, become responsive to both auditory and somatosensory information (Kupers & Ptito, 2011). The cross-modal reorganisation of the visual cortex in blind animals is thought to be potentially caused by two processes - the first involves the formation of new connections from the intact sensory systems so that deprived visual regions are rewired to process information in the spared senses (Bavelier & Neville, 2002; Desgent & Ptito, 2012; Driver & Noesselt, 2008; Kadosh & Walsh, 2006). This process is considered to involve the development of new thalamo-cortical connections from the intact sensory systems that are routed through the thalamus to the visual cortex (Desgent & Ptito, 2012). Indeed, new projections from the inferior colliculus (involved in auditory relay) to the LGN have been observed in enucleated hamsters (Izraeli et al., 2002), congenitally blind mice (Chabot et al., 2007, 2008), and the low-vision blind mole rat (Bronchti et al., 2002; Doron & Wollberg, 1994; Kudo et al., 1997; Rehkämper et al., 1994).

The second process is suggested to involve the enhancement or unmasking of existing inputs from the intact sensory cortices that are activated in the absence of competing visual input (Desgent & Ptito, 2012). Existing connections between the other sensory cortices and the visual cortex have been demonstrated in sighted mammals, including cats, ferrets, non-human primates, hamsters and mice (Bizley et al., 2007;

Budinger et al., 2006; Clavagnier et al., 2004; Falchier et al., 2002; Hall & Lomber, 2008; Innocenti et al., 1988; Izraeli et al., 2002; Laramée et al., 2011; Rockland & Ojima, 2003). As demonstrated in studies of sighted animals, these connections appear to contribute to the multisensory processing of some neurons within the visual cortex, which can respond to auditory and somatosensory information (Bental et al., 1968; Fishman & Michael, 1973; Horn, 1965; Morrell, 1972; Murata et al., 1965; Spinelli et al.,1968). These existing afferent connections to the visual cortex are suggested to serve as a route of non-visual information into the visual cortex in blind animals and in some cases have indeed been shown to be amplified as a result of blindness (Laramée et al., 2011). More specifically, connections between the primary auditory cortex and the primary visual cortex have been demonstrated to be amplified in enucleated hamsters as compared to intact hamsters (Laramée et al., 2011).

In general, the results in animal models of blindness demonstrate that visual deprivation can cause large-scale changes in the physical structures that make up the visual system and can impact the structural organisation of the intact sensory systems. As well, physical changes in the form of new thalamo-cortical connections and the enhancement of existing cortico-cortical connections are suggested to contribute to the cross-modal recruitment of deprived visual regions to support auditory and somatosensory processing.

1.2.2 HUMAN STUDIES

The anatomical correlates of vision loss in humans include changes in the physical characteristics of the optic pathway, visual cortex, intact sensory systems and higher-level cortical regions. The absence of visual input has been associated with significant atrophy of the LGN in early blind individuals (Ptito et al., 2008; Ptito, Paré, et al., 2021; Shimony et al., 2006), optic nerve (Ptito et al., 2008, 2021) optic tract (Pan et al., 2007; Ptito et al., 2008, 2021) and optic radiation (Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008), and the degree of atrophy can be predicted in some cases by the age of onset of blindness (Noppeney et al., 2005; Pan et al., 2007).

Alterations in early visual cortical areas have also been demonstrated, including reduced volume in V1/V2 (Bauer et al., 2017; Bridge et al., 2009; Leporé et al., 2010; Pan et al., 2007; Ptito et al., 2008; Shimony et al., 2006; Yang et al., 2014). Reductions in cortical volume in visual areas can be accompanied by increased cortical thickness in early visual regions (Bauer et al., 2017; Bridge et al., 2009; Jiang et al., 2009; Park et al., 2009; W. Qin et al., 2013; Voss & Zatorre, 2012). Increased cortical thickness in visual processing areas is suggested to be the result of a lack of synaptic pruning (the elimination of extra synapses) within the visual cortex due to a lack of visual input during the sensitive period for visual cortex development (Kupers & Ptito, 2014). The co-occurrence of increased cortical thickness and decreased cortical volume in the visual cortex can be explained by greater decreases in cortical surface area relative to the increases observed in cortical thickness (cortical volume = surface area x thickness), which has been observed in some cases (Park et al., 2009). Factors that can affect cortical thickness measurements in blind individuals include age of onset of blindness, which has been shown to be correlated to increased cortical thickness in early visual regions (Jiang et al., 2009; Voss & Zatorre, 2012). Cortical thickness covariance between the visual cortex and other brain regions has also been observed, with reduced covariance between right visual occipital regions and regions within the dorsal visual stream (Voss & Zatorre, 2015). Anatomical covariance is considered to be a reflection of brain connectivity, as brain regions that are highly correlated in size are often part of systems that underlie specific cognitive or behavioural functions (Alexander-Bloch et al., 2013; Lerch et al., 2006). Overall, this suggests that early sensory experience can induce changes in visual cortical structure and influence the relationship between cortical structure and function.

Within the intact sensory systems, anatomical changes can potentially be driven in an experience-dependent manner. For example, increased cortical space devoted to the fingers has been observed in blind multi-finger braille readers (Sterr et al., 1998). Blind individuals have been demonstrated to have increased olfactory abilities (Rombaux et al., 2010), which has been linked to increased olfactory bulb volume (Rombaux et al., 2010). Finally, expansion of the auditory tonotopic map in early blind individuals has also been found (Elbert et al., 2002), which suggests that a greater reliance on the intact sensory systems can cause use-dependent cortical expansion. Other changes have been reported in hippocampus regions typically associated with navigation (Chebat, Chen, et al., 2007; Leporé et al., 2009). Blind individuals cannot use visual cues to aid in wayfinding and must rely extensively on memory to map and navigate through their surroundings (Fortin et al., 2008; Leporé et al., 2009). As such, blindness has been associated with superior route-learning skills and larger overall hippocampal volumes as compared to sighted controls (Fortin et al., 2008). Despite overall larger volumes, specific volumetric reductions within the hippocampus have been observed in blind individuals, particularly in the right posterior hippocampus (Chebat, Chen, et al., 2007; Leporé et al., 2009). Increases in right posterior hippocampus volume have previously been associated with navigational experience (Maguire et al., 2000, 2003) and this region has been suggested to store allocentric spatial representations (Maguire et al., 2000, 2003). Observations of a decrease in right posterior hippocampal volume in blind individuals is therefore thought to potentially reflect differences in how blind individuals encode spatial information, specifically that blind individuals rely more on egocentric spatial representations (Leporé et al., 2009; Noordzij et al., 2006).

Metabolic changes in the brain have also been observed in blind individuals. Early blind individuals have been shown to have increased glucose metabolism in the visual cortex compared to sighted controls (Veraart et al., 1990; Volder et al., 1997; Wanet-Defalque et al., 1988), however no difference in metabolism has been observed between later blind individuals and sighted controls (Veraart et al., 1990). Elevated metabolism is thought to be caused by increased neural activity related to increased synaptic density, potentially as a result of reductions in normal synaptic pruning (Volder et al., 1997). These changes have been observed in both primary and secondary visual regions (Kupers & Ptito, 2014), suggesting that early blindness can prevent the normal synaptic pruning that occurs during development, leading to altered energy consumption within widespread visual regions.

1.3 IMPACT OF BLINDNESS ON PERCEPTUAL PROCESSING

What happens to the intact sensory systems following vision loss? Do blind individuals develop superior or enhanced skills when processing information in the remaining senses, a process known as compensatory plasticity? These questions have been studied across a variety of domains, however a clear consensus in the literature has not emerged. The following sections discuss the evidence for compensatory plasticity in blind individuals in the non-visual intact senses.

1.3.1 TACTILE PROCESSING

Does the use of a tactile reading system (braille) in blind individuals affect tactile processing abilities? Blind braille readers have been shown to have better tactile skills across a variety of tasks, including letter recognition (Craig, 1988), grating detection (Goldreich & Kanics, 2006), grating orientation discrimination (Boven et al., 2000; Goldreich & Kanics, 2003; Norman & Bartholomew, 2011), tactile symmetry detection (Bauer et al., 2015), 3-D shape discrimination (Norman & Bartholomew, 2011), texture discrimination (Gurtubay-Antolin & Rodríguez-Fornells, 2017), and tactile acuity (Legge et al., 2008). These enhancements are sometimes limited to the finger used primarily for braille reading (Goldreich & Kanics, 2003), or extend to the remaining fingers as well (Boven et al., 2000). Importantly, enhancements are not demonstrated to correlate with age of onset of blindness (Goldreich & Kanics, 2003, 2006), age at which braille was learned, amount of braille use, nor braille reading speed (Goldreich & Kanics, 2006; Legge et al., 2008). The lack of correlation between superior tactile skills and braille reading suggests that the superior tactile skills seen in blind individuals may not be related to braille reading per se, but instead be a function of the active touch employed by blind individuals during day-to-day life or due to visual deprivation itself leading to increases in tactile processing ability.

The question as to whether the enhancements observed are the result of a greater reliance on active touch or because visual deprivation in general leads to greater tactile sensitivity was addressed by a few studies directly. Wong et al., (2011) compared grating orientation acuity of the fingers and lips among blind participants with and without braille reading ability, and sighted controls. Both blind groups outperformed sighted controls, but only with the fingers and not lips. Proficient braille readers performed better with their reading index finger compared to the opposite non-reading finger and also outperformed blind participants naive to braille (Wong et al., 2011). If the superior performance on tactile tasks observed previously was due to a general enhancement in tactile abilities as the result of visual deprivation, blind individuals would be expected to perform similarly using both their fingers and lips. However, the results obtained suggest that enhancements are due to a greater everyday reliance on the sense of touch in their fingers (Wong et al., 2011).

It should be noted, however, that a few studies have not demonstrated superior tactile processing skills in blind individuals. Blind participants have been shown to perform comparably to sighted controls on finger-based tasks that involve texture perception (Heller, 1989), ridge width, and spatial acuity dependent grating orientation (Grant et al., 2000). As well, although blind participants perform better than sighted controls on tactile hyperacuity tasks after a single session, group differences can be eliminated following multiple exposures (over 4 sessions) to the task (Grant et al., 2000).

Blind individuals can be trained to recognize and discriminate electro-tactile stimulation on their tongue via a device called a tongue-display unit (TDU). This process is known as sensory substitution, in which the information usually transmitted via a deprived sensory system is instead transmitted through an intact sensory system (Bach-y-Rita & Kercel, 2003). Blind participants have been shown to utilise TDUs to successfully detect differences in object orientation (Ptito et al., 2005), motion (Matteau et al., 2010), shape (Ptito et al., 2012), and tactile- “visual” acuity (Chebat, Rainville, et al., 2007). In all cases, blind groups perform comparably to sighted groups, although at an individual subject level, some blind participants significantly outperformed matched sighted controls (Chebat, Rainville, et al., 2007).

When comparing brain activations in sighted and blind individuals associated with tactile processing, blind individuals have been shown to uniquely recruit occipital regions (Lubbe et al., 2010), including the peri-calcarine cortex, the lateral occipital cortex (Bauer et al., 2015), V1 (Merabet et al., 2007; Müller et al., 2019; Wittenberg et al., 2004), the right superior occipital gyrus (Sadato et al., 2004) and extrastriate visual areas (for early blind) and V1 (for later blind individuals) (Büchel et al., 1998). In early blind individuals, tactile discrimination relative to an active control condition has also been shown to reduce activation in extrastriate cortical regions (V2, V3, V3a, hV4), with concurrent activation of V1 (Merabet et al., 2007). This is thought to potentially reflect a top-down inhibitory effect of tactile processing on later-stage visual areas, and a bottom-up excitatory effect of tactile processing on V1 (Merabet et al., 2007). Training with a TDU has been shown to result in a significant increase in cerebral blood flow (CBF) to occipital regions in blind, but not sighted participants (Ptito et al., 2005), and involves key regions of the ventral visual stream (Ptito et al., 2012), and the motion sensitive middle temporal cortex (hMT+, (Matteau et al., 2010), suggesting sensory substitution via electo-tactile stimulation can activate the visual cortex. Tactile information may reach the visual cortex through cortico-cortical pathway from S1 (Fujii et al., 2009; Ioannides et al., 2013; Kupers et al., 2006; A. Leo et al., 2012; Ptito et al., 2005; Wittenberg et al., 2004) or through a thalamo-cortical pathway involving the LGN (Müller et al., 2019).

1.3.2 SOUND LOCALIZATION

Blind individuals must rely heavily on sound information for spatial awareness and this could lead to increased or sharpened abilities, in a use-dependent manner. In a seminal study, (Lessard et al., 1998) demonstrated that blind individuals are able to use binaural auditory cues to understand their spatial environment as accurately as sighted controls. Other work subsequently confirmed this finding, particularly in the horizontal plane (Ashmead et al., 1998; Röder et al., 1999). In some instances, blind individuals are able to localise sounds better than their sighted counterparts (Fieger et al., 2006; Lessard et al., 1998; Röder et al., 1999; Voss et al., 2004), although not all studies demonstrate this effect (Lewald, 2002; Zwiers et al., 2001). Blind individuals have also been shown to outperform sighted counterparts on tasks that require monaural sound localisation, in which one ear is covered (Gougoux et al., 2005; Lessard et al., 1998; Voss et al., 2011). The superior abilities observed in blind individuals, particularly related to monaural sound localization, have been linked to a greater reliance on spectral cues (Doucet et al., 2005; Voss et al., 2011), i.e. the specific way in which sounds are filtered by the head and outer ear (Middlebrooks & Green, 1991). For example, when blind participant's ability to use spectral cues to localize sound is inhibited, they make more localization errors (Doucet et al., 2005). This enhancement has been observed for both early and later blind individuals (Fieger et al., 2006; Voss et al., 2004).

The neural underpinnings of these changes in sound localization abilities may be attributed to an increase in cortical space devoted to auditory processing (Lazzouni & Lepore, 2014; Rauschecker, 1995). In particular, multiple studies have demonstrated the recruitment of the visual cortex during auditory spatial processing in people who are blind (Gougoux et al., 2005; Voss et al., 2008; Weeks et al., 2000). In the case of Gougoux et al., (2005), a significant correlation was observed between performance on a monaural sound localisation task and CBF in the right lingual gyrus, superior occipital gyrus and V1, demonstrating a possible functional relationship between visual cortex recruitment and sound localization in the blind. There is evidence demonstrating that repetitive transcranial stimulation (rTMS) to the dorsal extrastriate cortex impairs auditory spatial processing, but not pitch or sound level processing, suggesting that the right dorsal extrastriate cortex is functionally specialised for sound localization in the blind (Collignon et al., 2007).

1.3.3 PITCH

Pitch discrimination abilities have been shown to be enhanced in blind individuals (both early and late blind) compared to sighted controls (Gougoux et al., 2004; Voss & Zatorre, 2012). Wan et al., (2010) examined several metrics, including pitch discrimination, pitch-timbre categorization, and pitch working memory across groups of blind individuals who lost their sight at different ages. Congenitally blind participants showed better performance on pitch discrimination and pitch-timbre categorization than later blind individuals or sighted controls. Pitch discrimination thresholds are lower in congenitally blind individuals compared to sighted controls (Rokem & Ahissar, 2009). Similar results are seen for pitch change detection (Arnaud et al., 2018). Absolute pitch refers to the ability to identify the exact pitch of a Western musical scale without an external cue (Kupers & Ptito, 2014). The prevalence of absolute pitch among blind individuals with musical training has been reported to be higher than for sighted controls with similar levels of training (Hamilton et al., 2004). The neural resources associated with absolute pitch are different for blind and sighted individuals as well, with greater activations in blind individuals compared to sighted individuals within visual association areas and the lingual gyrus, whereas sighted individuals recruit the auditory cortex and the cerebellum to a greater extent than blind individuals (Gaab et al., 2006).

1.3.4 ECHOLOCATION

Echolocation is a form of spatial hearing that involves an individual producing a sound in order to detect, locate and identify objects in the environment and can provide information about the characteristics of objects, including object size, distance, texture and density (King, 2015; Kolarik et al., 2014; Thaler & Goodale, 2016). Blind individuals who use echolocation produce sounds (with a cane, vocal clicks, foot tapping, fingers) and interpret the return of these sound waves binaurally (Griffin, 1944). Blind participants outperform sighted controls on echolocation tasks (Dufour et al., 2005; Schenkman & Nilsson, 2009). The effect of age of onset of blindness is variable, with some research suggesting that an earlier onset of blindness can contribute to better echolocation abilities (Teng et al., 2012), but another study found no such effect (Dufour et al., 2005). More recently, research has investigated whether congenitally blind and sighted individuals naive to echolocation can learn the skill over a 10-week training program (Norman et al., 2021). Both groups were able to improve similarly over the course of training, and in some instances performed comparably to expert echolocators (Norman et al., 2021). Blind participants from this study were also tested on their auditory localization abilities following training, however no improvements in localization abilities were observed (Thaler & Norman, 2021), suggesting the auditory processing skills associated with echolocation may not always generalise to other auditory domains.

1.3.5 SPEECH AND VOICE PERCEPTION

Blind individuals have been shown to outperform sighted individuals on tasks involving speech detection in noise (Muchnik et al., 2009; Niemeyer & Starlinger, 1981; Rokem & Ahissar, 2009). For example, Rokem & Ahissar (2009) found that blind participants had lower (dB) speech detection thresholds in background noise, as compared to sighted controls. Other areas of performance enhancements for blind individuals with regards to speech perception include faster lexical decision times (Röder et al., 2003), improved ability to distinguish between vowels (Ménard et al., 2009), superior prosody detection (Klinge, Röder, et al., 2010) and better syllable parsing (Hugdahl et al., 2004). Blind individuals often rely on text-to-speech applications, which can be manually adjusted to artificially increase the speed at which speech utterances are transmitted. Indeed, blind individuals have been shown to understand spoken language at a faster rate (22 syllables/second) than sighted controls (8 syllables/second) (Dietrich et al., 2011, 2013).

Blind individuals cannot use visual cues to recognize people and must instead learn to associate an individual person with the sound of their voice, which could in theory contribute to superior voice processing or discrimination abilities. As well, it has been suggested that the visual cortex may be tuned to speech perception, given that neurons within the primary visual cortex of blind individuals have been demonstrated to synchronise to the temporal dynamics of speech (Ackeren et al., 2018). However, the data on blind individuals' voice discrimination abilities and how they compare to sighted individuals is mixed. Some evidence suggests they are more accurate than sighted controls when recognizing previously heard speakers (Bull et al., 1981), and learn the association between names and speakers more quickly and identify speakers based on novel voice samples more accurately (Föcker et al., 2012). Other work has shown a superiority for both early and late blind individuals compared to sighted controls in their ability to recognize voices, but only after a delay period of two weeks (Pang et al., 2020). However, not all work has demonstrated superior voice recognition/discrimination abilities in blind individuals, and instead suggests they perform similarly to sighted controls (Gougoux et al., 2009; Günzburger et al., 1987; Winograd et al., 1984). Blind individuals also perform similarly to sighted controls on tasks that involve assessing a person's height based on their voice (Pisanski et al., 2016) and in the assessment of social stereotypes (trustworthiness, competence, warmth) based on vocal pitch (Oleszkiewicz et al., 2017).

1.3.6 OLFACTION/GUSTATION

The literature on the impact of blindness on smell and taste processing is relatively small and results are mixed, with some research reporting enhanced capacities, while other research reports no difference in ability when compared to sighted individuals. Blind individuals have been shown to have increased odour discrimination and identification abilities (Cuevas et al., 2009) and blind children are faster than sighted controls at identifying odours (Rosenbluth et al., 1999). Beaulieu-Lefebvre et al., (2011) observed lower odour detection thresholds in congenitally blind adults, but no performance enhancements related to discrimination or identification. One study that reported increased odour detection and discrimination abilities in blind individuals as compared to sighted controls also reported increased olfactory bulb volume in blind participants. However, a few studies have reported conflicting results. Smith et al., (1993) failed to observe any difference between blind individuals (both early and late blind) and sighted controls in odour detection, discrimination or identification, and Murphy & Cain, (1986) reported a lower odour detection threshold in sighted controls, not blind participants. Finally, Kupers et al., (2011) did not observe differences between blind and sighted controls for odour detection, or in odour intensity and valence ratings.

Blind individuals may have poorer taste sensitivity (as indicated by higher discrimination/identification thresholds) compared to sighted controls (Gagnon et al., 2013), and taste perception in blind individuals involves the primary gustatory cortex, but not the visual cortex, which contrasts with the recruitment of visual regions for auditory, tactile and olfactory processing (Gagnon et al., 2015). However, the literature on taste perception in people who are blind is limited and affected by methodological limitations (Kupers & Ptito, 2014). It has been suggested that the lower taste sensitivity and lack of crossmodal recruitment of visual areas may be due to differences in how blind individuals shop for food, cook and eat out (Bilyk et al., 2009) leading to lack of exposure to a variety of taste stimuli (Gagnon et al., 2015; Gagnon et al., 2013; Kupers & Ptito, 2014).

1.3.7 PAIN PROCESSING

Vision plays an important role in pain perception, particularly through an analgesic effect (Longo et al., 2009, 2012; Mancini et al., 2010; Zubek et al., 1964). Viewing the body can reduce feelings of acute pain (Longo et al., 2009, 2012; Mancini et al., 2010), and prolonged visual deprivation (induced by blindfolding sighted participants for 5 consecutive days) can cause an increase in pain and heat sensitivity (Zubek et al., 1964). Blind individuals have been shown in several studies to be hypersensitive to painful temperatures (Slimani et al., 2016; Slimani et al., 2013, 2014). This effect is stronger for congenital vs. later blind individuals (Slimani et al., 2014) and has been associated with faster transmission times through C fibres, which are nociceptive nerve fibres (Slimani et al., 2014). Blind individuals are better at discriminating small changes in non-painful heat stimuli and are affected more by the spatial summation of heat, which refers to the cumulative effect of multiple stimuli applied at the same time in different locations (Moini et al., 2021; Slimani et al., 2015). Finally, blind individuals and sighted controls are equally anxious when uncertain about the intensity of impending painful stimuli, but only blind individuals rate subsequent stimuli as more painful (Holten-Rossing et al., 2018). Overall, this suggests that people who are blind are hypersensitive to noxious thermal stimuli (Holten-Rossing et al., 2018; Kupers & Ptito, 2014).

1.4 IMPACT OF BLINDNESS ON COGNITION

The study of blindness and its impact on neural development and function offers a unique window into the inherent plasticity of the brain and the flexibility of cognitive systems, as early visual deprivation represents a large-scale change from typical developmental experience. Given the evidence of widespread changes in perceptual processing and ability in blind individuals, research has also investigated how visual deprivation could impact cognitive networks. In particular, studies have investigated how brain systems that would typically support visual perceptual processing are driven to take on a role in higher-level cognitive behaviours, including language and memory. The following sections first give a brief overview of the language system in the brain focusing on the ventral processing stream in particular and then deal with the nature of neuroplastic changes that occur as the result of blindness in the language system, including those related to reading and auditory language processing, and how blindness may impact cognitive function and behaviour, particularly as it relates to verbal memory.

1.4.1 THE LANGUAGE SYSTEM IN THE BRAIN

Studies involving sighted individuals indicate that the brain regions relevant for language processing are located in the inferior frontal cortex and temporal cortices (middle and superior temporal cortices), as well as parts of the parietal lobe including the angular gyrus and inferior parietal gyrus, typically within the left hemisphere (Friederici, 2011; Hickock & Poeppel, 2007). These regions are consistently activated during auditory language processing, regardless of language spoken (Malik-Moraleda et al., 2022). The broadly accepted view is that these regions are incorporated into ventral and dorsal pathways that subserve different aspects of auditory linguistic processing (Friederici, 2011, 2012; Hickock & Poeppel, 2007; Smith & Johnsrude, 2003). According to this "dual-stream" view, the ventral stream is responsible for sound-to-meaning mapping, while the dorsal stream is responsible for sound-to-motor mapping (Hickock & Poeppel, 2004; Hickock & Poeppel, 2007; Rauschecker, & Scott, 2009). More recent evidence suggests that both streams may be further subdivided (anatomically and functionally); the dorsal stream may also be involved in complex syntactic processing and the ventral pathway's function goes beyond basic sound-to-meaning mapping and incorporates syntactic processing more generally (Friederici, 2012).

The anatomical connections of the dorsal and ventral pathways have been studied using diffusion tensor imaging (DTI) and can be described as follows (Friederici, 2011).

The dorsal pathway(s) consist of a connection between the superior temporal gyrus (STG) and the premotor cortex via the arcuate fascicle and the superior longitudinal fascicle, and a connection between the STG and Broca's area (BA 44) via the arcuate fascicle and superior longitudinal fascicle (Saur et al., 2008; Friederici et al., 2006). The ventral pathway(s) consist of a connection between Broca's area (BA 45) and the temporal cortex via the extreme fibre capsule system (EFCS) and a connection between the frontal operculum and the anterior temporal STG/STS via the uncinate fascicle (Saur et al., 2008; Friederici et al., 2006). Note however that DTI cannot determine directionality of these pathways.

The initial stages of sound-to-meaning mapping in the ventral pathway involve the acoustic analysis of speech input, which occurs in the auditory cortex (Smith & Johnsrude, 2003). Regions in the auditory cortex and adjacent areas that are involved in the acoustic analysis of speech include Heschl's gryus (HG), the planum temporale, the planum polare, and the STG/STS (Friederici, 2011; Johnsrude et al., 2002; Hall et al., 2002; Blesser, 1972). The specific identification of phonemes (differentiation between speech and non-speech sounds) occurs in the STS/STG, anterolateral to HG (Binder et al., 2000; Cohen et al., 2004; Liebenthal et al., 2005; Hickok & Poeppel, 2007). The STS in particular is associated with phonological processes in both speech reception and production, and in the maintenance of phonological information (Hikock & Poeppel, 2004; Buchsbaum, Hickok & Humphries, 2001; Hickok et al., 2003).

After basic phonemic processing, information regarding the syntactic and semantic content of the speech signal is extracted. Word-level lexical-semantic access occurs quickly and has reliably been demonstrated to involve the middle temporal gyrus

— which maps phonological input from the STS to distributed semantic representations (Friederici, 2012; Hickok & Poeppel, 2000)— and to a lesser extent the anterior temporal lobe (Hickok & Poeppel, 2004). The anterior STG has also been implicated in word-level semantic processing, as patients with anterior STG damage demonstrate difficulty with word and picture naming tasks (Ralph & Patterson, 2008). Syntactic phrase structure building (the process of assigning words to classes or categories) has been demonstrated to the involve the frontal operculum and anterior STG (Friederici et al., 2006; Friederici et al., 2003) and in some instances (such as during language development or during second language acquisition) recruit the IFG (Brauer & Friederici, 2007; Rüschemeyer et al., 2005). Posterior temporal regions, including the posterior STG/STS, are activated by sentence-level semantic and synactic information, particularly as it relates to resolving the relationships between sentence elements (i.e. the relationship between verbs and arguments) and during the processing of syntactically complex sentences (Friederici, 2011).

Language information is further transferred to the inferior frontal gyrus (via ventral anatomical connections, Weiller et al., 2011), particularly Broca's area, which is involved in high-level semantic and syntactic processing (Amunts et al., 1999). Broca's area is anatomically and functionally subdivided into BA 44, which supports syntactic processing and BA 45, which supports semantic processes (Friederici, 2011). Syntactic functions carried out in the IFG involve high-level sentence-level phrase structure combinations, with regions in the dorsal portion of BA 44 in particular supporting syntactic working memory (Fiebach et al., 2005). High-level semantic processes (e.g., semantic fit between sentence elements) are carried out in more anterior regions of the

IFG, including BA 47 and the anterior portion of BA 45 (Rodd et al., 2005). Semantic and syntactic processes are highly integrated in the IFG (Tyler & Marslen-Wilson, 2008), however, the posterior temporal cortex also has a functional role in semantic-syntactic integration (Newman et al., 2010).

In addition to the above-described regions, a region within the ventral occipitotemporal cortex (vOTC), called the visual word form area (VWFA), is also involved in auditory language processing. The VWFA was originally proposed to serve a specific function, namely the decoding of visual written words (Cohen et al., 2000). Anatomically located lateral to the middle section of the fusiform gyrus, it has been suggested to provide a direct connection between visual regions and language regions involved in reading (Bouhali et al., 2014; Yeatman et al., 2013). Indeed, direct anatomical connections from the VWFA to left hemispheric perisylvian language areas and to ventral visual field regions — including V1 and V2 — have been demonstrated (Bouhali et al., 2014; Yeatman et al., 2013). Further, deafferentations of the VWFA from the visual cortex are associated with reading impairments (Cohen et al., 2003).

However, activations during spoken language tasks have also been observed in sighted individuals, particularly those that involve orthographic processing, i.e. judging the spelling of auditory words, or whether words contain a specific letter or a specific number of letters (Booth et al., 2002; Ludersdorfer et al., 2015, 2016). The VWFA is also active during spoken language tasks that involve sentence processing; more specifically, the region in the vOTC that responds to written text also responds during sentence comprehension tasks (Planton et al., 2019). Finally, activations have been observed during both productive (speaking/writing) and receptive (reading/listening) tasks (Qin et al., 2021), which suggests it may be involved in meaning-binding more generally. In people who are blind, activations of the VWFA have been demonstrated during Braille reading (Rączy et al., 2019; Reich et al., 2011; Sadato et al., 1998; Tian et al., 2021), suggesting functionality related to word identification regardless of input modality. Activations associated with auditory language processing have also been demonstrated, including during tasks involving sentence-level semantic processing and verb generation (Abboud & Cohen, 2019). The VWFA has also been shown to take on higher-level linguistic processing, including sensitivity for grammatical complexity in spoken sentences (Kim et al., 2017).

There are two competing hypotheses that attempt to explain the functional role of the VWFA in auditory language processing in sighted people. The orthographic tuning hypothesis (Cohen et al., 2004; Dehaene and Cohen, 2011; Dehaene et al., 2005) suggests that neurons within the VWFA are selectively tuned to written language and are activated in top-down fashion once speech is converted to orthographic code. This hypothesis is typically referenced to explain the demonstrations of VWFA activity during auditory single-word processing where top-down activation of orthographic information may occur (Booth et al., 2002; Ludersdorfer et al., 2015&2016). This hypothesis cannot however account for the evidence of VWFA activations during sentence-level processing, in which the online activation of orthographic information is unlikely (Price & Devlin, 2011). In contrast, the interactive account of the VWFA (Price and Devlin, 2011) suggests that neurons within the VWFA are not selectively tuned to written language and instead the functional specialization of that region is due to the integration of bottom-up input and top-down predictions based on prior association between visual input and semantic/phonological information. Within this framework, the VWFA is more broadly integrated into the networks subserving semantic and phonological processing and activations during auditory sentence-level processing are not due to the concurrent activation of orthographic information (Planton et al., 2019). While these competing hypotheses were specifically proposed to explain VWFA function in people who are sighted and have not been formally applied to explain the functional role of the VWFA in people who are blind, the interactive account may provide a useful framework to interpret the results within the blind population as well.

1.4.2 BRAILLE READING

Braille is a tactile system that is used by people with vision loss to read text (Sadato, 2005). Invented by Louis Braille in 1821, the system consists of squares of space (called Braille cells) that are filled with patterns of six raised dots. A single cell can represent an individual letter, a number, punctuation symbols, or can be used as an abbreviation for a whole word. Braille reading requires a high degree of tactile acuity, given that braille cells are small and successful reading requires two-point discrimination ability below 4 mm (Sadato, 2005). As discussed above, blind individuals have been shown to demonstrate superior tactile skills when compared to sighted individuals, and this ability has been linked to a greater reliance on active touch in day-to-day life, which includes braille reading.

Early work on the nature of neuroplastic changes associated with braille reading involved investigations into the possible changes in the cortical space devoted to the fingers. Several studies have demonstrated an enlargement of the representative space in the sensorimotor cortex devoted to the fingers, particularly the finger(s) used to read

(Pascual-Leone et al., 1995; Pascual-Leone & Cammarota, 1993; Pascual-Leone & Torres, 1993). Multi-finger reading, a strategy employed by some braille readers, has also been shown to cause topographic disordering of the organization of the fingers in the sensorimotor cortex (Sterr et al., 1998). However, when comparing the somatic representation of the fingers in braille readers, it should be noted that representations measured following a period of intense braille reading activity are larger when compared to representations measured following periods of rest (Pascual-Leone et al., 1995). This suggests rapid use-dependent changes in cortical representations are possible, and the timing of data collection should be considered when interpreting results. Note that not all studies have demonstrated an increased representation of the fingers associated with braille reading ability (Burton, Snyder, Conturo, et al., 2002), which the authors suggest could potentially be related to the nature of the stimuli used, i.e., balanced tactile and motor demands between braille and active control conditions.

When investigating other neural plastic changes associated with reading braille, a significant body of evidence suggests a functional involvement of the visual cortex. Early work investigating the development of visual prosthesis devices suggested a possible involvement of the visual cortex in braille reading: surgical interventions involving the application of electrical stimulation spatially organised like a braille cell directly to the visual cortex enabled a blind individual to read “cortical” braille (Dobelle et al., 1974; Dobelle et al., 1976). Additional early work showed that patterns of visual cortex activity (as measured by scalp-recorded slow negative electrical potentials) differed between blind and sighted controls during both braille reading and other tactile tasks (Uhl et al., 1991). Subsequent work measured visual cortex activity with PET (positron emission tomography) while early blind individuals read braille, and demonstrated activation of the primary visual cortex during tactile discrimination of both braille characters and non-braille stimuli (Sadato et al., 1996), with greater activity for braille. This activity was later demonstrated to be functionally relevant, as disrupting visual cortical activity with transcranial magnetic stimulation (TMS) caused a reduction in tactile acuity in blind individuals and impaired their ability to discriminate braille characters and disrupted braille reading speed (Cohen et al., 1997; Hamilton & Pascual-Leone, 1998; Kupers et al., 2007). TMS of the visual cortex also induces somatotopically organised sensations in the fingers of blind braille readers, while it only induces visual sensations in sighted controls (Ptito et al., 2008). Finally, evidence from the clinical literature has indicated that damage to the bilateral visual cortex due to stroke can result in alexia for braille in early blind individuals (Hamilton et al., 2000). The involvement of the visual cortex (including primary and extrastriate visual regions) in braille reading in people who are blind has since been replicated by many studies (Amedi et al., 2003; Beisteiner et al., 2015; Bhattacharjee et al., 2010; Bola et al., 2019; Büchel et al., 1998; Burton et al., 2002; Burton & McLaren, 2005; Cohen et al., 2014; Cohen et al., 1999; Debowska et al., 2016; Dzięgiel-Fivet et al., 2021; Fujii et al., 2009; Hamilton et al., 2000; Hamilton & Pascual-Leone, 1998; Heine et al., 2015; Lane et al., 2017; Likova et al., 2016; Liu et al., 2007; Martiniello & Wittich, 2020; Melzer et al., 2001; Pishnamazi et al., 2016; Ptito et al., 2008; Rączy et al., 2019; Sadato et al., 1998; Sadato et al., 2004; Sadato, 2005; Siuda-Krzywicka et al., 2016; Sterr et al., 1998; Tian et al., 2021; Wittenberg et al., 2004).

Research has investigated the effect of age of onset of blindness and braille proficiency on the degree and nature of visual cortex involvement in braille reading. Age of onset of blindness, but not braille experience, has been shown to affect braille fluency, with an earlier age of onset of blindness being associated with increased braille reading fluency. In terms of the relationship between age of onset of blindness and cross-modal changes in visual regions, the evidence is not entirely consistent. For instance, Büchel et al., (1998) compared visual cortex responses to braille reading and auditory language processing in individuals who were early blind or late blind. They observed greater activation in extrastriate visual cortex during braille reading compared to auditory language processing in the early blind group and additional recruitment in primary visual areas during braille reading in the late blind group (Büchel et al., 1998), with similar results reported by Melzer et al., (2001), indicating a stronger relationship between braille reading and activation in V1 in later blind individuals compared to early blind individuals. This contrasts with evidence suggesting that individuals who are congenitally or early blind show greater activation in the primary visual cortex during braille reading when compared to individuals who lost their sight later in life and disruption of the visual cortex with TMS disrupts braille reading in congenital and early blind individuals, but not late blind individuals (Cohen et al., 1999). The authors suggest a possible sensitive period for functional changes associated with braille reading in the visual cortex to occur prior to the age of 14 (Cohen et al., 1999). Other work by Burton et al., (2002) has shown robust activation in both V1 and V2 during braille reading tasks for individuals who lost their sight both early and late in life. Finally, the effects of braille training on brain organisation and function in sighted people indicates braille training can induce rapid grey and white matter reorganisation in early visual regions and increase functional connectivity between the visual cortex and somatosensory and motor regions (Bola et al., 2017), but does not induce permanent changes in visual cortex recruitment specific to braille reading (Matuszewski et al., 2021; Merabet et al., 2008; Siuda-Krzywicka et al., 2016).

How does tactile information reach the visual cortex? According to Bavelier & Neville (2002) there are three possible routes of information. The first is a subcortical route, in which information reaches the primary visual cortex directly from the lateral geniculate nucleus, which is reorganised to process visual input. A second model predicts cortico-cortical connections originating in primary somatosensory regions (S1). This is considered to be a feedback pathway that routes through the multimodal integration areas in the posterior parietal cortex (Bavelier & Neville, 2002; Fujii et al., 2009). Finally, the third pathway involves direct long-range connections between S1 and the primary visual cortex.

Research into which of the three potential pathways constitute the route of tactile information into the visual cortex has been conducted. During tactile spatial discrimination, congenitally blind individuals have been demonstrated to show increased functional connectivity between the left inferior parietal lobe and visual regions, although not V1 (Leo et al., 2012). As well, early blind individuals show increased activation in visual areas when rTMS is applied over S1 (Wittenberg et al., 2004). While these results suggest a degree of connectivity between S1 and the visual cortex, they are not able to distinguish between a cortico-cortical route and a direct feedback pathway between S1 and visual regions. Fujii et al., (2009) compared the two possibilities directly using DCM (see Figure 1.2). Bayesian model comparison indicated that the cortico-cortical model was more likely and tactile information reaches primary visual regions through a route that includes dorsal visual regions (Fujii et al., 2009).

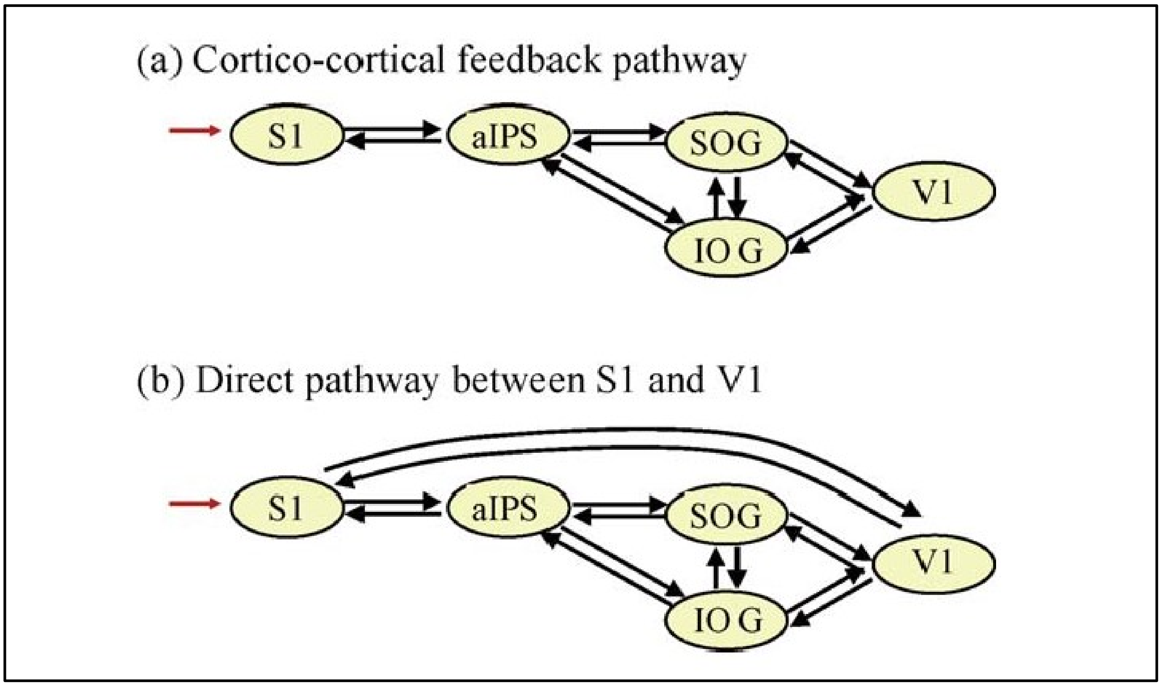

Figure 1.2: DCM models accounting for the possible route of tactile information into the visual cortex in early blind individuals, reprinted from (Fujii et al., 2009)

Overall, this suggests a functionally significant role of the visual cortex in braille reading in people who are blind. Activity is not exclusively related to basic tactile processing, and instead is suggested to support functioning unique to reading. Evidence for the effect of age of onset of blindness on this effect are mixed, however the reorganisation of visual regions to support reading is consistently observed regardless of when an individual became blind. Finally, tactile information in people who are blind is suggested to reach the visual cortex through unique connectivity between visual regions and the primary somatosensory cortex.

1.4.3 AUDITORY LANGUAGE PROCESSING

Following the demonstration of visual cortex involvement in braille reading, questions regarding its potential involvement in auditory language processing arose. Cross-modal activity related to the perceptual processing of basic auditory information had been well established (as discussed in Section 1.3 above), but whether the visual cortex could acquire the capacity to integrate higher-level cognitive information transmitted auditorily was yet unknown. Röder et al., (2002) compared early blind individuals to sighted controls on an auditory sentence processing task that manipulated syntactic complexity and semantic content and observed that only blind individuals demonstrated visual cortex (striate and extrastriate) involvement during speech comprehension. Crucially, visual cortex recruitment was enhanced for more syntactically complex sentences and for semantically meaningful sentences compared to meaningless sentences, suggesting that the visual cortex is sensitive to the linguistic demands of a task. Subsequent work has demonstrated visual cortex involvement in auditory linguistic tasks that involve verb generation (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002; Ofan & Zohary, 2007), semantic and phonological processing (Bedny et al., 2011; Burton et al., 2003; Noppeney et al., 2003), and sentence level processing (Deen et al., 2015; Röder et al., 2002), including combinatorial structure (Bedny et al., 2011) and syntactic movement (Lane et al., 2015; Pant et al., 2020).

Evidence that this activity is specific to linguistic processing, and not simply a reflection of non-specific cortical activity associated with perceptual processing or increased task demands, comes from studies showing reduced verb generation ability in blind (but not sighted) individuals following disruption of the occipital pole with TMS

(Amedi et al., 2004), and greater visual cortex recruitment for language tasks when compared to tasks that involve linguistically-degraded stimuli (i.e. jabberwocky), sequence memory tasks, and tasks that involve mathematical operations (Bedny et al., 2011; Deen et al., 2015; Lane et al., 2015; Pant et al., 2020). It should also be noted that across studies, blind participants also reliably activate the regions within the typical left-lateralized fronto-temporal language network (Dronkers et al., 2004; Martin, 2003; Turken & Dronkers, 2011), although there is evidence of reduced left-lateralization associated with language processing in blind individuals. As well, left-lateralization within the typical network is associated with left-lateralization within language-responsive visual regions (Lane et al., 2017).

The visual regions activated by language processing in blind individuals encompass both striate (V1), prestriate (V2) and extrastriate regions. Verb generation broadly activates bilateral V1, V2, V3, V3a, V4, V7 & V8, with greater left hemisphere responses (Amedi et al., 2003; Burton, 2003; Burton et al., 2002; Burton, Snyder, Diamond, et al., 2002; Ofan & Zohary, 2007). Some evidence suggests that word-level semantic processing leads to more widespread activation of the visual cortex as compared to phonological processing (Burton et al., 2003), however word-level semantic retrieval (i.e. semantic decisions on auditory words according to auditory, visual, hand action or body motion features)has also been shown to activate primarily extrastriate regions (Noppeney et al., 2003). Sentence-level semantic processing also produces similar results, with activity observed broadly across visual regions, including V1 (Bedny et al., 2011; Röder et al., 2002). Other instances of sentence-level processing, including combinatorial structure and syntactic movement, also produce broad activity across the visual cortex, with activity in V1 in particular being selective for syntactic movement (Bedny et al., 2011; Lane et al., 2015; Pant et al., 2020).

Other research has attempted to determine how the onset of blindness impacts visual cortex plasticity as it relates to language processing and establish if there is a sensitive or critical period for changes to occur, given that age of onset has been shown to impact plasticity in the auditory and tactile domains (Voss, 2013). In general, the recruitment of the visual cortex during language processing is not only observed for those individuals who are congenitally or early blind; late-onset blindness also results in visual cortex recruitment in both auditory language and reading tasks (Aguirre et al., 2016; Büchel et al., 1998; Büchel et al., 1998; Burton et al., 2003; Burton, Snyder, Conturo, et al., 2002; Burton & McLaren, 2005; Pant et al., 2020). Increased functional connectivity between visual regions and frontal language regions are also present in individuals with both early- and late-onset blindness (Sabbah et al., 2016). One study reported robust visual cortex activity for a verb generation task in both languages of an early blind individual who acquired their non-native language after the age of ten (Ofan & Zohary, 2007). However, the difference between congenital/early onset individuals and late-onset individuals is that early blindness typically results in more widespread and more robust recruitment of visual regions (Bedny et al., 2012; Burton et al., 2003; Burton, Snyder, Conturo, et al., 2002; Pant et al., 2020; Sadato et al., 2002), and measurements of functional connectivity between visual regions and language networks are stronger with earlier onset (Kanjlia, Pant, et al., 2018). This suggests that while the responsiveness of the visual cortex to linguistic stimuli is a characteristic associated with both early and late onset blindness, there does appear to be a sensitive period for the effects of visual deprivation on the reorganisation of the language system.

1.4.4 VERBAL MEMORY

Developmental constraints related to sensory deprivation have been associated with differences in higher-level cognitive processing. When assessing for differences in cognitive ability between blind and sighted individuals, blind participants consistently show better performance on a variety of verbal memory tasks, including long-term recall (Amedi et al., 2003; Pasqualotto et al., 2013), recognition (Amedi et al., 2003; Röder et al., 2001) and serial word order (Raz et al., 2007). Verbal memory is a broad term that refers to memory for verbally presented items (Tatsumi & Watanabe, 2009). The general suggestion for the discrepancy between verbal memory ability for blind and sighted individuals is due to a compensatory effect related to a greater reliance on verbal material and memory in day-to-day life for blind individuals because of a lack of visual cues (Amedi et al., 2003). The advantage seen in blind participants is not limited to one specific facet of verbal memory, given the improvements observed in tasks that involve both long-term memory (long-term recall and recognition of previously presented verbal material) and short-term memory (serial repetition). This memory enhancement does not appear to be domain-general, given that blind participants do not show similar effects with regards to spatial memory (Cornoldi et al., 1991; Occelli et al., 2017; Ruggiero & Iachini, 2010), which some have suggested may again reflect a greater reliance on verbal information and could potentially be linked to the recruitment of the visual cortex (Occelli et al., 2017).

Of interest to the current investigation is verbal working memory ability in people who are blind and how the visual cortex may support verbal working memory function. Working memory is a memory system distinct from long-term and short-term memory. According to the multicomponent model of working memory (Baddeley & Hitch, 1974) working memory refers to the component or components involved in actively keeping information available so it may be used while performing a task (Baddeley, 1992, 2003a, 2003b). It is closely related to short-term memory, in that both refer to the capacity to temporarily store or maintain information for a limited amount of time, but working memory is considered distinct in the sense that it consists of multiple subsystems that work together to facilitate performance on a range of tasks (Baddeley & Hitch, 1974). The original conceptualization of these subsystems consisted of a phonological loop, a visuospatial sketchpad and a central executive, as seen in Figure 1.3.

Figure 1.3: The original multicomponent model of working memory, as proposed by Baddeley & Hitch (1974), reprinted from (Baddeley, 2003a)

The central executive acts as the attentional control system and is supported by two short-term storage systems, one for visual information, the visuospatial sketchpad, and one for auditory/verbal information, the phonological loop (Baddeley, 2003a). The original model has since been updated to include another component, called the episodic buffer (Figure 1.4). This component is accessible to conscious awareness and is proposed to temporarily store a limited capacity of chunks of multidimensional information across sensory modalities and functions to bind together information from different sources (Baddeley, 2010).

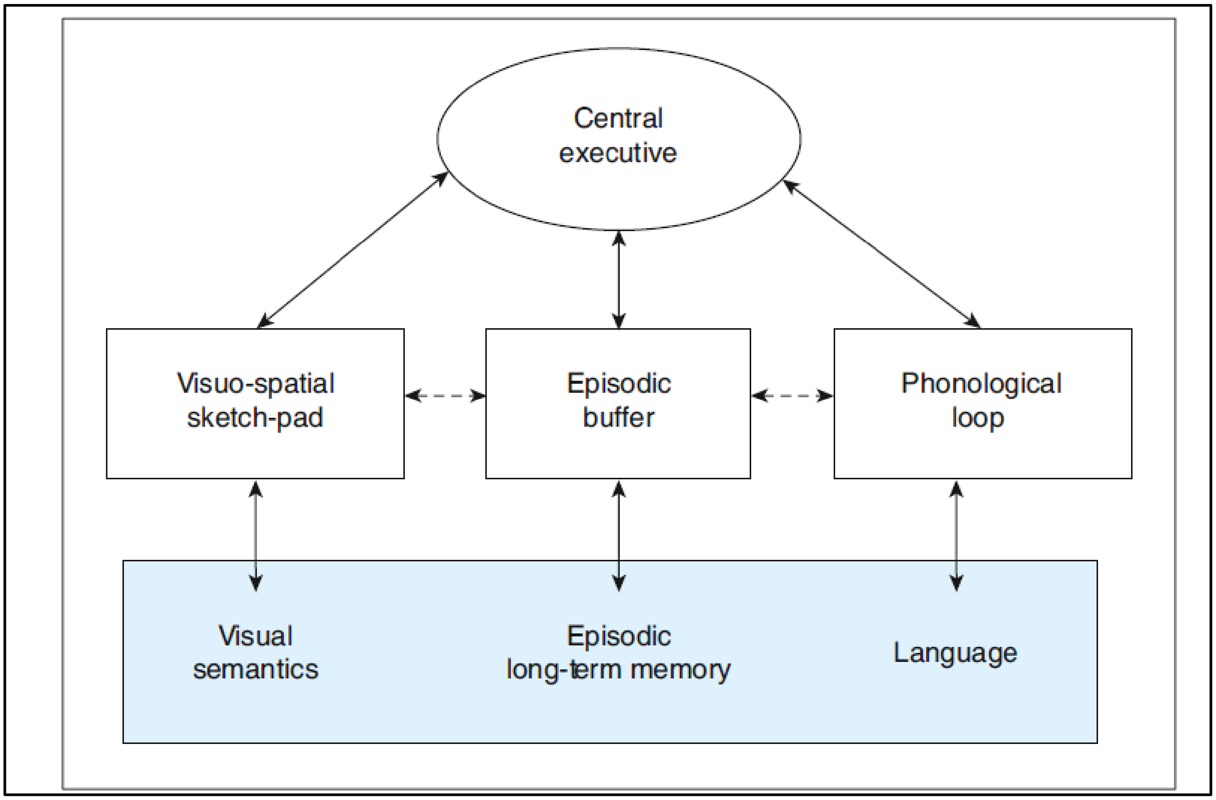

Figure 1.4: Further development of the multicomponent model of working memory includes links to long-term memory and an episodic buffer, reprinted from (Baddeley, 2010)

1.4.4.1 PHONOLOGICAL LOOP

The phonological loop is composed of two parts - a storage component, that can hold memory traces for a few moments until they fade and an articulation component (Baddeley, 2003a, 2010). Items are maintained and refreshed in the storage component through re-retrieval and articulation. Articulation or subvocalization is an active process and is sensitive to the characteristics of the items being rehearsed. For example, the similarity of items can affect immediate recall, with more phonologically similar items being harder to recall than dissimilar items (Baddeley, 1966). As well, verbal working memory capacity is inversely related to the length of items being recalled, in that immediate memory span declines as word length increases in syllables (Baddeley et al., 1975). Maintenance through subvocal rehearsal can be blocked by irrelevant speech (i.e., requiring a person to repeat an unrelated word) as this blocks rehearsal (Baddeley, 2003a). In general, the phonological loop is believed to serve a functional purpose when learning new vocabulary, in both native and foreign language acquisition and it has also been suggested to be necessary for task switching and action control (Baddeley et al., 2001). In this sense, subvocal speech may assist with maintaining strategic control over behaviour (Baddeley, 2003a).

Investigations into the nature and function of the phonological loop specifically in people who are blind are limited. When comparing early blind and sighted individuals on factors that typically disrupt the phonological loop (i.e., word length and irrelevant speech), early blind individuals are sensitive to the word length effect, meaning performance decreases as word length increases, but irrelevant speech does not impact recall (Kattner & Ellermeier, 2014). This suggests that the superior auditory abilities observed in blind individuals may allow them to prevent irrelevant speech from entering the phonological store, but they still rely on the same subvocal rehearsal mechanism as sighted individuals for item maintenance (Kattner & Ellermeier, 2014). When comparing blind and sighted children, blind children perform better on tasks that directly involve the phonological loop but perform comparably on tasks that primarily involve the executive system (Swanson & Luxenberg, 2009). This suggests that congenital blindness can impact verbal working memory subsystems, potentially due to concomitant increases in auditory abilities due to a greater reliance on auditory or verbal material in the absence of visual input.

1.4.4.2 VISUO-SPATIAL SKETCHPAD

The visuo-spatial sketchpad is the component of working memory that handles the storage and manipulation of spatial, visual, and kinaesthetic information. Its functional relationship to language processing is less direct than that of the phonological loop, but it has been suggested to support reading behaviour via the maintenance of the spatial characteristics of pages of text (Baddeley, 2003a). The spatial mapping has been shown to be involved in series recall, in which a list or series of items needs to be remembered in order, with items occurring first in the list being associated with the left side of space and items occurring later being associated with the right-side of space (Dijck et al., 2013; Dijck & Fias, 2011; Ginsburg et al., 2014). Visual experience can affect the spatial organisation of series recall, as early blind individuals have been shown to not hold any association between serial position and space, whereas late blind and sighted individuals do (Bottini et al., 2016). The lack of linkage between ordered items and space has been attributed to experiential differences in how sighted and blind people supplement working memory (writing things down versus using voice recordings or other non-visual memory aids, (Bottini et al., 2016)).

A lack of visual experience has also been shown to affect tactile working memory, particularly as it relates to Braille reading (Cohen et al., 2010). Completely blind individuals show similar effects of articulatory suppression on Braille tactile working memory tasks to sighted controls on a comparable visual working memory task. As well, completely blind individuals demonstrate better tactile working memory compared to blind individuals with some residual sight. Finally, disruption of the tactile working memory system in completely blind individuals is greatest when performing a concurrent mental displacement task (i.e. mentally moving numbered blocks around a grid), as opposed to a mental arithmetic task, suggesting that the tactile working memory system in blind individuals is indeed spatial in nature (Cohen et al., 2010). This suggests that a lack of visual experience and a reliance on tactile orthography can serve to drive the function of the working memory system, particularly as it relates to tactile and spatial mapping processes.

1.4.4.3 OVERALL ABILITY

In general, the overall performance of blind individuals on tasks measuring verbal working memory specifically is mixed. Evidence from the developmental literature has demonstrated an advantage for blind children on tasks assessing working memory ability (Tillman & Bashaw 1968; Smits & Mommers 1976; Hull & Mason 1995; Withagen et al. 2013), although group differences between blind and sighted children are not always observed (Swanson & Luxenberg, 2009). This inconsistency extends to the adult literature, with some reports demonstrating a verbal working memory advantage for blind individuals compared to sighted controls (Arcos et al., 2022; Dormal et al., 2016; Loiotile et al., 2020; Occelli et al., 2017; Pigeon & Marin-Lamellet, 2015), although the advantage is more apparent for reaction times compared to accuracy on the *N*-back (Pigeon & Marin-Lamellet, 2015), and has been demonstrated in early blind, but not late blind individuals (Dormal et al., 2016). Other studies report comparable performance in blind and sighted groups on tasks measuring verbal working memory performance (Castronovo & Delvenne, 2013; Park et al., 2011; Rokem & Ahissar, 2009; Wan et al., 2010).

1.4.4.4 INVOLVEMENT OF THE VISUAL CORTEX

As mentioned above, early blind individuals have been demonstrated to show enhanced abilities on some measurements of verbal memory, particularly long-term/episodic recognition memory and serial recall. In some instances, verbal memory ability has been tied to the unique recruitment of the visual cortex during cognitive processing seen in blind individuals. The first demonstration of the functional relationship between the visual cortex and verbal memory in blind individuals came from (Amedi et al., 2003). They demonstrated that early blind participants, and not sighted controls, showed significant recruitment of the visual cortex, including the primary visual cortex V1, during a verbal memory task which involved recalling items from previously learned word lists. A follow-up study conducted 1 year later using the same group of participants tested for episodic recognition memory for items learnt in the first scan (Raz et al., 2005). They again observed significant V1 activation during the episodic recognition task, which was again not observed in the sighted control group.

In both studies, the relationship between behavioural performance on the verbal memory tasks and degree of V1 recruitment was assessed. In the Amedi (2003) study, two standardised memory assessments (Digit Span and auditory verbal subtests of the Weschler Memory Scale) were administered immediately following the fMRI scan, and recognition for word-list items was measured 6 months after the initial scan. Blind participants performed better than sighted controls on the long-term recognition task, and the auditory verbal subtests of the Weschler memory scale, although a comparison of behavioural scores for the Digit Span task was not reported. Performance on the-long term recognition task and both standardised memory assessments correlated with the degree of activation observed in V1 during the initial scan for blind participants, but not sighted controls. Raz et al, (2005) observed similar results when the blind and sighted participants from the Amedi (2003) study returned 1 year later and performed a follow-up scan which involved an episodic recognition task for word-list items administered during the first study. Again, blind participants remembered significantly more items than sighted controls and performance on the recognition task was correlated with the degree of activation observed in V1. This is taken to suggest that the visual cortex, particularly V1, is involved in memory processes that involve verbal material and the additional recruitment of visual cortical regions may underlie the increased memory abilities observed in blind participants.

The above studies suggest some involvement of visual regions in verbal memory tasks, specifically memory tasks that involve long-term or episodic memory. Understanding the function of the visual cortex as it relates to verbal working memory is also necessary, particularly given the mixed evidence regarding if blind individuals (both adults and children) perform differently than their sighted counterparts on verbal working memory tasks. As well, working memory, as discussed in more detail above, is distinct from long- and short-term memory systems because it involves a computation component, in addition to a basic storage system. The attentional demands associated with working memory typically (in sighted people) activate a network of regions in the lateral prefrontal cortex and parietal lobe (Cabeza & Nyberg, 2000). In sighted individuals, there is evidence of increased activation in frontal-parietal working memory networks as working memory task demands increase (Braver et al., 1997; Höller-Wallscheid et al., 2017; Owen et al., 2005; Smith et al., 1998; Wager & Smith, 2003).

These working memory networks are typically left-lateralized (Reuter-Lorenz et al., 2000), but the additional recruitment of cross-hemisphere resources (bilaterality) has been associated with increases in working memory task demands (Höller-Wallscheid et al., 2017).

Some work has attempted to elucidate the role of the visual cortex in working memory in people who are blind, particularly as it relates to integration into the typical working memory functional networks (Park et al., 2011). Working memory was shown to broadly recruit occipital regions across working memory domains (verbal, auditory, spatial) in blind but not sighted participants, and only blind participants showed increased effective connectivity (as measured by Granger causality) between the occipital lobe and left hemisphere frontal-parietal working memory components, suggesting that congenital blindness alters working memory brain networks (Park et al., 2011). In particular, it has been suggested that challenging the working memory system drives the integration of visual regions into working memory networks. This latter point is supported by evidence showing that blind, but not sighted individuals, demonstrate stronger integration of the visual cortex into functional auditory working memory networks following auditory working memory training (Gudi-Mindermann et al., 2018; Rimmele et al., 2019). However, whether challenges in the form of increasing working memory task demands lead to additional or more widespread recruitment of visual regions, is yet to be established.

1.5 IMPACT OF BLINDNESS ON FUNCTIONAL NETWORKS

Cognitive functions are supported by interconnected networks of brain regions. Understanding the nature of interregional connectivity, and how it may change depending on experience and/or task demands, can aid in the understanding of how individual regions contribute to a specific function and how the network operates as a whole. This is particularly relevant in the case of blindness, given the considerable evidence that visual deprivation induces cross-modal changes such that visual regions become involved in high-level cognitive functions, including language and memory. Cognitive information is thought to potentially reach the visual cortex through the unmasking of cortico-cortical connections from regions within established cortical networks subserving high-level cognitive functions, although the exact nature of these connections remains an open question. The following sections discuss the existing research on the nature of the interregional connections in the functional networks supporting cognitive processing in blind individuals.

1.5.1 FUNCTIONAL CONNECTIVITY

Functional connectivity refers to the temporal association of neural activity between two spatially distinct brain regions (Aertsen et al., 1989; Friston et al., 1992). More specifically, two brain regions can be considered functionally connected if there is a statistically significant relationship between the activity recorded at each region. Functional connectivity can be measured at rest, which involves estimating the correlation in spontaneous neural activity between brain regions during periods in which a participant is not performing a task. This is in contrast to task-based or state-dependent functional connectivity, which estimates the correlation between neural activity recorded between brain regions while participants are performing a specific task. Both resting-state and task-based analysis of functional connectivity in blind individuals have been conducted and are discussed below.

1.5.1.1 RESTING STATE FUNCTIONAL CONNECTIVITY

Investigations into the patterns of resting state functional connectivity in blind individuals have revealed several instances of altered connectivity between visual regions and between the visual cortex and other association cortices as well as higher-level cognitive networks. Reduced connectivity between regions within the visual cortex has been observed (Hou et al., 2017; Jiang et al., 2009; Liu et al., 2007), in addition to reduced connectivity between visual regions and other sensory regions, including the auditory and somatosensory cortices (Bauer et al., 2017; Burton et al., 2014; Kanjlia et al., 2021; Liu et al., 2007; Pelland et al., 2017; W. Qin et al., 2013; Yu et al., 2008)**.** This effect can be potentially eliminated following vision restoration. When investigating the effect of vision restoration on the reduced connectivity between the visual and auditory cortices, results indicate that three years post restoration, connectivity is significantly increased compared to baseline (Mowad et al., 2020). On the other hand, instances of increased functional connectivity are typically observed between the visual cortex and regions within language (Abboud & Cohen, 2019; Bedny et al., 2011; Deen et al., 2015; Heine et al., 2015; Striem-Amit et al., 2015), memory (Abboud & Cohen, 2019; Burton et al., 2014; Deen et al., 2015) or attention/executive control networks (Abboud & Cohen, 2019; Burton et al., 2014; Kanjlia et al., 2021; Striem-Amit et al., 2015).

Two interesting investigations of resting state functional connectivity patterns in blind individuals include research into the effect of partial blindness, and a comparison between eyes-open and eye-closed states. Retinitis pigmentosa (RP) is a disease that causes progressive disintegration of the retina resulting in gradual vision loss. When comparing fully blind individuals with RP to individuals with RP resulting in tunnel vision, fully blind individuals demonstrate increased connectivity between Broca's area and both central and peripheral V1 were observed, whereas in individuals with tunnel vision, only peripheral V1 shows increased functional connectivity to Broca's area (Sabbah et al., 2016). This suggests that altered connectivity is specific to deprived areas and can expand as blindness progresses. As well, functional connectivity patterns differ between eyes-open and eyes-closed states in blind individuals. More specifically, the evidence of reduced connectivity between visual and non-visual association areas in blind individuals compared to sighted controls appears to be sensitive to eye-state, as this effect is only evident in an eyes-closed state and is eliminated in an eyes-open state (Guerreiro et al., 2021). It is common to blindfold blind participants during fMRI data collection, which has implications for the aforementioned research showing reduced connectivity between visual regions and other sensory regions in blind individuals, including the auditory and somatosensory cortices (Bauer et al., 2017; Burton et al., 2014; Kanjlia et al., 2021; Liu et al., 2007; Pelland et al., 2017; W. Qin et al., 2013; Yu et al., 2008).

1.5.1.2 STATE-DEPENDENT FUNCTIONAL CONNECTIVITY

Within the context of cross-modal changes associated with blindness, the finding of reduced resting state connectivity between visual and other association cortices is in contrast to the large body of evidence showing enhanced visual cortex recruitment during the processing of auditory and tactile stimuli (see Section 1.3). Pelland et al., (2017) investigated this apparent contradiction directly by comparing resting state connectivity patterns to those measured during an auditory discrimination task. They found reversed patterns of functional connectivity between active states and at rest, and reversed patterns between blind and sighted groups. More specifically, blind participants showed reduced visual cortex-temporal lobe connectivity at rest, compared to during active auditory discrimination, while the sighted group showed the opposite pattern (Pelland et al., 2017). Consideration should therefore be taken before assuming that group differences in connectivity established based on resting-state measures generalise to active cognitive processing.

Other work in this domain suggests that during tactile spatial discrimination and motion perception, blind individuals show increased functional connectivity between regions in the visual cortex and a region roughly corresponding to the inferior parietal/anterior intraparietal sulcus, which serves as a gateway to the visual cortex for tactile information from the somatosensory cortex (Leo et al., 2018). As well, the human middle temporal cortex (hMT+) is functionally connected to primary somatosensory and primary visual regions during tactile motion perception in people who are blind (Sani et al., 2010). Similar results are observed within the auditory domain, with increased functional connectivity in blind individuals observed between visual regions sensitive to auditory information and the regions within the networks associated with integrating audio-visual information, specifically the intraparietal sulcus and superior frontal gyrus (Collignon et al., 2011). This suggests that contrary to results obtained at rest, active auditory and/or tactile processing in people who are blind involves the integration of the visual cortex into auditory and/or tactile functional networks in the brain.

1.5.2 EFFECTIVE CONNECTIVITY

Effective connectivity is a method that can be used to estimate the direction of functional connectivity between brain regions. It is distinct from functional connectivity because, rather than relying on (non-directional) correlations, it instead estimates the causal relationship between regions, i.e., it allows for the estimation of how activity in one brain region affects activity in another. Given that the cross-modal changes observed in the visual cortex, particularly those related to high-level cognitive functions, are thought to be the result of input from already established functional cognitive networks, understanding the effective connectivity between existing networks and visual regions is a necessary line of inquiry. Two common methods used to estimate causal connectivity are Granger causality (GC) and dynamic causal modelling (DCM, (Friston et al., 2013)).

Several studies have used effectivity connectivity analyses to investigate how auditory, tactile and higher-level cognitive information may reach the visual cortex via connections with existing brain networks. During auditory discrimination, blind participants demonstrate significant forward connectivity from the primary auditory cortex to the primary visual cortex, but not between the subcortical medial geniculate nucleus and the primary visual cortex (Klinge, Eippert, et al., 2010). Wong & Bhattacharjee (2011) observe that this result is supported by evidence that anatomical connections between the primary auditory and visual cortices present in sighted animals are more abundant in blind animals (see Section 1.2.1 above for further details). Further work replicated the finding that visual cortex activity associated with auditory processing is most likely driven by input from the primary auditory cortex and extended it to suggest that this may only be true for congenital or early blind individuals (Collignon et al., 2013). Later blind individuals, in contrast, appear to have stronger effective connections from the intraparietal sulcus to the visual cortex (Collignon et al., 2012).

In terms of tactile information, work by Fujii et al., (2009) demonstrates that visual regions receive information from the primary somatosensory cortex (S1) via cortico-cortical connections, although the route does not involve a direct connection from S1 to V1, and instead involves regions in the dorsal visual stream, including the superior occipital gyrus. These cortico-cortical connections are stronger in early blind individuals compared to later blind individuals. This work is in line with results in the auditory domain demonstrating that auditory information reaches the visual cortex through cortico-cortical connections with the primary auditory cortex, although auditory information is received directly from A1 and is not mediated through other regions (Klinge, 2010). As well, although the work by Fujii et al., (2009) deals with data stemming from a braille tactile discrimination task, it does not specify how linguistic content may reach the visual cortex, and instead deals with basic sensory information.

Other work has attempted to reveal the flow of higher-level cognitive information to visual regions, although that work has thus far been limited to working memory. Specifically, GC analyses have shown that visual cortex activity during working memory tasks in blind individuals can be explained by effective connections from regions in the fronto-parietal working memory network to the occipital lobe (Park et al., 2011). However, whether the same holds true for linguistic information has yet to be established. While there is evidence showing increased resting-state connections between visual regions and higher level cognitive networks, including those related to language processing and it seems likely that direct driving connections from language regions to the visual cortex are ultimately responsible for the visual cortex's functional involvement in language, the specific nodes within the language network that may be involved, the temporal dynamics of those connections and how information flows through those networks is unclear.

1.6 OVERVIEW OF METHOD - DCM

Dynamic causal modelling, or DCM, is a method that can be used to explain the underlying neural states responsible for observed fMRI data (Friston et al., 2003). More specifically, it aims to determine the inter-regional interactions between brain regions within a network, in order to explain a specific pattern of functional data (Friston, 2002, 2009; Friston, 1994). The inter-regional interactions in this case are examples of causal or effective connectivity, as opposed to functional connectivity, which typically describes a correlational relationship between brain regions. DCM can be characterised by a set of features that make it a useful method for estimating effective connectivity, as described in detail by Stephan et al., (2010):

- DCM uses linear (or nonlinear) differential equations to describe dynamic neural states ("state equations").
- DCM is causal in that it describes how the state of one neural population affects the state of another neural population, and how this relationship can be modulated by external manipulations.
- DCMs should make sense given the neurophysiological characteristics of the system being explained.
- DCMs are forward models in that they link underlying neural dynamics described by models to measurable data (i.e., regional hemodynamic time series in fMRI data).
- DCMs are Bayesian.

At the outset, DCM was designed to test specific hypotheses about the underlying neuronal states that may give rise to experimentally observed brain responses and model data that comes from controlled external stimuli (Friston, 2009; Stephan et al., 2010). This task-based version of DCM is known as *deterministic* DCM (Friston et al., 2003). In deterministic DCM, the state equations specifically account for how experimental factors affect the dynamic interactions within a modelled network; that is, external manipulations are entered into the model as inputs that induce regional changes or modulate connection strengths (Stephan et al., 2010). For the purposes of the research described below, we relied on the implementation of *deterministic* DCM, given that we were interested in the underlying network dynamics associated with specific external manipulations. More specifically, we were interested in how inter-regional interactions between visual cortical regions and regions within the typical left-lateralized frontotemporal language network can explain the observation of functionally significant visual cortex recruitment during speech processing in early blind individuals. The typical steps of a DCM analysis are described in detail within the Methods section (3.2.2) of Chapter 3, which allows for a discussion of the procedure within the context of our specific study.

While DCM is a widely used and established method in neuroimaging analysis, considerations regarding correct implementation of the method and associated limitations should be made. First, DCM is not an exploratory method. It should be used to test biophysically motivated hypotheses about the latent neuronal states that may give rise to experimentally observed data (Stephan et al., 2010). Experiments should therefore be designed in such a way as to facilitate the discrimination between different hypotheses/models. As well, model space definition is highly subjective and as such, model definition should be carefully motivated by a priori knowledge about the underlying neuronal state and the potential mechanisms that could account for the phenomenon in question. This includes taking into consideration evidence regarding the presence or absence of long-range connections between regions, evidence regarding the functional role of different nodes within the network and evidence regarding the possible functional connection between regions (Stephan et al., 2010).

Considerations should also be made regarding feature selection, i.e., selection of regions to include in models. Inter-subject variability can make defining consistent regions of interest across subjects difficult (Daunizeau, et al., 2011). It should also be noted that DCM for fMRI cannot be used to determine which regions should or should not be included within a model (although this is possible using other methods, such as EEG/MEG, Stephan et al., 2010). This makes evaluating hypothesis regarding the comparison of networks containing different regions unfeasible, which is particularly constraining when conducting between-group comparisons in which there are differences between groups in regions showing experimental effects (Daunizeau et al., 2011). A further limitation regarding feature selection concerns "missing" regions, or unmodelled regions or activations (Daunizeau et al., 2011). This latter point is considered to be a significant methodological limitation, as there is currently no method to determine if the effect of "missing" regions are significant enough to invalidate the entire DCM analysis (Daunizeau et al., 2011).

Finally, it should be noted that DCM and Bayesian model selection cannot falsify or prove models. Model evidence is relative in that it reflects the probability that one model is more or less likely than other models in the comparison set (Stephan et al., 2010; Daunizeau et al., 2011). If the accuracy of models is poor (i.e. models are a poor explanation of the data), this can make it difficult to accurately determine which model has the best evidence. This is usually reflected by lower model evidence values (Stephan et al., 2010).

1.7 OVERVIEW OF THESIS CHAPTERS

The overarching goal of this thesis is to provide new knowledge concerning the effect of early blindness on the underlying neural mechanisms of auditory language processing and verbal working memory, and how early blindness can impact verbal working memory ability. Data for all research questions and objectives was obtained at once, in a single session for each participant, with two groups of participants (early blind individuals and sighted controls). For the purposes of conciseness, this thesis contains a general methods section (Chapter 2) that details information relevant to all research questions, including participant characteristics, study protocol and procedures, and fMRI data pre-processing. However, data is then subsequently described in two separate chapters, focusing on distinct analyses. The first (Chapter 3) details the results of the investigation into the effect of early blindness on the neural mechanisms associated with auditory language processing and the second (Chapter 4) details the investigation into the effect of early blindness on the neural mechanisms associated with verbal working memory and verbal working memory ability. This is followed by a general discussion (Chapter 5) of the main findings of the studies, and limitations.

1.7.1 AIMS AND HYPOTHESES

1.7.1.1 AUDITORY LANGUAGE (CHAPTER 3)

Aims: To understand the involvement of the visual cortex in auditory language processing in people who became blind at an early age by examining 1) differences in brain activity between early blind participants and sighted controls on an auditory task involving semantic, phonological and perceptual processing, specifically related to group differences in visual cortex activity and, 2) measurements of the effective connectivity (via DCM) between brain regions activated by linguistic processing in the early blind group, specifically related to connections between the visual cortex and regions within the left-lateralized fronto-temporal language network.

Hypotheses:

H3.1: both early blind and sighted participants were expected to show significant activation within regions typically associated with semantic and phonological processing (this includes, but is not limited to, activation in the left inferior frontal gyrus, precentral gyrus, middle frontal gyrus, superior/middle/inferior temporal gyrus, fusiform gyrus and ventral occipito-temporal cortex).

H3.2: blind participants were expected to show greater activity in the visual cortex during both semantic and phonological processing compared to sighted participants.

H3.3: for blind participants, activity within the visual cortex associated with linguistic processing (semantic/phonological) was expected to be greater than activity associated with perceptual processing.

H3.4: for blind participants, we expected to observe a significant effective connection, as measured using DCM, from a region (or regions) within the left-lateralized fronto-temporal language network demonstrating significant activity during semantic and phonological processing and the region within the visual cortex demonstrating significant activity during semantic and phonological processing. It should be noted that for this last hypothesis, *specific* regions are not given a priori, as regions are typically identified based on the results of a GLM analysis. Please see Chapter 3 for more detail regarding the hypotheses of the DCM analysis.

1.7.1.2 VERBAL WORKING MEMORY (CHAPTER 4)

Aims: to understand the involvement of the visual cortex in verbal working memory in people who are blind and how visual cortex involvement affects verbal working memory ability by examining 1) differences in brain activity between early blind and sighted participants during an auditory *N*-back task, specifically related to group differences in visual cortex activity, 2) how verbal working memory load modulates activity within the visual cortex of early blind participants, 3) differences in verbal working memory ability between early blind and sighted participants and 4) if verbal working memory ability is correlated to visual cortex recruitment in early blind participants.

Hypotheses:

H4.1: both blind and sighted participants were expected to show significant activation in fronto-parietal regions typically associated with verbal working memory (including, but not limited to, prefrontal cortex, inferior frontal gyrus, supramarginal gyrus, supplementary motor area and premotor cortex).

H4.2: only blind participants were expected to show visual cortex recruitment during verbal working memory and crucially, increased verbal working memory demands would be associated with greater and/or more widespread visual cortex involvement.

H4.3: blind participants were expected to show better performance on behavioural measurements of verbal working memory ability.

H4.4: verbal working memory ability was expected to be correlated with visual cortex activity in blind, but not sighted participants

CHAPTER 2 - GENERAL METHODS

This study was approved by the Nova Scotia Health Authority Research Ethics Board (#1023318). Funding was provided by the Natural Science and Engineering Research Council (NSERC), a Nova Scotia Health Research Foundation Development and Innovation Grant, and the Toronto Neuroimaging Facility.

2.1 PARTICIPANTS

Twenty-one adults participated (11 congenital/early blind, 8 women, age: 48±12; 10 sighted controls, 9 women, age: 37±22, $t(21) = 1.26$, $p = .21$). Blind participants were fully blind from birth or before the age of two, and all causes of blindness were due to dysfunction at the level of the eye. Blind participants were recruited through advertisements distributed by the Canadian National Institute for the Blind (CNIB), word of mouth, and social media posts. Blind participants were asked to indicate at what age they began learning Braille and self-rate their Braille reading proficiency. Please see Table 2.1 for more information regarding blind participant's characteristics. All participants were right-handed as determined by the Edinburgh Handedness Inventory, spoke English as a first language and had normal hearing (defined as a hearing threshold of 30 dB or lower in the worse ear at 1000 Hz, confirmed via pure-tone audiometry using a portable audiometer (Interacoustics AS605)). Participants were screened for cognitive impairment using the Montreal Cognitive Assessment (MOCA) and the adapted version MOCA-Blind. Participants were given a $50 honorarium upon completion of the study.

Table 2.1: Blind participant demographic information

Age	Sex	Age of Onset of Blindness	Cause of Blindness	Light Perception	Learned Braille	Braille Proficiency (/10)
57	F	Birth	Glaucoma	No	5	10
44	M	Birth	ROP	Yes	11	8
64	F	Birth	ROP	No	6	8
38	F	< 2 years	Retinoblastoma	No	6	10
65	F	< 2 years	ROP	Yes (right)	5	10
38	M	< 2 years	Cataracts/RP	Minimal	9	7
38	F	Birth years	ROP	Minimal	3	10
33	F	< 2 years	LCA	Minimal	7	8.5
52	M	Birth	LCA	No	5	7
38	F	< 1 year	ROP	Minimal	4	10
62	F	Birth	Cataracts/Glaucoma	No	5	8.5

Note: ROP = retinopathy of prematurity, LCA = Leber congenital amaurosis. Braille proficiency was self-rated. Age of onset of blindness refers to the onset of full blindness and was either congenital (fully blind since birth) or as having occurred prior to the 1st or 2nd year of life. Some participants reported remaining light perception, however no participant had remaining form perception.

2.2 COGNITIVE ASSESSMENTS

Participants in both groups were assessed for verbal working memory ability using the Digit Span subcomponent of the Weschler Adult Intelligence Scale (WAIS). The Digit Span test requires participants to verbally repeat back series of digits in increasing length. As described in Raiford et al., (2010), the forward subcomponent, participants repeat back digits in the same order as they are read aloud by the administer. In the backward subcomponent, participants repeat back digits in the opposite (or backward) order as they are read aloud by the administer. In the sequencing subcomponent, participants are required to repeat back digits in chronological order. Each level of the Digit Span test contains two trials, and the test is stopped when the participant makes two consecutive errors (Raiford et al., 2010). To ensure consistency between groups in terms of vocabulary, vocabulary knowledge was assessed using the vocabulary subcomponent of the Weschler Abbreviated Scale of Intelligence (WASI). Most standardised measurements of vocabulary rely on picture naming and are therefore not adaptable or suitable for people who are blind. The vocabulary subcomponent of the WASI includes picture naming for the first three items before transitioning to vocabulary (i.e., definitions of words given verbally). The picture items were omitted for both the blind and sighted groups and only the vocabulary portion of the test was administered. No difference in vocabulary scores between blind and sighted participants was observed (blind: 39.2 +/- 4.2; sighted: 42.2 +/- 4.1; $t(20) = 1.71$, $p = .10$).

2.3 STIMULI

The stimuli for this study comprised spoken English words and pseudowords that were 1-4 syllables in length. Details of how these were selected are given below for each experimental condition. Pseudowords were generated by phoneme substitution of the real words. Each spoken item was recorded in a sound-attenuated booth using Audacity software (stereo, 44100 Hz, 32-bit float) by two native English speakers (male, female) using neutral intonation.

Five conditions were used in the fMRI paradigm (semantic = SEM, phonological = PHON, perceptual = PER, one-back = OB, two-back = TB). In the SEM condition, word pairs were either semantically related or unrelated (e.g., *dog/cat* or *stove/banker,* respectively). Words were taken from previously used stimuli lists from our lab (O’Neil et al., 2017; O’Neil et al., 2015) and paired with a semantically related item from semantic association databases (Buchanan et al., 2013; Hutchison et al., 2013). Words that were used in the semantically related condition were not used in the semantically unrelated condition. To create semantically unrelated pairs, stimuli lists were randomly sorted, and items were paired together. After random sorting, pairs were checked to ensure lack of semantic relatedness. Words in both semantically and semantically unrelated pairs did not rhyme and were of similar word length. In the PHON condition, pseudoword pairs either rhymed or did not rhyme (e.g., *sloam/broam* OR *guck/hewl*). Rhyme pairs were created by changing the first phoneme or the first consonant cluster prior to the vowel of the pseudoword. In the PER condition, word pairs consisted of the same word or pseudoword repeated (e.g., *dog/dog* or *wug/wug*) with either the same speaker or a different speaker for each word. Half of PER trials were real words and half were pseudowords. In both the OB and TB conditions, words were presented as a list of individual words or pseudowords. Again, half of OB/TB trials were real words and half were pseudowords. Items were not repeated across conditions within a participant; however, two versions of the paradigm were created such that each word was included in another condition, across participants.

Normative information on stimuli were gathered from the English Lexicon Project (ELP), and calculations were based on a restricted 40,000 word lexicon (Balota et al., 2007). Real words in the semantically related list were matched to real words in the semantically unrelated list based on log frequency (related words: 9.6, SE = 0.09, unrelated words: 9.3, SE = 0.11), number of syllables (related words: 3.8, SE = 0.8, unrelated: 4.0, SE = 0.8) and number of phonemes (related words: 1.3, SE = 0.4, unrelated words: 1.3, SE = 0.4). For the pseudowords, matching between the rhyming list and the non-rhyming list was based on number of syllables (rhymed pseudowords: 3.8, SE = 0.5, non-rhymed pseudowords: 4, SE = 0.5) and number of phonemes (rhymed pseudowords: 1.3, SE = 0.4; non-rhymed pseudowords: 1.3, SE = 0.3). Finally, all real words were matched to all pseudowords based on number of syllables (real words = 3.9, SE = 0.3, pseudowords = 3.9, SE = 0.6) and number of phonemes (real words: 1.3, SE = 0.3, pseudowords:1.3, SE = 0.3).

2.4 STUDY PROTOCOL

After completing informed consent, participants were screened for normal hearing ability and cognitive ability (MOCA and MOCA-Blind). They then completed background questionnaires (language and Braille reading history), the handedness assessment and tests of their vocabulary (WASI) and verbal working memory ability (WAIS). Prior to entering the MRI scanner, all participants completed a practice run of the experimental paradigm on a laptop computer. This practice paradigm was again administered once participants were set-up in the scanner to adjust the sound levels as necessary to ensure participants could hear the auditory stimuli clearly.

2.5 EXPERIMENTAL PROCEDURE

Experimental stimuli were presented using Psychopy 1.84.2 software (Peirce et al., 2019). Participants were blindfolded and instructed to keep their eyes closed during the experiment. Stimuli were presented in five runs of acquisition, each lasting six minutes. During each run, stimuli were presented in 10 blocks lasting 31.5 seconds each. Each run started with 15 seconds of rest followed by five test blocks (one of each condition, randomised). After another 15 second rest block, five more randomised test blocks (one of each condition) were shown, followed by a final 15 second rest block. See Figure 2.1 for a schematic of the overall paradigm protocol.

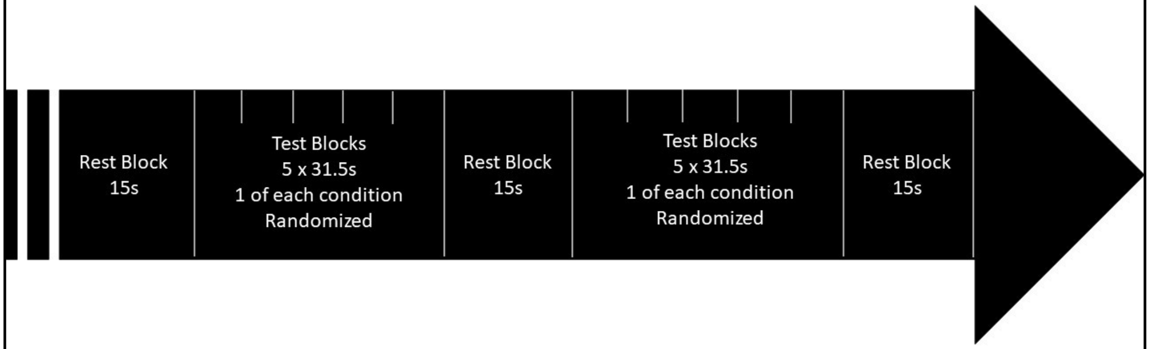

Figure 2.1: Schematic of fMRI paradigm protocol. Represents a single run, each participant completed five runs in total.

Each rest block was cued by a 1 second distinct auditory tone, followed by a spoken prompt of "brief rest". Each test block was cued by an 0.5 second auditory tone, which was different than the one used to cue the rest blocks. After the auditory tone, a 5 second auditory cue indicating the type of trials and the response required (e.g., "Press the left button if the words rhyme and the right button if they do not") followed. For the SEM, PHON and PER conditions (seen in Figure 2.2), both related and unrelated trials required a response. For the OB/TB conditions (seen in Figure 2.3), a response was only required when the item matched a previous item. Response hand (left or right) was counterbalanced across participants. Twelve stimulus items were presented (stimulus onset asynchrony= 2 seconds) during each test block – for the SEM/PHON/PER conditions, this consisted of six stimulus pairs (half match/half mismatch, i.e., rhymed/non rhyme, semantically related/unrelated, same/different speaker). Each new pair was cued by a fixation tone lasting 0.25 seconds. For the OB/TB conditions, stimuli were presented as a list of 12 stimulus items with six items matching previous items. To ensure comparable motor activations across all conditions, the number of required responses was kept constant (i.e. 6 responses required for 6 pairs in the SEM/PHON/PER conditions, and 6 responses requires for 6 targets in OB/TB conditions). For the PER and OB/TB conditions, one test block consisted of pseudowords while the other consisted of real words.

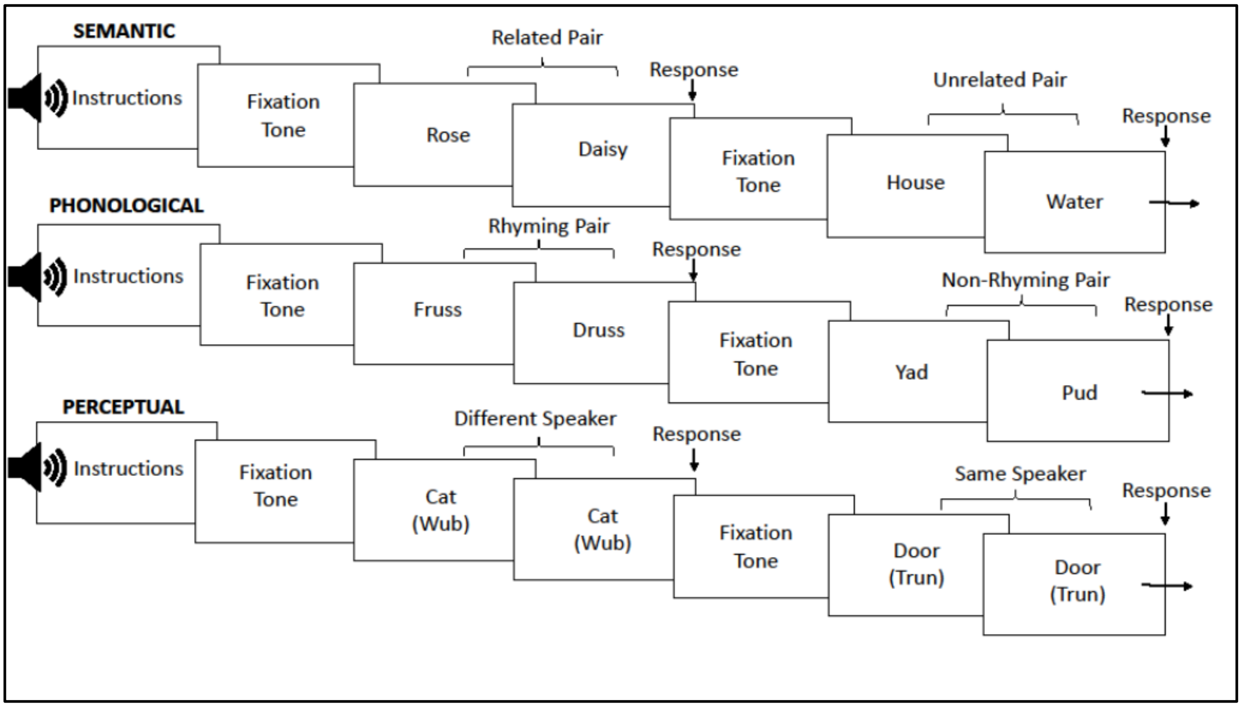

Figure 2.2: Depiction of SEM/PHON/PER trial procedure. For PER condition, half of the trials were real words and half were pseudowords (i.e. one block of each), both types depicted above for explanation purposes only.

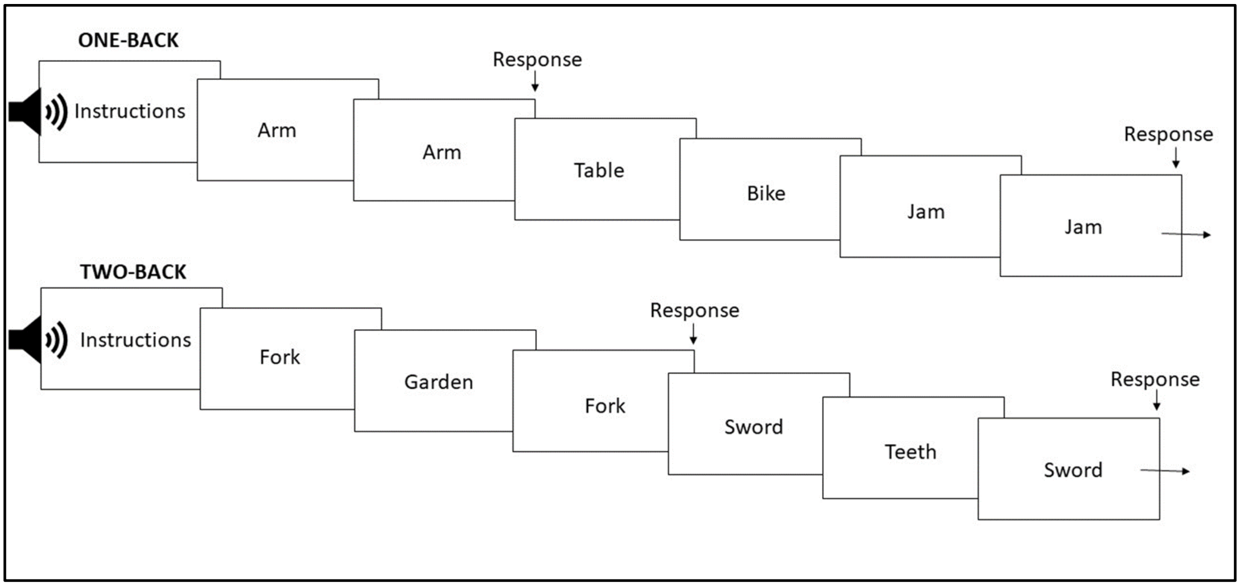

Figure 2.3: Depiction of OB and TB trial procedure. 12 stimulus items were presented, with 6 stimulus items matching a previously presented item.

2.6 DATA ACQUISITION

Data acquisition occurred at two sites, the Toronto Neuroimaging Facility in Toronto (6 blind participants, 10 sighted controls) and Biomedical Translational Imaging Centre in Halifax (5 blind participants). Data collection was terminated in March 2020 due to the COVID-19 pandemic.

Data in Toronto were acquired using a Siemens Sigma 3T full body MRI scanner equipped with a 32-channel head coil. Participants completed testing in one session, consisting of five functional runs and an anatomical scan that occurred between functional scans two and three. The functional scans acquired 180 volumes using a multiband echo-planar-imaging sequence with a TR = 2s, TE = 31 ms, flip angle = 70°, 220 x 220 matrix resulting in 2 mm x 2 mm in-plane voxel size, with 69, 2 mm thick axial slices (no gap, interleaved slice acquisition). The 3-D T1-weighted anatomical scan was obtained using magnetization prepared rapid acquisition gradient echo sequence with

GRAPPA, TR = 2 s, TE = 2.4 ms, TI = 1.1 s, flip angle = 9°, FOV = 256 mm, matrix 256 x 256 resulting in 160, 1 mm thick axial slices.

Data in Halifax were acquired using a GE 3T MRI scanner equipped with a 32-channel head coil. Participants completed testing in one session, consisting of five functional runs and an anatomical scan that occurred between functional scans two and three. The functional scans acquired 210 volumes using a multiband echo-planar-imaging sequence with a TR = 2 s, TE = 31 ms, flip angle = 70°, 110 x 110 matrix resulting in 2 mm x 2 mm in-plane voxel size with 69, 2 mm thick axial slices (no gap, interleaved slice acquisition). The first 30 volumes were acquired as dummy scans and were dropped from subsequent processing, resulting in 180 functional volumes. The T1-weighted anatomical scan was acquired using a inversion-recovery-prepped fast spoiled gradient recalled echo sequence, inversion time = 450 msec, TR = 4.0 msec, TE = 1.33 msec, flip angle = 9°, 256 × 256, 184 sagittal slices at 1-mm thickness, autocalibrating reconstruction for Cartesian imaging (ARC) phase acceleration = 1, ARC slice acceleration = 1.

2.7 FMRI PREPROCESSING

fMRI data were pre-processed and analysed using MATLAB.R 2019b (MathWorks) and SPM12 (Wellcome Centre for Human Neuroimaging, https://www.fil.ion.ucl.ac.uk/spm/). Data pre-processing included motion correction of functional images, high-pass temporal filtering (128 s cut-off), slice timing correction to account for differences in slice time acquisition (reference slice = 1), rigid-body spatial co-registration of functional images to anatomical images, normalisation to MNI space with a resampling resolution of 2 mm, and spatial smoothing using a Gaussian kernel of 8 mm.

CHAPTER 3 - AUDITORY LANGUAGE PROCESSING IN THE VISUAL CORTEX OF BLIND INDIVIDUALS

3.1 INTRODUCTION

Visual deprivation in the form of early blindness leads to the functional reorganization of the language system whereby regions typically associated with visual processing are recruited to serve language function in the absence of visual input. Language processing has been widely demonstrated to activate the occipital cortex in early blind individuals, across a variety of tasks, including Braille reading (Beisteiner et al., 2015; Burton et al., 2002; Cohen et al., 1997; Fujii et al., 2009; Hamilton et al., 2000; Melzer et al., 2001; Sadato et al., 1996), verb generation and verbal memory (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002), semantic and phonological processing (Burton et al., 2003) and higher level sentence comprehension (Bedny et al., 2011; Lane et al., 2015; Pant et al., 2020; Röder et al., 2002). This activation is thought to serve a functional purpose, as disruption of the visual cortex due to cortical damage or with transcranial magnetic stimulation impairs Braille reading and verbal functioning (Amedi et al., 2004; Cohen et al., 1997; Hamilton et al., 2000). The variety of tasks shown to extensively activate the visual cortex have prompted attempts to determine if visual cortex activity is preferential for certain types of linguistic processing. To that end, semantic and phonological processing have both been shown to activate the visual cortex in the early blind, with more widespread recruitment observed for semantic processing (Burton et al., 2003). Additionally, visual subregions (V1, V2) are recruited in late blind individuals, but only for semantic processing (Burton et al., 2003). This suggests that regions of the visual cortex may show specificity for semantic processing. Occipital regions involved in these language processes vary and include the primary visual cortex (Amedi et al., 2003; Bedny, 2017; Bedny et al., 2015; Lane et al., 2015; Pant et al., 2020; Pelland et al., 2017), as well as secondary regions (Bedny et al., 2012; Burton et al., 2002; Noppeney et al., 2003; Röder et al., 2002).

The process through which the visual cortex takes on language function in people who are blind is also yet to be fully understood. It has been suggested that the recruitment of the visual cortex during language processing is caused by an unmasking of input from typical fronto-temporal language regions (Bedny, 2017). In the absence of competing visual input, visual regions take on linguistic functions due to input received from language networks during development. Activity in distributed language networks ultimately drives activity in the visual cortex and results in visual cortex involvement across a variety of language tasks. Evidence for this theory primarily comes from studies showing altered resting state functional connectivity profiles between language regions and the visual cortex in blind people (Abboud & Cohen, 2019; Bedny et al., 2011; Deen et al., 2015; Dzięgiel-Fivet et al., 2021; Heine et al., 2015; Striem-Amit et al., 2015). Language regions that consistently demonstrate increased functional connectivity to the visual cortex in blind individuals include the left inferior frontal gyrus (LIFG) (Bedny et al., 2011; Deen et al., 2015; Sabbah et al., 2016), including Broca's area (Abboud & Cohen, 2019; Heine et al., 2015; Striem-Amit et al., 2015), and the VWFA, defined according to a Braille functional localiser(Dzięgiel-Fivet et al., 2021). However, functional connectivity analyses can only give an indication of correlations between brain activity within typical language regions and the visual cortex and do not provide evidence that activity within the visual cortex is directly caused by input from language network regions. To fully understand how the visual cortex takes on language function in people who are blind, an investigation into the nature of the direct causal connectivity between higher-level language regions and the visual cortex during language processing is necessary.

The goal of this study was to assess visual cortex integration into the language system associated with semantic and phonological processing. Brain activity from early blind (congenital or before the age of two) and sighted controls was collected during an auditory language task in which participants had to make relatedness (meaning/rhyme/speaker) decisions about pairs of words. This paradigm is loosely adapted from similar investigations into the neural underpinnings of semantic and phonological processing in sighted people (e.g., Poldrack et al., 1999), in which the control — i.e., non-linguistic — condition involves judging the case of letters. Here, we adapted this to the auditory domain by having participants judge whether the speaker of a pair of identical stimuli was the same. Semantic processing was assessed via a meaning relatedness judgement and phonological processing was assessed via a rhyme judgement of pseudowords.

We used dynamic causal modelling (DCM) to determine how semantic and phonological processing reach the visual cortex in blind individuals (Friston et al., 2003). DCM is a method that can be used to estimate the coupling between brain regions and how that coupling can be influenced by external input (Friston et al., 2003; Stephan et al., 2007, 2010). In practice, DCM can be used to better understand how underlying neuronal states produce experimentally observed data, specifically as it relates to the causal interactions between brain regions under certain experimental conditions. Models consist of hypothesis driven assumptions about how external factors affect regional activity (inputs), underlying or context independent endogenous connections between brain regions and how inter-regional connections are modulated by processing demands (Stephan et al., 2010). The best model is determined through a Bayesian model selection procedure, in which the model with the most evidence is that which has the highest probability of having produced a specific dataset (Stephan et al., 2009).

Here, we were interested in how visual cortex activity during language processing (i.e., evidence of visual cortex activation during language-related tasks) is caused by interactions between the visual cortex and typical left-lateralized fronto-temporal language regions. Specifically, we were interested in which regions within the typical language network show endogenous connectivity to the visual cortex and how those connections are modulated depending on the type of language processing occurring. Ultimately, we were interested in where and how language information reaches the visual cortex. Model definition was informed based on results from the GLM analysis, specifically as it relates to the definition of regions showing experimental effects.

3.2 METHODS

See Chapter 2 for general methods.

3.2.1 FMRI ANALYSIS

We first performed first-level analysis in which, for each subject, each condition (SEM/PHON/PER) was convolved with a canonical hemodynamic response function (HRF). Movement parameters derived from realignment (three translations and three rotations) were included in the design matrix as multiple regressors of no interest. The general linear model was then used to produce parameter estimates for each subject, at each condition, at each voxel. Statistical parametric maps were generated from linear contrasts of the HRF parameter estimates for each of the three conditions. Statistical analyses were then performed at the individual and group level. At the individual level, we computed linear contrasts to determine brain regions involved in linguistic processing (SEM > Rest, PHON > Rest, SEM + PHON > Rest) as well as linguistic vs perceptual processing (SEM > PER, PHON > PER, SEM + PHON > PER). At the group level, contrast maps generated for individual participants were entered into second-level random effects analyses to test for within-groups effects (one sample *t* tests) and between-groups effects (two sample *t* tests). Considering the small sample size, we chose to assess the main effects of semantic/phonological processing and determined regions active in the typical language network across the two groups.

We also conducted a within-group analysis region of interest (ROI) analysis to assess whether activation in the visual cortex (defined according to an anatomical mask containing the bilateral occipital lobe (V1/V2/V3d/V3v/V3A/V4/V5/V6), generated using the SPM *anatomy* toolbox (Eickhoff et al., 2006)) for blind participants related to linguistic processing (semantic/phonological) was greater than for perceptual processing. First-level participant contrasts for the blind group (SEM > PER and PHON > PER) were entered into second-level one sample *t* tests.

Finally, we performed an ROI analysis into group differences in activity in the visual cortex specifically. We conducted a between-groups analysis focused on activation in the visual cortex related to semantic and phonological processing. We entered first-level participant contrasts (SEM > Rest, PHON > Rest, PER > Rest, SEM + PHON >

Rest, SEM + PHON > PER) into second-level between samples *t* tests to test for group differences (blind > sighted and sighted > blind).

For all analyses, cluster-wise activation was family-wise error (FWE) corrected at a threshold of p < 0.05. Only the coordinates for the peak activation within a cluster are reported, except when the cluster contained multiple distinguishable peaks (each at a threshold of p < 0.05, FDR corrected).

3.2.2 DCM ANALYSIS

The typical steps of DCM analysis are depicted in Figure 3.1. The following sections describe the DCM process in detail.

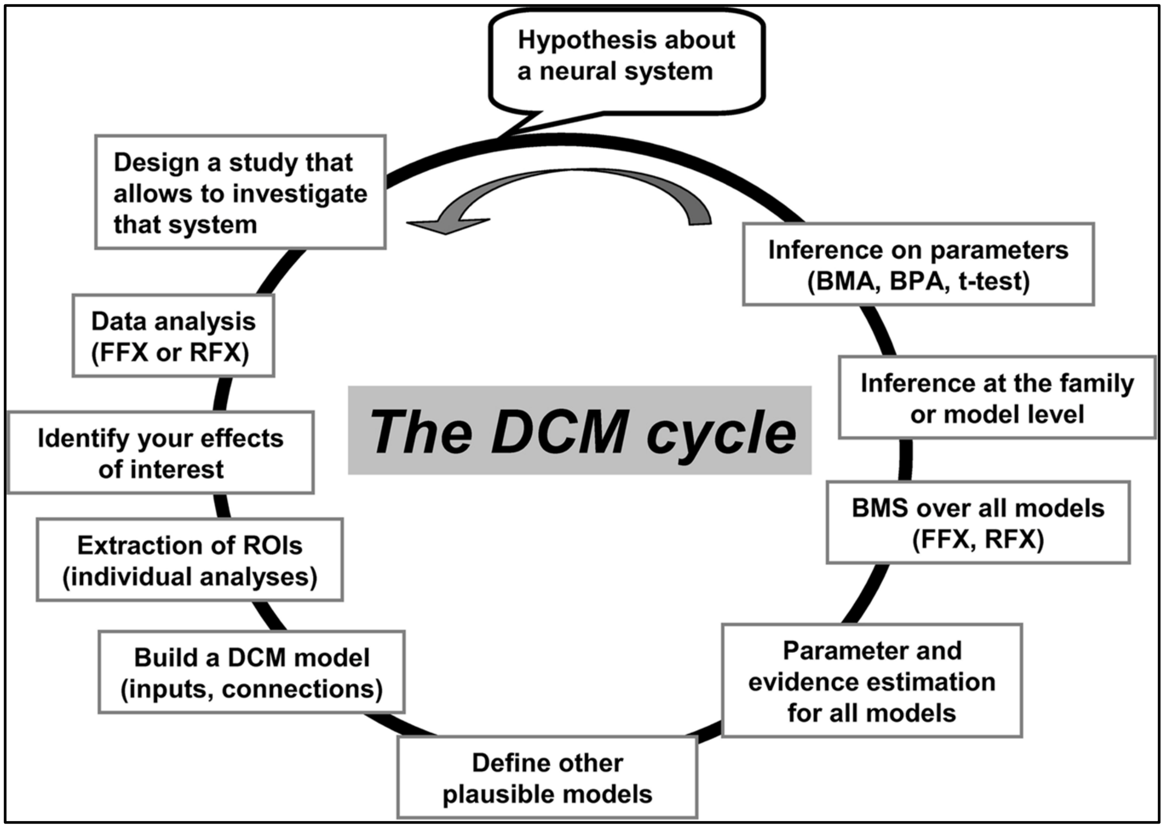

Figure 3.1: Illustration of typical steps in a DCM analysis, reprinted from (Seghier et al., 2010). FFX = fixed-effects analysis, RFX = random-effects analysis, ROIs = region of interest, BMS = Bayesian model selection, BMA = Bayesian model averaging, BPA = Bayesian parameter averaging

3.2.2.1 DCM VOI DEFINITION AND TIME SERIES EXTRACTION

In *deterministic* DCM, regions are typically those that show an experimental effect, i.e. demonstrated task-related activity as determined by the general linear model (GLM), typically used to analyse task-based fMRI data (Seghier et al., 2010; Stephan et al., 2007, 2010).We defined three volumes of interest (VOI) showing significant group-level experimental effects according to the second-level random effects GLM: two in the typical language network and one visual region. For regions in the typical language network, we first identified language network regions showing experimental effects of linguistic processing in the whole group analysis (blind & sighted), according to the contrast SEM + PHON > Rest. Given that effects of linguistic processing in the visual cortex are typically limited to blind individuals, the visual region was selected based on the between group analysis (blind > sighted), again according to the contrast SEM + PHON > Rest. When conducting a DCM analysis, coordinates of brain regions used for time series extraction should be selected so as not to bias the measurements of effective connectivity associated with that region (Klinge, Eippert, et al., 2010). When one group shows significant effects in a region while another does not, coordinates should be selected based on conjunction analysis across groups, wherever possible (Klinge, Eippert, et al., 2010). However, in our case, no sighted participant showed significant activity within the visual cortex associated with linguistic processing, eliminating the possibility of including a visual cortex VOI for that group. For this reason, we excluded sighted participants from any subsequent DCM analysis (Collignon et al., 2013; Klinge, Eippert, et al., 2010).

Typically, coordinates for a region are selected based on the group level local maximum within a cluster showing an experimental effect of interest (Stephan et al., 2010). Participant-level data is then extracted at the participant-specific maximum located within a certain pre-defined radius of the group level coordinates for the region. Given that we limited our analyses to the blind group alone, and VOIs were identified based on across- and between-group analyses that included sighted participants, we confirmed local maximum (at a threshold of $p < 0.05$, FDR corrected) in the blind group within 5 mm sphere of whole group- level coordinates for each VOI mentioned above. These coordinates for local maximum within the blind group were then used for subsequent time-series extraction. Thus, the blind group level MNI coordinates used for each VOI were as follows; left opercular part of the inferior frontal gyrus (-52, 10, 6), the left fusiform gyrus (-44, -46, -18), and the left extrastriate cortex, V3 (-20,-80,-12). The region in the left opercular part of the inferior frontal gyrus is consistent with cytoarchitectural probability maps of Broca's area (-46, 10, 4; (Amunts et al., 1999)), the region in the fusiform gyrus is consistent with the approximate location of the visual word form area (-48, -53, -16; (Cohen et al., 2000)). Note that for non-visual modalities (i.e., auditory or tactile), fusiform activations are typically more anterior, with an average $y = -43$ (Cohen et al., 2002), which is consistent with the VOI coordinates used here ($y = -46$).

Time series data were then extracted for each blind participant at each VOI. The time-series of each VOI can be considered a summary of the activity within that region, represented by the principal eigenvariate of the region, i.e., the first principal component of the local multivariate time series over all voxels within that region (Friston et al., 2003; Stephan et al., 2010). This method is recommended instead of other summary methods, such as computing the average time-series over all voxels within a region, because it accounts for heterogeneity in activation within a VOI (Friston et al., 2006; Habeck, 2010). For each subject, at each VOI, we defined an 8 mm sphere centred at the blind group level coordinates defined above and then located the individual participant maximum within that sphere, based on an uncorrected threshold of $p < 0.05$. Then, we centred each VOI at each individual participant maximum and then extracted the time-series for each VOI by computing the first eigenvector of all voxels within a 5-mm radius sphere.

3.2.2.2 MODEL DEFINITION

Model space definition, which includes a description of the possible models that can account for the observed data, is a crucial step in the DCM procedure. The goal of the model selection procedure is to choose the model, from a set of defined alternatives, that is the most accurate, in terms of explaining the observed data, while at the same time balancing complexity (Pitt & Myung, 2002). The model with the highest evidence may not necessarily be a perfect description of the underlying process that generated the observed data, but it can be considered the simplest model that most accurately accounts for the observed data (Friston et al., 2020). Three factors should be considered when defining the model space: compatibility, size, and plausibility. Compatibility between models is ensured by requiring that all models are fit on the same data, i.e., contain the same regions (Seghier et al., 2010). In our case, this was ensured by restricting the DCM analyses to the blind participants, given that sighted participants did not exhibit significant activation within the visual cortex associated with linguistic processing. Size refers to the size of the model space, meaning the total number of possible models to be compared. For large networks, with many regions and possible inputs, the number of plausible models can become computationally impractical, while for smaller networks, with few regions and possible inputs, testing all possible iterations of inter-regional connectivity is more manageable. Model space size should therefore be informed by *a priori* knowledge about the system in question, gathered from previous empirical data such that each model is realistic, interpretable, and plausible (Seghier et al., 2010; Stephan et al., 2010). In general, model space definition should be motivated by the hypothesis to be tested and should aim to maximise generalizability and interpretability, while also balancing accuracy.

We defined 8 different models for each subject (see Figure 3.2). Each model contained three regions, the left inferior frontal gyrus (LIFG), the visual word form area (VWFA) and VOI within the extrastriate visual cortex (V3). The driving input to all models was the VWFA, given that our model did not include an auditory VOI, which is consistent with previous DCM investigations of language network dynamics during semantic/phonological processing (Perrone-Bertolotti et al., 2017). All models included full endogenous connectivity between VOIs. We were primarily interested in determining how linguistic processing modulates the connectivity between regions in the typical language network and visual regions. Prior evidence indicates an increased resting-state functional connection between the visual cortex and the LIFG in people who are blind (Bedny et al., 2011; Deen et al., 2015; Sabbah et al., 2016; Abboud & Cohen, 2019; Heine et al., 2015; Striem-Amit et al., 2015), therefore we included a model in which semantic and phonological information reach the visual cortex via input from the LIFG.

As well, evidence of an increased functional connection during speech processing between the VWFA and the visual cortex has been shown in blind individuals (Dzięgiel-Fivet et al., 2021), therefore we included a model in which semantic and phonological information reach the visual cortex via input from the VWFA. We also wanted to allow for the possibility that semantic and phonological information may reach the visual cortex via separate connections, therefore we included models in which semantic and phonological information reach the visual cortex via distinct inputs from the LIFG and/or the VWFA.

Thus our model space includes iterative models whereby 1) semantic and phonological processing modulate the connection from LIFG to the visual cortex; 2) phonological processing modulates the connection from LIFG to the visual cortex and semantic processing modulates the connection from the VWFA to the visual cortex; 3) semantic processing modulates the connection from LIFG to the visual cortex and phonological processing modulates the connection from the VWFA to the visual cortex and; 4) semantic and phonological processing both modulate the connection from the VWFA and the visual cortex. In all cases, semantic and phonological processing were expected to modulate the connection between LIFG and the VWFA (Perrone-Bertolotti et al., 2017), although this is outside our primary scope of interest. These four models were constructed once with top-down modulation only (i.e., from language regions to the visual cortex, models 1-4, Figure 3.2) and then iterated upon with bidirectional modulation (i.e., between language regions and the visual cortex, models 5-8, Figure 3.2), for a total of 8 models.

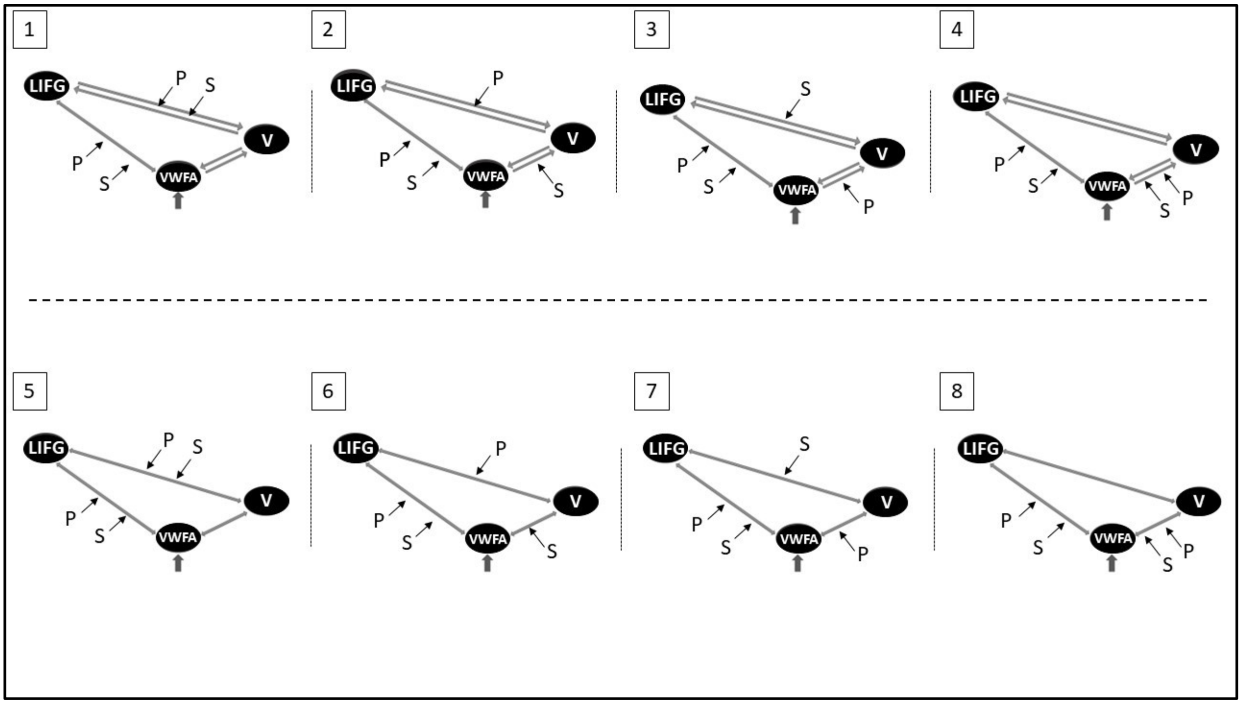

Figure 3.2: Model space definition. Eight iterative models were compared using a random-effects BMS procedure. Models include different routes of linguistic information to the visual cortex and both one-way and bidirectional modulatory connectivity between the visual cortex and other VOIs. P = phonological, S = semantic, V = visual cortex

3.2.2.3 MODEL SELECTION

Bayesian model selection (BMS) was used to compare models. BMS is a procedure that relies on the computation of a value corresponding to the approximation of the model evidence, p(y | m), i.e. the probability of data y, given model m . Model selection was completed using random-effects Bayesian model selection (BMS), implemented in SPM12 (Stephan et al., 2009). This method is in contrast to previously suggested fixed effects methods of model selection, in which individual Bayes factors (representing the likelihood of one model over another) are multiplied across subjects to produce a group Bayes factor (GBF) (Stephan et al., 2007). The GBF reflects the relative probability that data are reflected by one model compared to another, under the assumption that data from all subjects are produced by the same model (Stephan et al., 2009). In contrast, the random effects BMS technique can account for heterogeneity across subjects, in which individual subject data can be explained by different models, which may be especially true for higher-level cognitive functions (Price & Friston, 2002; Stephan et al., 2009). In random effects BMS, model selection can be represented by the exceedance probability (EP, φ_k). The EP reflects the belief that, according to the group data, a given model (*k*) is more likely than any other model tested (Stephan et al., 2009). Thus, inference on model selection is reported based on the EP calculated at the group level.

3.2.2.4 MODEL PARAMETERS

For a single DCM, three parameters are estimated; 1) the input parameter, which is a measurement of where information enters the system, 2) endogenous parameters, which are a measurement of context-independent connectivity between regions and 3) modulatory parameters, which are a measurement of how inter-regional effective connectivity is modulated by experimental conditions (Friston et al., 2003). The estimation of model parameters is a posterior density analysis performed under Gaussian assumptions and provides the posterior density of the parameter, which is known as the maximum a posteriori (MAP) estimator (Friston et al., 2003). Estimated parameters are quantified in Hertz (Hz).

Following best model selection using random-effects BMS, we then tested the parameter estimates of model input, endogenous connections, and modulatory connectivity. Parameter estimates from the best model were extracted for each participant and used to conduct group level summary statistics. This method approximates a second-level analysis in which individual participant parameters are treated as random effects. We used one-sample *t*-tests (against the null hypotheses of zero) to assess significance regarding driving input to the VWFA, endogenous connectivity parameters between VOIs, and linguistic modulations of connectivity. We also used a paired-samples *t*-test to assess differences in modulatory strength associated with phonological and semantic processing. Bonferroni correction for multiple comparisons was applied according to the number of comparisons within each parameter class.

3.3 RESULTS

3.3.1 BEHAVIOURAL RESULTS

Accuracy data (see Figure 3.3) was analysed using mixed effects generalised binomial logistic regression (Jaeger, 2008). Analyses were performed using the *glmer* function in the *lme4* library (Bates, Maechler & Bolker, 2009) in R version 3.0.2 (R Core Team, 2013). To compare accuracy between groups, condition (SEM/PHON/PER) and group (blind/sighted) were used as fixed effects, and random slopes and intercepts were included for both participants and items. The best model was chosen as that with the smallest AIC value (Akaike information criterion; Wagenmakers & Farrell, 2004). For all results, *p* values were determined using the upper-bound estimate for degrees of freedom (Bates, 2005).

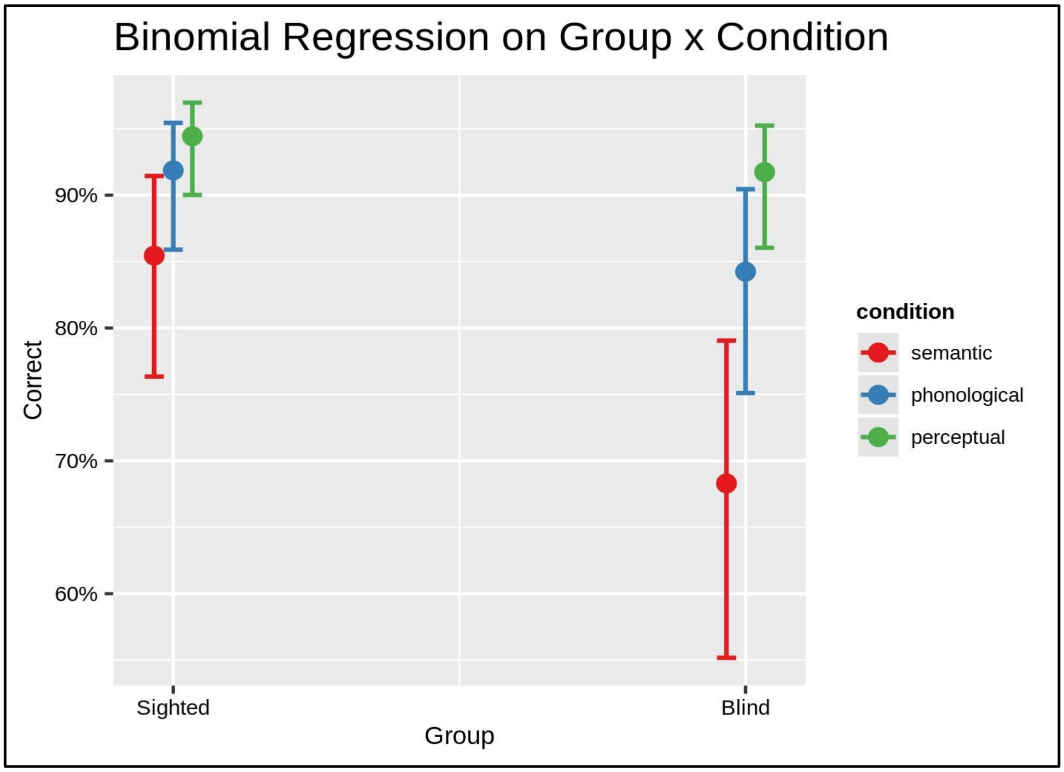

Figure 3.3: Binomial regression of responses for linguistic and perceptual conditions for both groups. Percentage of correct responses is shown on y axis, while conditions are shown on the x axis, according to participant group. Error bars represent 95% CI

Results indicate a main effect of group, indicating higher accuracy in the sighted group compared to the blind group ($p = 0.04$). The main effect of condition was also significant ($p < .001$), as was the interaction between condition and group, $F(2, 57) = 2.91$, $p = .05$. Follow up comparisons (detailed in Table 3.1) investigating the interaction revealed that accuracy differed between groups for the semantic condition, with higher accuracy for the sighted group compared to the blind group. Accuracy between groups did not differ for the phonological or perceptual conditions.

Table 3.1: Results of mixed effects generalised binomial regression investigating accuracy for blind and sighted participants during semantic, phonological and perceptual conditions

Comparison	*β*	SE	*z*	*p*
Blind semantic - Sighted semantic	1.00	0.41	2.47	0.013
Blind phonological - Sighted phonological	0.75	0.41	1.79	0.073
Blind perceptual - Sighted perceptual	0.42	0.43	1.00	0.319
Blind semantic - phonological	0.91	0.17	5.43	< .001
Blind semantic - perceptual	1.63	0.18	9.33	< .001
Blind phonological - perceptual	0.73	0.18	4.06	< .001
Sighted semantic - phonological	0.65	0.19	3.30	< .001
Sighted semantic - perceptual	1.06	0.20	5.23	< .001
Sighted phonological - perceptual	0.41	0.21	1.90	0.057
Semantic - phonological	0.81	0.14	5.63	< .001
Semantic - perceptual	1.47	0.15	9.69	< .001
Phonological - perceptual	0.61	0.15	4.05	< .001

For blind participants, accuracy in the semantic condition was lower than both the phonological and perceptual conditions. As well, accuracy in the phonological condition was lower than accuracy in the perceptual condition. For sighted participants, accuracy in the semantic condition was also lower than accuracy in the phonological and perceptual conditions, but accuracy between the phonological and perceptual conditions did not differ. Finally, across groups, accuracy in the semantic condition was lower than accuracy in the phonological and perceptual conditions, and phonological accuracy was lower than accuracy in the perceptual condition.

We also compared reaction times (see Figure 3.4) on correct trials using a Group (blind/sighted) × Condition (SEM/PHON/PER) two-way ANOVA. The interaction between group and condition was not significant, $F(2, 57) = 0.43$, $p = 0.6$. The main effect of condition was significant ($p < 0.001$), while the main effect of group was not ($p = 0.7$). Follow-up Tukey's HSD comparisons revealed that, across groups, reaction times in the perceptual condition were faster than for the phonological condition ($p < .001$) and the semantic condition ($p < .001$), but the phonological and semantic conditions did not differ ($p = .12$).

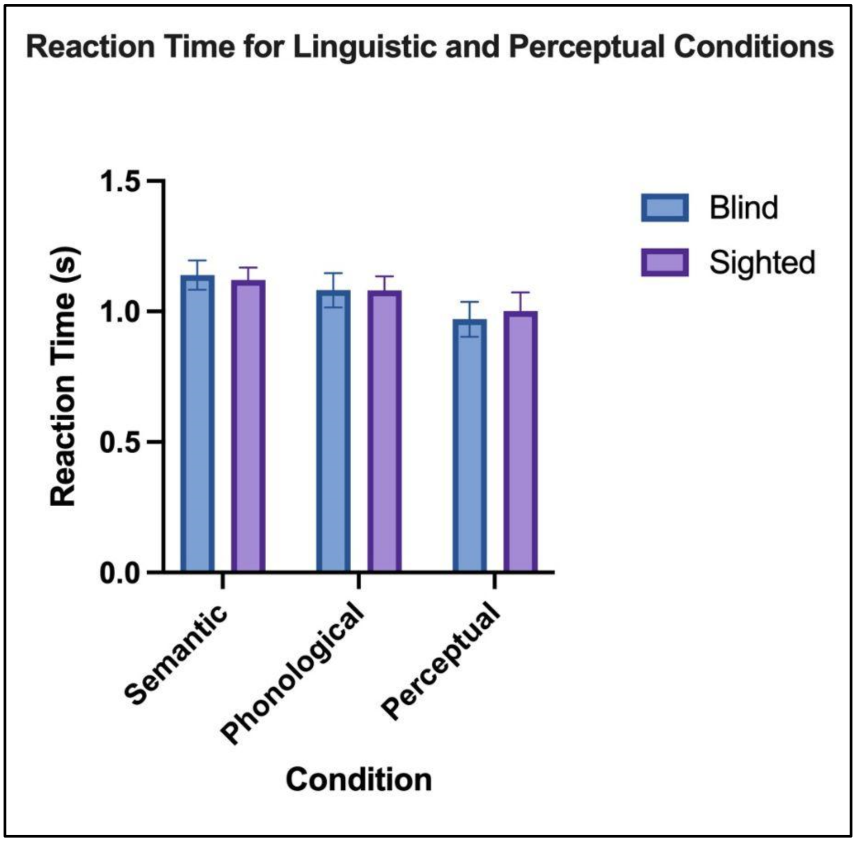

Figure 3.4: Reaction time for linguistic (semantic and phonological) and perceptual conditions, for both groups (blind and sighted). Error bars represent 95% CI

3.3.2 WHOLE BRAIN ANALYSIS ACROSS GROUPS

To broadly identify regions in the typical language network sensitive to experimental effects of interest (semantic/phonological/perceptual processing), we performed whole-brain analyses across groups (see Figure 3.5). Activation for each condition was first contrasted with rest to establish the broad networks engaged in each condition. Details of these results are provided in Table 3.2.

Table 3.2: Whole-brain activation data (condition > rest), across groups

Contrast	Region	*t*	*z*	*k*	Coordinates (x, y, z)
semantic > baseline	L fusiform gyrus	7.83	5.4	1076	-42 -42 -20
	L IFG	8.26	5.39	5613	-52 14 4
	R anterior insula	6.12	4.54	329	40 20 0
phonological > baseline	L precentral gyrus	8.17	5.36	1426	-52 8 22
	L premotor/SMC	7.53	5.13	1806	-8 -2 64
	L fusiform gyrus	6.37	4.65	298	-42 -46 -16
	R opercular IFG	6.18	4.57	305	48 10 20
	L supramarginal gyrus	5.88	4.43	536	-46 -38 44
perceptual > baseline	L pre SMA	6.43	4.68	300	-10 16 44
sem + phon > baseline	L precentral gyrus	9.87	5.89	2763	-54 10 24
	L opercular IFG	7.55	5.13		-50 12 4
	L fusiform gyrus	7.5	5.12	638	-44 -46 -16
	L SMC	7.22	5.01	2094	-8 12 52
	R opercular IFG	6.17	4.57	297	46 10 26
	R frontal operculum	5.21	4.09	267	40 22 0

Note: We report two distinct peak activations for a single cluster in one case (sem + phon > rest) due to its large size (L precentral gyrus and L opercular IFG). Both peaks were significant based on a threshold of $p < 0.05$, FDR corrected. IFG = inferior frontal gyrus. SMC = supplementary motor cortex. L = left hemisphere, R = right hemisphere.

For the SEM condition, activation was observed in the left posterior fusiform gyrus, opercular inferior frontal gyrus and right anterior insula. For the PHON condition, activation was observed in the left precentral gyrus, left premotor/SMC, right opercular IFG and left supramarginal gyrus. Significant activity for the perceptual condition was restricted to the left pre supplementary motor area (SMA). Combining the two linguistic conditions (SEM + PHON > Rest) revealed significant activation in the left precentral gyrus, bilateral opercular IFG, left posterior fusiform gyrus, left SMC and right frontal operculum.

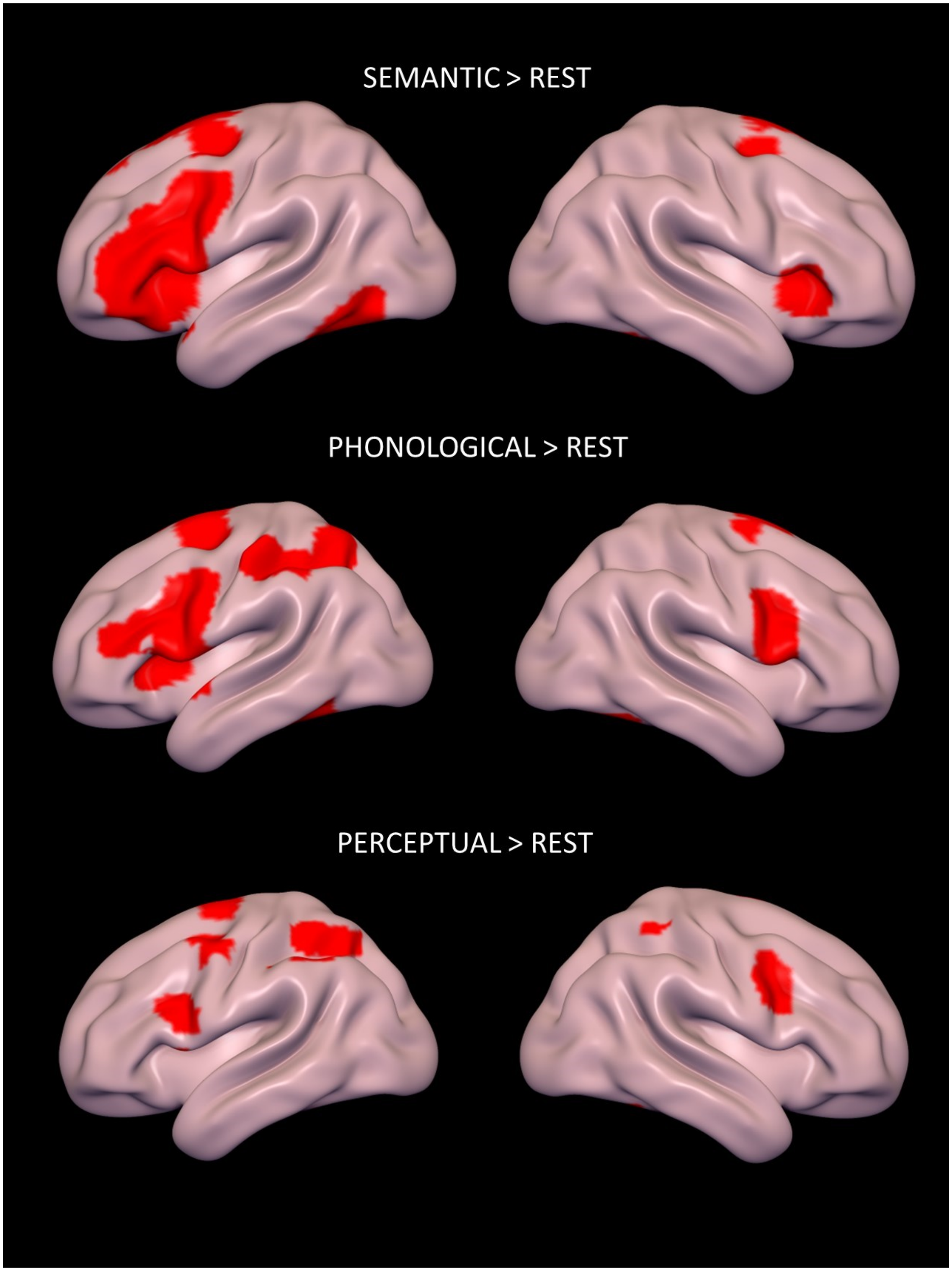

Figure 3.5: Results of across group (blind & sighted) analysis showing whole brain activations (in left and right hemisphere) of linguistic (semantic and phonological) and perceptual conditions compared (>) to rest. Activation is cluster corrected, FWE p < .05, with a cluster threshold of 247 voxels.

We then contrasted the linguistic conditions (semantic/phonological) against the perceptual control condition, as seen in Figure 3.6. For the SEM > PER comparison, activation was observed in the left triangular IFG. The PHON > PER comparison did not reveal any significant clusters of activation. The comparison investigating linguistic activation over perceptual processing (SEM + PHON > PER) showed activation in the left ventral ITG, left pars orbitalis and left medial superior frontal gyrus. Details of these results are provided in Table 3.3.

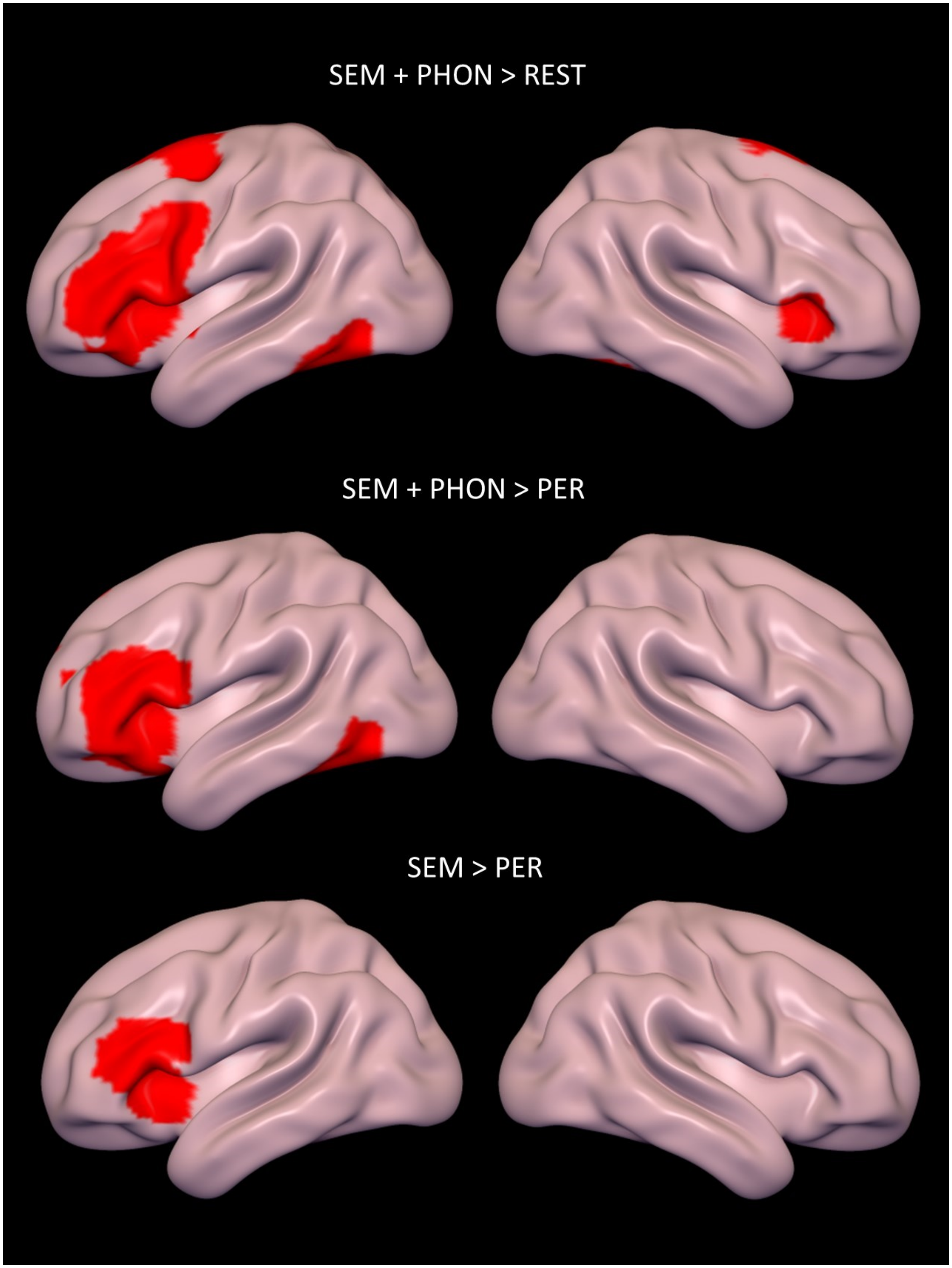

Figure 3.6: Results of across group (blind & sighted) whole brain activations for comparison of linguistic (semantic and phonological) conditions to perceptual condition, in the left and right hemisphere. Activation is cluster corrected, FWE p < .05, with a cluster threshold of 267 voxels.

Table 3.3: Whole brain activations (linguistic conditions > perceptual) across groups

Condition	Region	*t*	*z*	*k*	Coordinates (x, y, z)
Semantic> perceptual	L triangular IFG (Broca's area)	6.80	4.84	662	-50 28 6
Phonological > perceptual	-				
sem+phon> perceptual	L inferior temporal gyrus	7.22	5.01	1011	-46 -40 -18
	L pars orbitalis	6.70	4.80	1766	-34 30 -12
	L medial superior frontal gyrus	5.63	4.31	677	-6 30 38

3.3.3 WITHIN GROUP

We additionally performed an ROI analysis investigating activity associated with semantic and phonological processing in the visual cortex of blind participants and whether visual cortex recruitment in blind participants is greater for auditory tasks that involve linguistic processing (i.e., semantic and phonological conditions) compared to tasks that involve auditory perceptual processing. Given the discrepancy between individual subjects or subject groups and single-subject anatomical atlases (Nieto-Castanon et al., 2003; Poldrack, 2007) peak activations were localised based on probabilistic cytoarchitectural maps as part of the *SPM anatomy* toolbox (Eickhoff et al., 2006). When comparing linguistic conditions to rest (SEM > Rest and PHON > Rest), activation was observed for semantic processing (SEM > Rest) in the visual cortex, with a significant cluster located within the left visual cortex, encompassing V1/V2/V3/V4, with a peak activation at V4. Phonological processing did not result in any suprathreshold activation within the visual cortex. With regards to the linguistic conditions compared to the perceptual control, planned contrasts (SEM > PER and PHON > PER and SEM + PHON > PER) did not reveal any suprathreshold activation within the visual cortex.

3.3.4 BETWEEN GROUP COMPARISON

We then performed an ROI investigation into group differences (blind > sighted) in experimental effects in the visual cortex. In general, for both the semantic and phonological conditions relative to rest, widespread visual cortex activity ($p < 0.001$, uncorrected) was observed across regions including the left primary visual cortex (V1). For the SEM condition (see Figure 3.7), a significant cluster was observed within the left visual cortex, encompassing regions including V1/V2/V3/V4, with significant peak activation for the blind group compared to the sighted controls in the left visual association areas (V3/V4). For the PHON condition (see Figure 3.7), a significant cluster was observed within the left visual cortex, encompassing regions including V2/V3/V4, with significant peak activation again within the left extrastriate cortex (V3).

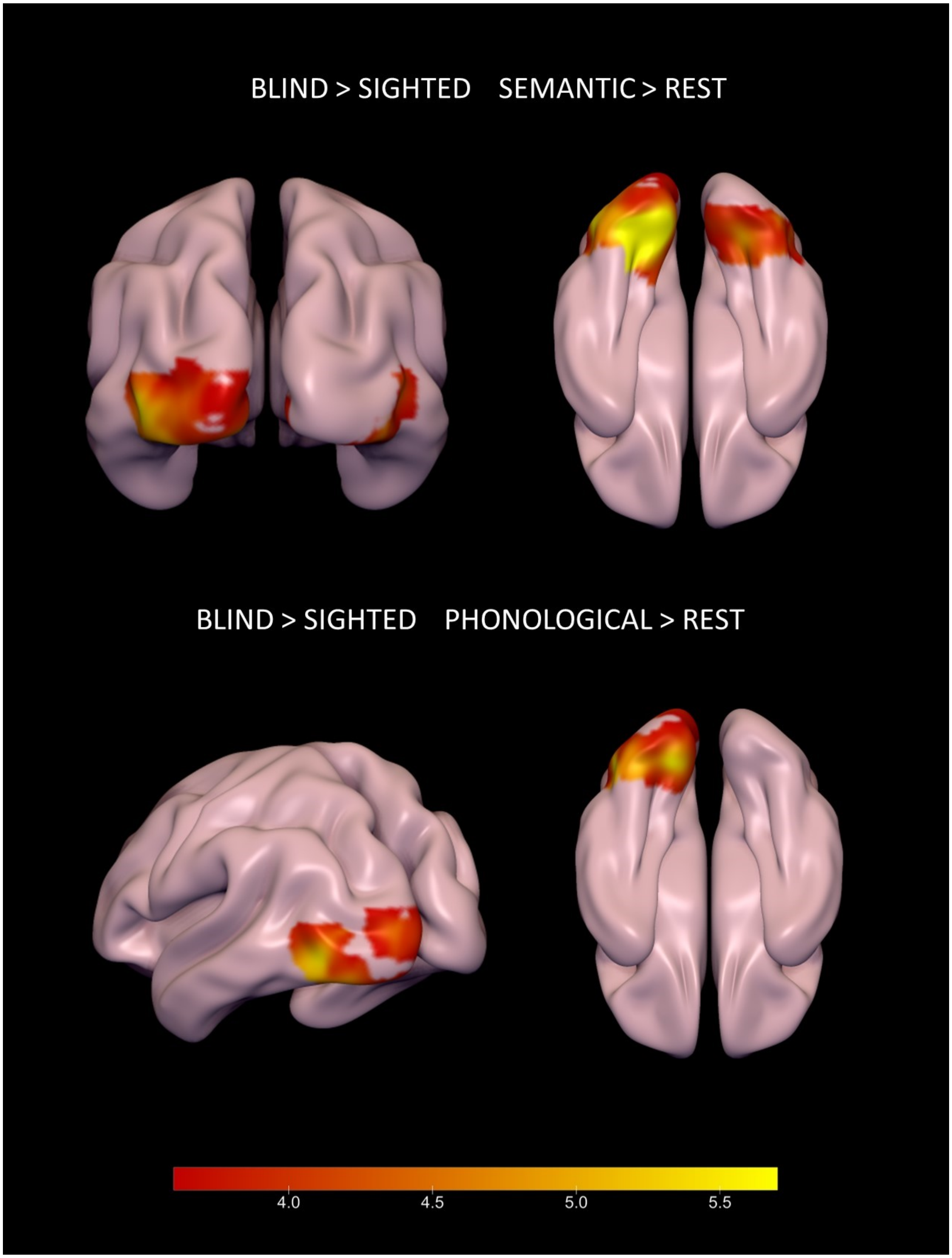

Figure 3.7: Group comparison (blind > sighted) of linguistic (semantic and phonological) conditions compared to rest in visual cortex ROI, defined according to an anatomical mask. Activation shown is significant clusters, FWE corrected at a threshold of $p < 0.05$, with a cluster threshold of 87 voxels. Colour bar represents z-values.

Comparing the linguistic conditions both to rest (SEM + PHON > Rest, Figure 3.8) revealed a significant cluster within the left visual cortex, encompassing V1/V2/V3/V4, with significant peak activation at V3. Finally, when comparing the linguistic conditions to the perceptual control condition (SEM + PHON > PER, Figure 3.8) revealed a significant cluster within the left visual cortex, encompassing V2/V3/V4, with significant peak activation at V3. No activity in the visual cortex was observed for the reverse contrast (sighted > blind). As well, the SEM > PHON and PHON > SEM contrasts revealed no suprathreshold activation. Details of these tests are provided in Table 3.4.

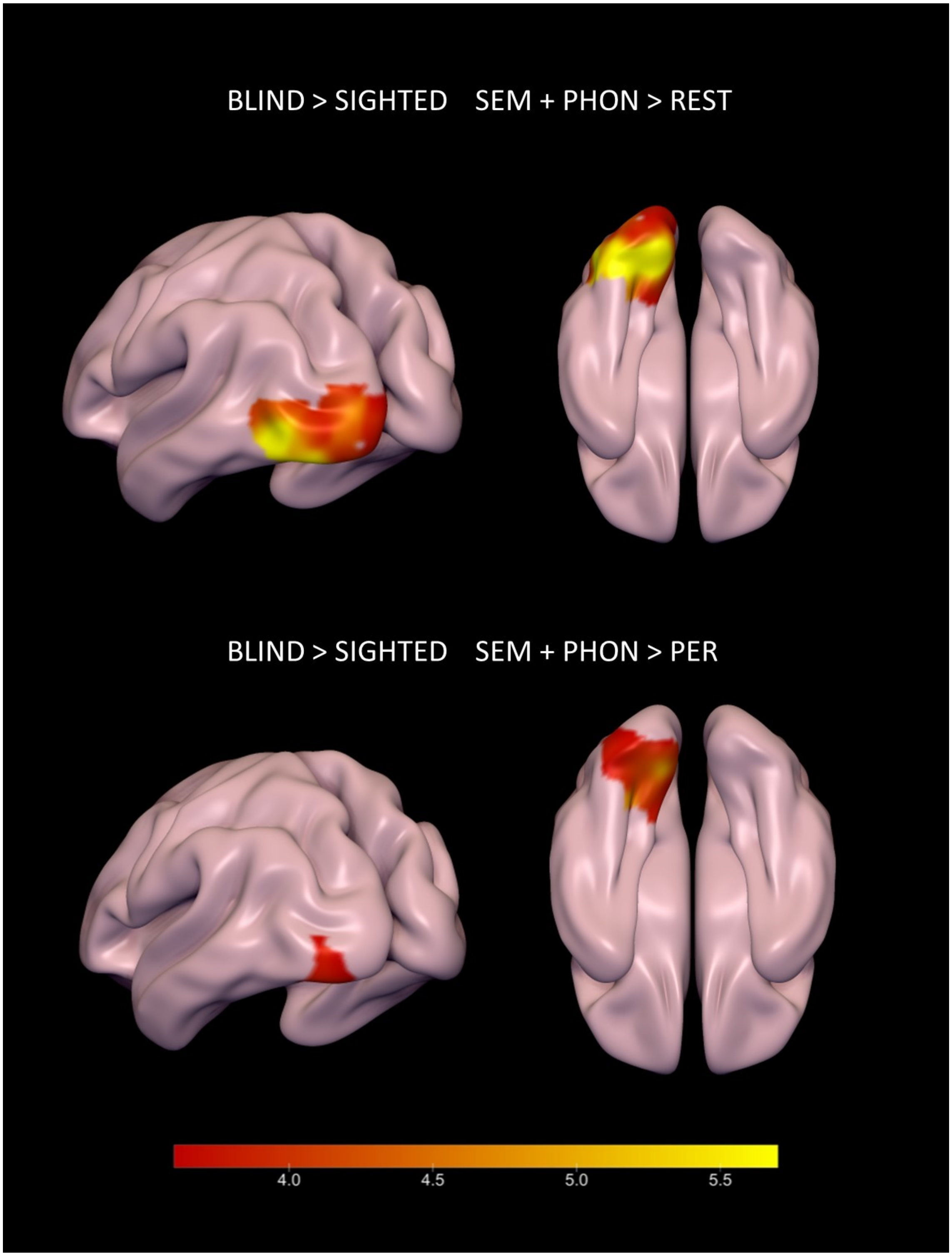

Figure 3.8: Group comparison (blind > sighted) of linguistic (semantic + phonological) conditions compared to rest and compared to the perceptual control condition, in visual cortex ROI, defined according to an anatomical mask. Activation shown is significant clusters, FWE corrected at a threshold of $p < 0.05$, with a cluster threshold of 108 voxels. Colour bar represents z-values

Table 3.4: Coordinates of local maximum within significant clusters for group differences in visual cortex activation (blind > sighted) at visual cortex ROI. The reverse comparison (sighted > blind) did not reveal suprathreshold activation within the visual cortex ROI

Condition	Region	*t*	*z*	*k*	Coordinates (x, y, z)
Semantic	L V3v	10.63	6.00	1315	-18 -78 -12
	R V4v	5.71	4.30	451	32 -74 -8
Phonological	L V3v	6.15	4.51	738	-18 -78 -10
Sem+Phon	L V3v	10.03	5.85	1236	-18 -78 -10
Sem+Phon>Perceptual	L V3v	5.30	4.10	457	-12 -74 -10
Sem > Phon	-				
Phon > Sem	-				

Note: No suprathreshold clusters were found for the SEM > PHON and PHON > SEM contrasts.

3.3.5 DCM RESULTS

We defined 8 models to investigate the potential interregional interactions that could account for the observation of visual cortex activity associated with linguistic processing in blind individuals (see Figure 3.2). Regions included (LIFG, VWFA and V3) were based on the results of the GLM analysis, described above. According to the random-effects BMS procedure (see Figure 3.9), the best model was determined to be model #8 with $\varphi_k = 0.19$, which represents the highest model evidence of all compared models (model evidence values sum to 1). Model #8 includes bi-directional modulation of the connection between the VWFA and the visual cortex by both semantic and phonological processing, suggesting that semantic and phonological information reach the visual cortex via input from the VWFA.

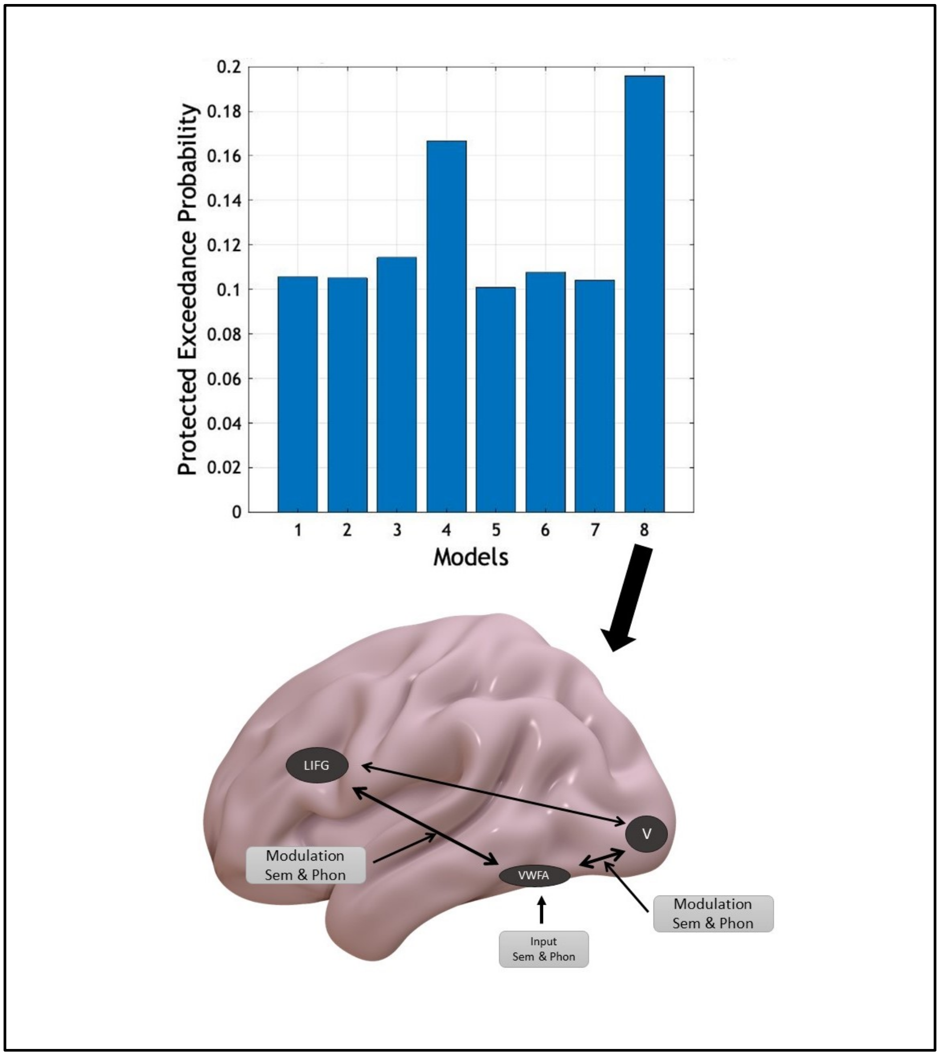

Figure *3.9*: Results of fixed effects Bayesian model selection procedure, the best model (#8) is reported as the one with the greatest exceedance probability (EP, φk). Specifics of the best model are shown at bottom.

Our next step was to assess the significance of the intrinsic input, endogenous connections and modulatory parameters, as detailed in Table 3.5. Bonferroni correction was applied, corresponding to the number of tests within each parameter class. Correcting for multiple comparisons is recommended and Bonferroni correction is a standard approach, albeit conservative considering that estimated parameters are highly dependent on each other (Stephan et al., 2010). Given this, we have chosen to report both the corrected and uncorrected *p* values, a similar approach taken by prior authors (Perrone-Bertolotti et al., 2017). However, inferences were made based on corrected *p* values.

Table 3.5: Parameter estimates of inputs, endogenous connections, and modulatory parameters

Parameter Class	Parameter	Mean +/- SD (Hz)	*t*	*p*	*p* (adjusted)
Intrinsic Input	**Phonological Input**	**0.127 +/- 0.12**	**3.30**	**0.007**	**0.014***
	Semantic Input	**0.159 +/- 0.16**	**3.30**	**0.008**	**0.016***
Endogenous Connection	V → LIFG	-0.09 +/- 0.18	-1.64	0.13	0.78
	VWFA → LIFG	**0.06 +/- 0.03**	**5.64**	**0.0002**	**0.0012***
	LIFG → V	0.075 +/- 0.09	2.61	**0.02**	0.12
	VWFA → V	**0.06 +/- 0.03**	**5.65**	**0.0002**	**0.012***
	LIFG →VWFA	0.0002 +/- 0.04	0.015	0.98	1.00
	V → VWFA	-0.08 +/- 0.11	-2.42	**0.03**	0.18
Linguistic Modulation	**Phon VWFA → V**	**0.70 +/- 0.49**	**4.70**	**0.0008**	**0.006***
	Phon V → VWFA	-0.13 +/- 0.70	-0.64	0.53	1.00
	Sem VWFA → V	**0.94 +/- 0.63**	**4.88**	**0.0006**	**0.0048***
	Sem V → VWFA	-0.19 +/- 0.41	-1.50	0.15	1.00
	Phon VWFA → IFG	**0.93 +/- 0.63**	**4.90**	**0.0006**	**0.0048***
	Phon IFG → VWFA	0.06 +/- 0.60	0.36	0.36	1.00
	Sem VWFA → IFG	**0.63 +/- 0.54**	**3.78**	**0.004**	**0.032***
	Sem IFG → VWFA	0.11 +/- 0.39	0.96	0.96	1.00
	Sem VWFA → V vs. Phon VWFA → V	-0.23	-1.30	1.00	

Note: The *p*-values were Bonferroni corrected for multiple comparisons according to the number of comparisons within each parameter class. Phon = phonological, Sem = semantic, V = visual cortex.

Both phonological input (*t*(10)=3.3, *p*=0.014) and semantic input (*t*(10)=3.3, *p*=0.016) were significant. Significant endogenous connectivity included the positive connection from the VWFA to the LIFG (*t*(10) = 5.64, *p*=0.0012) and from the VWFA to V (*t*(10) = 5.65, *p*=0.012). Both semantic and phonological processing positively modulated the connection from the VWFA to the visual cortex (*t*(10) = 4.88, *p*=0.004 and *t*(10)=4.70, *p*=0.006, respectively) and from the VWFA to the LIFG. The difference in modulatory strength on this connection by semantic vs phonological processing was not significant (*t*(10) = -1.30, *p*=0.99). See Figure 3.10 for a depiction of the final model.

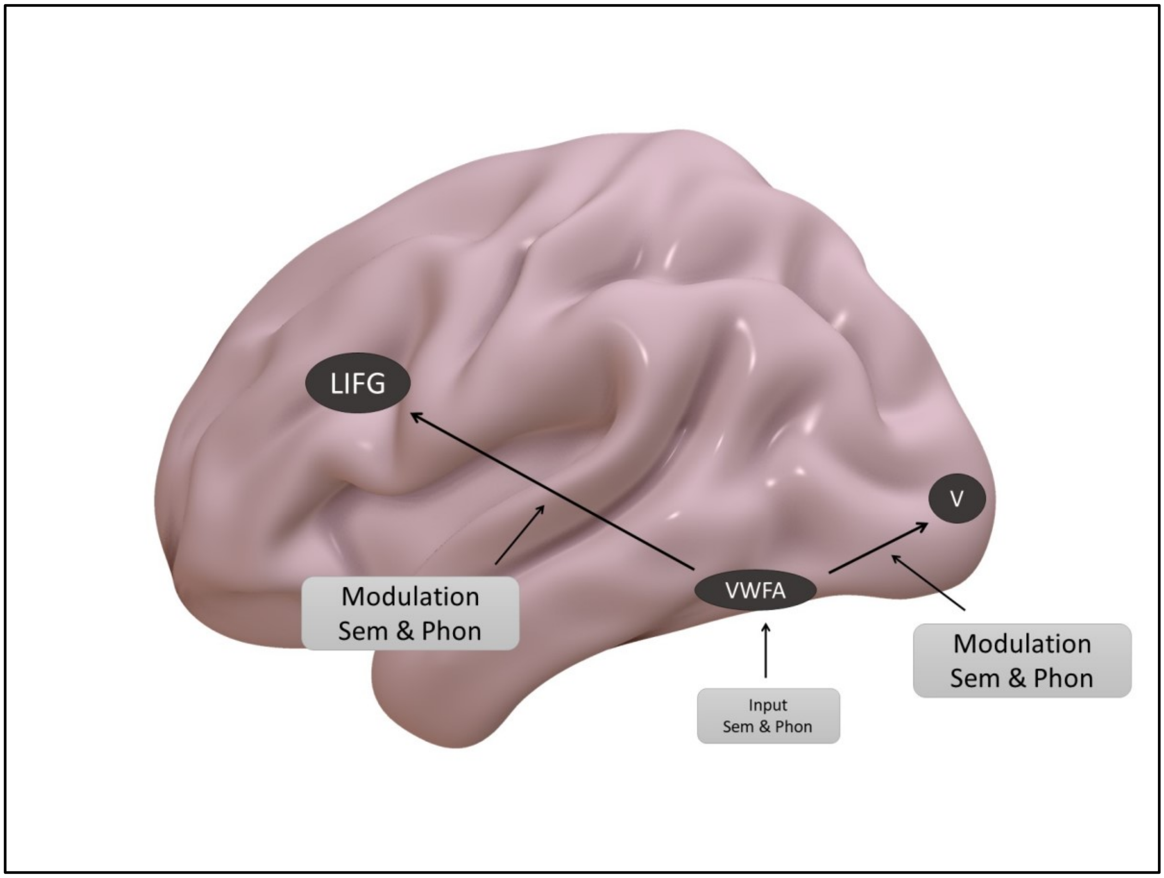

Figure 3.10: Significant model parameters, including endogenous connections between VWFA and LIFG/V, linguistic input to the VWFA and positive modulation by semantic and phonological processing of the VWFA to visual cortex connection and the VWFA to LIFG connection

3.4 DISCUSSION

The primary purpose of the current study was to explore the organisation of the underlying neural system responsible for the recruitment of the visual cortex during linguistic processing. More specifically, beyond identifying functionally relevant anatomical regions, we were interested in where and how linguistic information reaches the visual cortex via interactions with the typical language network. Our primary findings of interest were evidence of visual cortex involvement in processing linguistic information (replicating previous findings), and, to our knowledge for the first time, that this information may reach the visual cortex via direct input from the VWFA.

3.4.1 LINGUISTIC ACTIVATION IN THE VISUAL CORTEX

Here, we replicated previous findings of visual cortex recruitment for both semantic and phonological processing in people who are blind. Previous work by Burton et al. (2003) has suggested that the visual cortex recruitment in people who are blind may be preferential for semantic processing. In this case, when comparing brain activations between groups, both semantic and phonological processing recruited the visual cortex to a greater extent in blind individuals as compared to sighted individuals, although semantic activation was more widespread. No difference in activation levels were observed between conditions (SEM > PHON and PHON > SEM). It’s possible that the more widespread activity associated with semantic processing does not reflect a functional specialisation for semantic processing per se, and instead reflects a more general sensitivity to linguistic complexity. In addition to involving basic speech sound identification (i.e., phonological processing) the semantic condition also involved lexical access. Prior evidence in blind individuals indeed shows a sensitivity of the visual cortex for linguistic complexity, with greater activity observed for syntactically complex sentences compared to simpler sentences (Lane et al., 2015), semantically meaningful sentences compared to jabberwocky, and lists of unrelated real words compared to lists of unrelated pseudowords (Bedny et al., 2011). The suggestion that visual cortical regions may be more selective for one aspect of linguistic processing over another is not currently supported by much evidence and it is more likely that visual regions are responsive to linguistic information as a whole and are also sensitive to the level of complexity involved in the linguistic task.

We were also interested in whether there was visual cortex activity unique to semantic or phonological processing, over and above that seen during lower-level perpetual processing. We expected to see visual cortex recruitment for non-linguistic perceptual processing given previous demonstrations of visual cortex recruitment during auditory tasks (Araneda et al., 2021; Arnaud et al., 2018; Arno et al., 2001; Gaab et al., 2006; Gougoux et al., 2009; Kujala et al., 1995; Lubbe et al., 2010; Vetter et al., 2020) however we did not observe this relative to baseline. The lack of recruitment of the visual cortex during the perceptual control condition could potentially be related to task difficulty and that the task involved voice discrimination. The perceptual control condition involved discriminating between items based on speaker. On trials with different speakers, discriminating between speakers was not difficult, given that the gender of the speaker was always different (i.e., the speakers were obviously distinct). The nature of visual cortex recruitment during perceptual tasks has previously been tied to the difficulty of the perceptual discrimination - for example, ultra-fast speech comprehension specifically engages the primary visual cortex in blind individuals (Dietrich et al., 2013). As well, voice perception (i.e., the detection of voices vs non-vocal sounds) in blind individuals has been shown to activate the superior temporal sulcus (STS), but not the visual cortex (Gougoux et al., 2009), and voice discrimination abilities are correlated to the degree of recruitment of the STS. Moreover, studies of voice discrimination in blind individuals have found activations within the anterior fusiform gyrus, but not occipital regions specifically (Hölig et al., 2014). So, while previous evidence has suggested that the visual cortex is involved in auditory discrimination tasks (i.e., pitch, location), it’s possible that *voice* discrimination specifically does not involve the visual cortex. Finally, it should be noted that the perceptual condition yielded few above-threshold activations in general, which could have been the result of a priming effect. Previous investigations into voice priming have demonstrated that the BOLD signal is reduced to repeated presentations of identical vocal stimuli (Andics et al., 2010; Belin & Zatorre, 2003; Latinus et al., 2011). Given that half of the trials within the perceptual control condition were presentations of pairs of identical vocal stimuli, this could potentially account for the lack of significant activations observed within the visual cortex of blind individuals and whole-brain activations more generally across groups.

We did however observe that linguistic processing did yield significantly greater recruitment of the visual cortex compared to perceptual processing (i.e., SEM + PHON > PER). This is in line with previous results that have reported greater activation for linguistic stimuli compared to non-linguistic control conditions, including, for example, syntactic movement compared to sequence memory or mathematical tasks (Lane et al., 2015) and Braille reading compared to non-linguistic tactile discrimination (Sadato et al., 1996). Visual cortex recruitment has also been observed during memory recall of heard words (Amedi et al., 2003), and activation is greater during the processing of stimuli that have meaning (i.e. sentences vs non-word strings, (Röder et al., 2002), and during the processing of stimuli with grammatical structure (i.e. sentences and Jabberwocky compared to lists of words and non-words, (Bedny et al., 2011)). This suggests that while the visual cortex may take on a variety of functions in people who are blind, the functioning related to language is due to the processing of linguistic information specifically, and not a reflection of a general sensitivity to sensory information (Bedny, 2017).

3.4.2 DYNAMIC CAUSAL MODELLING

Our second aim was to understand the process through which the visual cortex begins to take on a role in linguistic processing in blind individuals. We used DCM to evaluate the causal connectivity between regions in the left lateralized language network, including the inferior frontal gyrus (LIFG) and the fusiform gyrus (roughly corresponding to the VWFA), and the region of the visual cortex (V) shown to be selective for linguistic processing. We evaluated several possible explanatory models of how linguistic information reaches the visual cortex during semantic and phonological processing, including a route through the VWFA that does not involve the LIFG, a route that directs language information to the visual cortex from the LIFG, and models that include separate routing of semantic and phonological processing through either the VWFA or the LIFG. The best model was determined to be the model that included bidirectional endogenous connectivity between the VWFA and the visual cortex, and direct input of linguistic information to the visual cortex from the VWFA.

When testing for significance of model parameters, we observed a significant endogenous connection from the VWFA to the visual cortex, and that both semantic and phonological processing positively modulate this connection from the VWFA to the visual cortex. This suggests an underlying, context-independent connection from the VWFA to the visual cortex, and further that visual cortex activity during semantic and phonological processing can be explained due to driving input from the VWFA. The endogenous connection from the VWFA to the visual cortex suggests a reorganisation of this pathway in blind individuals. These results should be interpreted with the caveat that we did not conduct the DCM analysis with sighted participants, so a comparison between groups is not possible here. However, evidence from prior investigations suggests that the results in blind participants here may be different than those observed previously in sighted participants. The VWFA was originally proposed to serve a specific function, namely the decoding of visual written words (Cohen et al., 2000). Anatomically located lateral to the middle section of the fusiform gyrus, it has been suggested to provide a direct connection between visual regions and language regions involved in reading (Bouhali et al., 2014; Yeatman et al., 2013). Indeed, direct anatomical connections from the VWFA to left hemispheric perisylvian language areas and to ventral visual field regions — including V1 and V2 — have been demonstrated (Bouhali et al., 2014; Yeatman et al., 2013). Further, deafferentations of the VWFA from the visual cortex are associated with reading impairments (Cohen et al., 2003). DCM studies in sighted individuals indicate the presence of a bidirectional endogenous connection between the VWFA and the IFG (Bitan et al., 2007; Booth et al., 2008; Perrone-Bertolotti et al., 2017) and a bidirectional endogenous connection between the VWFA and the visual cortex (Booth et al., 2008; Schurz et al., 2014). Thus, the endogenous connections of the VWFA observed here may reflect a unique reorganisation of its underlying anatomical and functional connectivity profile, although confirmation of reorganisation of anatomical pathways would require further investigation.

The function of the VWFA in blind individuals is particularly relevant given the current findings. Activation of the VWFA has been demonstrated during Braille reading in blind readers (Rączy et al., 2019; Reich et al., 2011; Sadato et al., 1998; Tian et al., 2021), suggesting functionality related to word identification regardless of input modality. Activations associated with auditory language processing have also been demonstrated, including during tasks involving sentence-level semantic processing and verb generation (Abboud & Cohen, 2019). The VWFA has also been shown to take on higher-level linguistic processing, including sensitivity for grammatical complexity in spoken sentences (Kim et al., 2017), which suggests that the VWFA may not be specific to reading in blind individuals, and may be incorporated into the frontotemporal language network to participate in higher-level language tasks. Taken together, this suggests that the VWFA responds to multiple levels of linguistic information across modalities, and that the positive modulation of the connection from the VWFA to the visual cortex that we observed positions the VWFA as the gateway into the visual system for auditory linguistic information. This represents a unique organisation of this pathway when compared to sighted individuals, in which this pathway has generally been suggested to facilitate the transfer of visual text information from the visual cortex to higher-level language regions involved in phonological or lexico-semantic processing (Cohen et al., 2003). Ultimately, the reorganisation of the visual cortex to support auditory linguistic processing may be the result of direct integration into the left-lateralized language network, via connections with the VWFA.

It should be mentioned that we did not observe a significant endogenous or modulatory connection between the LIFG and the visual cortex. This is interesting considering previous evidence demonstrating increased resting-state functional connectivity between the LIFG and visual regions in people who are blind (Bedny et al., 2011; Deen et al., 2015; Sabbah et al., 2016; Abboud & Cohen, 2019; Heine et al., 2015;

Striem-Amit et al., 2015). An important caveat to the interpretation of the current results is that the task employed involved word-level phonological and semantic information. Thus, it is possible that the VWFA only serves as a route of word-level auditory linguistic information into the visual cortex, and higher-level information, particularly sentence-level information, are routed through regions more specialised to perform sentence-level processing, including the LIFG. Further work is necessary to properly delineate the potential pathways of all levels of linguistic information into the visual cortex of blind individuals, which could include DCM investigations into the effects of sentence-level linguistic tasks on the modulation of the connections between the visual cortex and regions with fronto-temporal language network.

3.4.3 BEHAVIOURAL

Finally, it should be noted that sighted participants had higher behavioural accuracy than blind participants, specifically for the semantic condition. Research into how blindness affects semantic processing and conceptual development is somewhat limited, although some work suggests that blind children show impaired semantic development - for example, blind children overgeneralize less than sighted children and invent fewer words (Mills, 1988; Pérez-Pereira & Conti-Ramsden, 2013). However, group differences are typically eliminated by the age of ten (Pérez-Pereira & Conti-Ramsden, 2013). Indeed, blind adults perform comparably to sighted controls on semantic categorization tasks (Abboud et al., 2019) and rate concepts based on perceptual similarity comparably to sighted controls (Bottini et al., 2020). Other work has demonstrated that blind adults have conceptual understandings of visual phenomena (colour) similar to those of sighted people, developed specifically through semantic association (Kim et al., 2021; Saysani et al., 2021). Finally, electrophysiological brain indices of semantic processing (the N400) are elicited in blind individuals in response to semantically incongruent sentences, although with earlier onset and reduced lateralization, in comparison to sighted controls (Röder et al., 2000).

Here, participants were required to make a semantic judgement about pairs of words and decide if a pair of words was related in some way. "Related" in this context was broad - for example, items could be similar based on object category (i.e., both animals: *dog/cat*, both articles of clothing: *shirt/pants*) or based on usage (i.e., *letter/envelope, hat/head*). This was primarily because we were not interested in parcellating brain activation in blind individuals associated with different semantic or conceptual categories (i.e., visual vs. nonvisual concepts (Striem-Amit et al., 2018), objects/actions/places (Bottini et al., 2020)). It's possible that blind participants only perform comparably to sighted controls when asked to assign words to specific conceptual or semantic categories and over- or under generalise when they are asked to make broader relatedness assessments. Further work is necessary to understand the effect of blindness on language function, specifically as it relates to semantic processing and conceptual categorization.

3.5 CONCLUSION

Overall, the results of this study build on past studies by demonstrating the recruitment of the visual cortex during linguistic processing in people who are blind, with semantic processing in particular leading to more widespread recruitment of visual regions. We suggest that this reflects a sensitivity of the visual cortex in blind individuals for linguistic complexity as opposed to a specialisation for semantic processing, per se.

As well, our results showed that activity in the visual cortex in blind individuals associated with semantic and phonological processing is due to a driving input from the VWFA. We observed evidence of an endogenous connection from the VWFA to the visual cortex and a positive modulation of this connection by both semantic and phonological processing. We suggest that the VWFA may serve as a hub for the routing of linguistic information into the visual cortex in blind individuals.

CHAPTER 4 - VERBAL WORKING MEMORY AND THE VISUAL CORTEX IN BLIND INDIVIDUALS

4.1 INTRODUCTION

Cross-modal plasticity refers to processes that occur in the brain following unimodal sensory deprivation (i.e., deafness/blindness) such that deprived sensory regions may begin to process information transmitted via the remaining intact senses. In the case of blind individuals, deprived occipital regions begin to respond to auditory and tactile stimulation. There is a wide variety of information that can be transmitted cross-modally in this way, including perceptual information (e.g. tactile discrimination (Lubbe et al., 2010; Müller et al., 2019; Sadato et al., 2004), sound discrimination (Araneda et al., 2021; Arnaud et al., 2018; Arno et al., 2001; Gaab et al., 2006; Gougoux et al., 2009; Kujala et al., 1995; Lubbe et al., 2010; Vetter et al., 2020), spatial processing (Beer & Watanabe, 2009; Cecere et al., 2014; Collignon et al., 2011; Gougoux et al., 2005; Renier et al., 2010; Voss et al., 2011), auditory motion (Poirier et al., 2006) and linguistic information (e.g. Braille reading (Beisteiner et al., 2015; Burton et al., 2002; Cohen et al., 1997; Fujii et al., 2009; Hamilton et al., 2000; Melzer et al., 2001; Sadato et al., 1996), verb generation and verbal memory (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002), semantic and phonological processing (Burton et al., 2003) and higher level sentence comprehension (Bedny et al., 2011; Lane et al., 2015; Pant et al., 2020; Röder et al., 2002)).

The cognitive and behavioural correlates of the cross-modal recruitment of occipital cortices in people who are blind are yet to be fully understood. Compensatory mechanisms related to enhancements in auditory and tactile processing are relatively well-documented, including superior tactile (Alary et al., 2009; Bhattacharjee et al., 2010; D'Angiulla & Waraich, 2002; Goldreich & Kanics, 2003, 2006; Grant et al., 2000; Legge et al., 2008; Wong et al., 2011) and auditory processing (Doucet et al., 2005; Gougoux et al., 2004, 2005; Lessard et al., 1998; Röder et al., 1999; Voss et al., 2011). In some instances, visual cortex recruitment can directly predict behavioural performance on perceptual processing tasks (e.g., sound localization, Gougoux et al., 2005).

Within the domain of higher-level cognitive processes, there is evidence of behavioural differences between blind and sighted individuals related to verbal memory. Blind individuals show better verbal memory performance on a variety of tasks, including long-term recall (Amedi et al., 2003; Pasqualotto et al., 2013), recognition (Amedi et al., 2003; Röder et al., 2001), serial word order (Raz et al., 2007). However, the evidence for potential behavioural enhancements related to verbal *working* memory performance in blind individuals is mixed. While some studies demonstrate superior verbal working memory abilities in blind individuals as compared to sighted individuals (Dormal et al., 2016; Arcos et al., 2022; Loiotile et al., 2020; Occelli et al., 2017), other work demonstrates comparable performance between blind and sighted individuals on verbal working memory tasks (Park et al., 2011; Rokem & Ahissar, 2009; Castronovo & Delvenne, 2013; Pigeon & Marin-Lamellet, 2015; Wan et al., 2010).

There is some evidence that suggests behavioural enhancements related to verbal memory are tied to visual cortex involvement. For example, visual cortex recruitment in blind people has been directly correlated with performance on long-term word recognition, standardardized memory assessments (Amedi et al., 2003) and verbal episodic retrieval (Raz et al., 2005). As well, auditory working memory training has been shown to integrate the visual cortex into existing functional memory networks (Gudi-Mindermann et al., 2018; Rimmele et al., 2019). While this latter finding is noteworthy, the evidence for a relationship between visual cortex recruitment and behavioural performance on verbal working memory tasks in people who are blind is limited. As well, it does not directly suggest that the visual cortex recruitment observed in blind individuals is proportional to verbal working memory demands. So, while visual cortex recruitment has been correlated to long-term and episodic components of memory (Amedi et al., 2003; Raz et al., 2005), its functional relationship to verbal working memory (a system distinct from long-term memory, specifically the subcomponent of working memory related to linguistic information, Baddeley, 2003a; Caplan & Waters, 1999a; Smith et al., 1998) is less clear.

The purpose of the current study was to investigate the functional significance of visual cortex recruitment as it relates to verbal working memory in people who are blind. More specifically, we were interested in whether visual cortex recruitment is proportional to verbal working memory demands. As well, given the evidence that early blind individuals show superior abilities for some aspects of verbal memory compared to sighted controls, but evidence concerning behavioural differences related to verbal working ability is less clear, we were interested in whether blind individuals outperform sighted controls on tasks of verbal working memory abilities. Relatedly, we were interested in whether behavioural measures of verbal working memory abilities were correlated to the degree of engagement of the visual cortex during tasks that involve verbal working memory. Early blind individuals (congenital or fully blind before the age of two) and sighted control participants were measured on their verbal working memory abilities using the digit span subcomponent of the WAIS. Brain activity was measured during an auditory *N*-back task in which verbal working memory demands were increased across conditions. We addressed three primary research questions and hypotheses: 1) is visual cortex activity modulated by verbal working memory demands in early blind individuals 3) do verbal working memory abilities differ between early blind and sighted individuals and 4) does verbal working memory ability (as measured by Digit Span scores and behavioural accuracy on the *N*-back task) correlate to visual cortex recruitment during verbal working memory processing in early blind individuals.

4.2 METHODS

See Chapter 2 for general methods.

4.2.1 fMRI ANALYSIS

We first performed first-level analysis in which, for each subject, each condition of the auditory *N*-back task (1-back = OB and 2-back = TB) was convolved with a canonical hemodynamic response function (HRF). Movement parameters derived from realignment (three translations and three rotations) were included in the design matrix as multiple regressors of no interest. The general linear model was then used to produce parameter estimates for each subject, at each condition, at each voxel. Statistical parametric maps were generated from linear contrasts of the HRF parameter estimates for each of the two conditions. Statistical analyses were then performed at the individual and group level. At the individual level, we computed contrasts to determine brain regions involved in verbal working memory (OB > Rest & TB > Rest) as well as the brain regions involved in increased verbal working memory demands (TB > OB). At the group level, contrast maps generated for individual participants were entered into second-level random effects analyses to test for within-groups effects (one sample *t* tests) and between-groups effects (independent sample *t* tests).

We also conducted a between-groups ROI analysis focused on activation in the visual cortex specifically. We focused on activation in a search volume containing the bilateral occipital lobe (V1/V2/V3d/V3v/V3A/V4/V5/V6), calculated on the basis of an anatomical mask image generated using the SPM *anatomy* toolbox (Eickhoff et al., 2006). Given the discrepancy between individual subjects or subject groups and single-subject anatomical atlases (Nieto-Castanon et al., 2003) peak activations were localised based on probabilistic cytoarchitectural maps as part of the SPM *anatomy* toolbox (Eickhoff et al., 2006). We entered first-level participant contrasts (OB > Rest, TB > Rest, TB > OB) into second-level independent samples *t* tests to test for group differences (blind > sighted and sighted > blind).

We were also interested in whether working memory ability (as measured by the overall score on the Digit Span subcomponent of the WAIS and accuracy on the *N*-back task) is related to the degree to which the visual cortex is recruited during verbal working memory tasks in people who are blind. Blind participants' overall Digit Span scores and *N*-back accuracy scores were entered separately as within group second-level covariates to test for a correlation in signal change in specific contrasts of interest (OB > Rest, TB > Rest, TB > OB).

For all analyses, cluster-wise activation was FWE corrected at a threshold of $p < 0.05$. Only the coordinates for the local maximum within a cluster are reported, except when the cluster contained multiple distinguishable peaks (at a threshold of $p < 0.05$, FDR corrected).

4.3 RESULTS

4.3.1 BEHAVIOURAL RESULTS

4.3.1.1 DIGIT SPAN

We first compared Digit Span scores between groups (see Figure 4.1). We compared subcomponent scores using a 2 (group: blind/sighted) by 3 (condition: forward/backward/sequencing) two-way ANOVA. In the forward condition, participants repeat back digits in a series in the same order as they are read. In the backward condition, participants repeat back digits in a series in the reverse order as they are read. In the sequencing subcomponent, participants repeat back digits in a series in chronological order. The Group × Condition interaction was not significant, $F(2, 60) = 0.39$, $p = .68$, and the main effect of group was also not significant ($p = .27$). The main effect of condition was significant ($p = .0002$). Follow up Tukey's HSD comparisons investigating the main effect of condition revealed that forward subcomponent scores were higher than scores in the backward subcomponent ($p = .0004$) and the sequencing subcomponent ($p = .0018$), but scores between the backward and sequencing subcomponent did not differ ($p = .90$). An addition test was performed on overall scores, which reflect the total combined score on all three subcomponents (forward/backward/sequencing). Overall scores did not differ between groups (blind = 31.72 +/- 6.34, sighted = 29.63 +/- 4.22, $t(20) = 0.91$, $p = .37$).

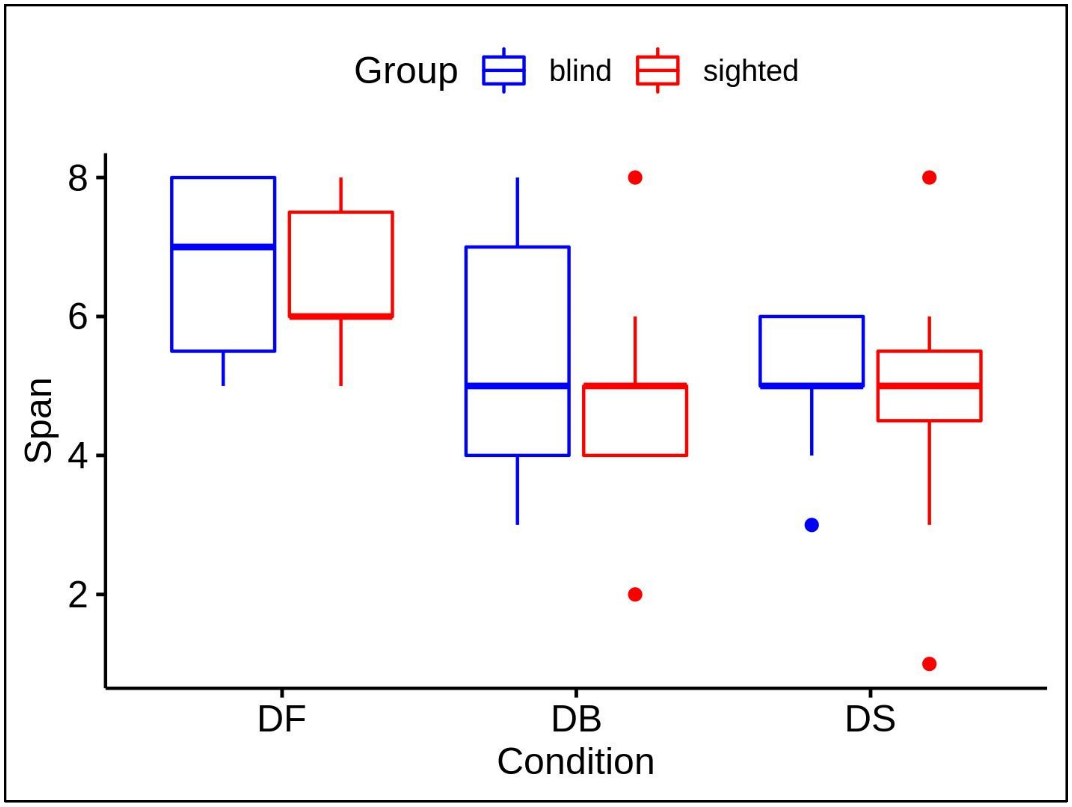

Figure 4.1: Comparison of Digit Span component scores for blind and sighted participants. DF = forward span, DB = backward span, DS = sequencing span

4.3.1.2 N-BACK

We chose to assess accuracy on the *N*-back task (OB & TB conditions, see Figure 4.2) by computing the sensitivity index *d*-prime (Haatveit et al., 2010; Macmillan & Creelman, 1990) and then comparing scores across groups using a 2 (group: blind/sighted) x 2 (condition: OB/TB) two-way ANOVA. The Group × Condition interaction was not significant ($F(1, 38) = .18$, $p = .67$ and the main effects of group ($p = .28$) and condition ($p = .94$) were also not significant.

We computed reaction time scores for hit trials (i.e., correct identification of a repeated item) for each condition (OB/TB) for each group (see Figure 4.2) and then compared reaction times between groups using a 2 (group: blind/sighted) by 2 (condition: OB/TB) two-way ANOVA. The Group × Condition interaction was not significant (*F*(1,

38) = 1.1, $p = .30$ and the main effects of group ($p = .38$) and condition ($p = .50$) were also not significant.

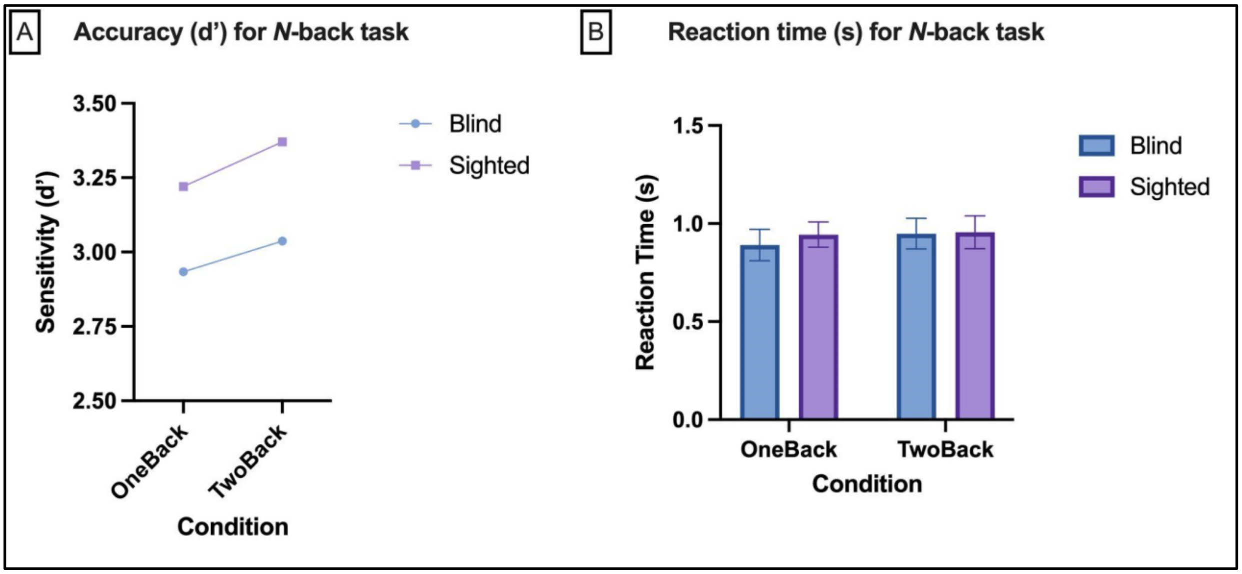

Figure 4.2: A) Accuracy, as measured by the sensitivity index d' for both N-back conditions, across groups. B) Reaction time for both N-back conditions, across groups. Error bars represent 95% CI

4.3.2 fMRI RESULTS

4.3.2.1 WHOLE-BRAIN GROUP LEVEL

We first looked at whole-brain activation associated with each of the *N*-back conditions within each group (details in Table 4.1). For sighted participants, activations associated with lower verbal working memory demands (OB > Rest, see Figure 4.3) included bilateral clusters within the parietal lobe, encompassing the left and right supramarginal gyrus and angular gyrus, as well as the bilateral clusters in the frontal lobe, encompassing the left inferior frontal gyrus, precentral gyrus, middle frontal gyrus, and right inferior frontal gyrus, precentral gyrus and frontal operculum. For blind participants, similar patterns of activity within frontal and parietal regions were observed for the lower verbal working memory condition (OB > Rest, see Figure 4.3). Activations included a cluster within the left parietal cortex, including the supramarginal gyrus, superior parietal lobe and postcentral gyrus. As well, blind participants also demonstrated activitations within a large frontal cluster, including the right superior frontal gyrus, pre SMA, precentral gyrus and left superior frontal gyrus, pre SMA, precentral gyrus and middle frontal gyrus.

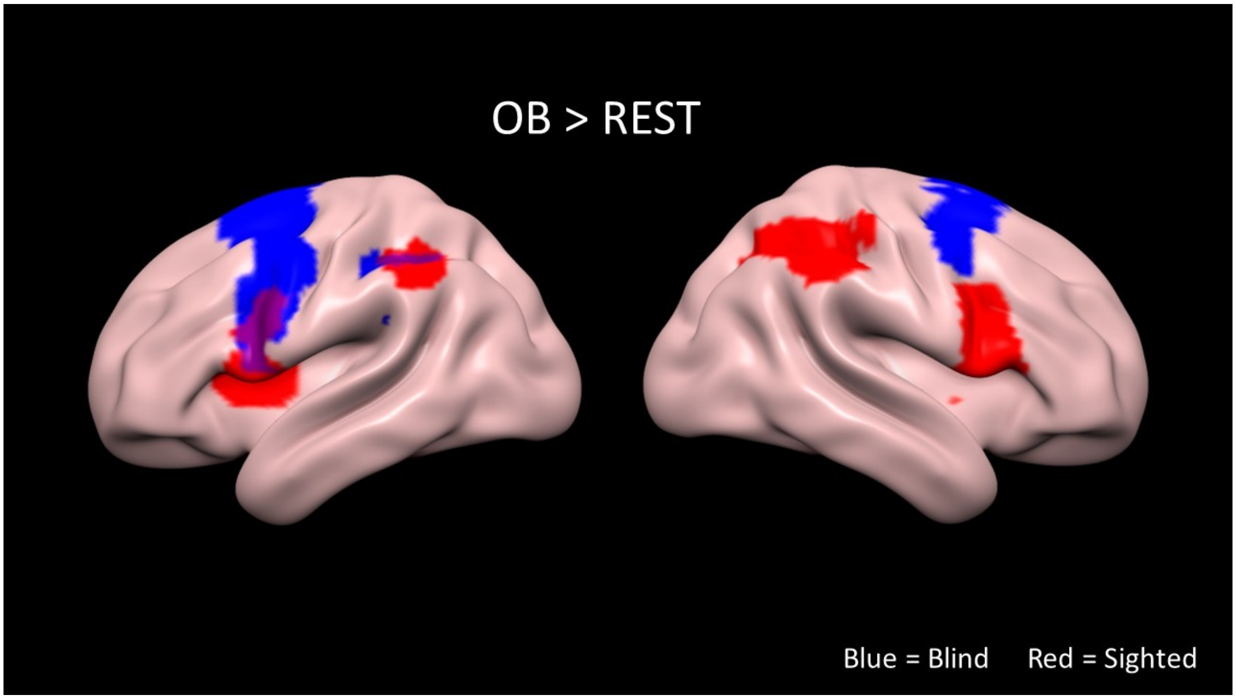

Figure 4.3: Whole brain activations of OB > Rest comparison within each group (blind = blue, sighted = red), in left and right hemisphere. Activation shown is significant clusters at a FWE correction threshold of $p < 0.05$, with a cluster threshold of 159 voxels. Purple indicates areas of overlapping activation between groups.

For sighted participants, activations associated with higher verbal working memory demands (TB > Rest, see Figure 4.4) included clusters within the bilateral parietal cortex included the left supramarginal gyrus and angular gyrus, and right supramarginal gyrus and angular gyrus. Additional activation was observed in bilateral clusters within the frontal lobe, encompassing the right inferior frontal gyrus (pars opercularis and triangularis), precentral gyrus, middle frontal gyrus, insula and frontal orbital cortex and left inferior frontal gyrus (pars opercularis and triangularis), precentral gyrus, middle frontal gyrus, insula, frontal operculum and left pre SMA. For blind participants, when investigating activations associated with greater working memory demands (TB > Rest, see Figure 4.4), blind participants again demonstrated activations within frontal and parietal regions. Activations included a left parietal cluster, including the superior parietal cortex and supramarginal gyrus. Additional bilateral frontal clusters were observed, which included the right superior frontal gyrus, pre SMA, precentral gyrus, middle frontal gyrus, paracingulate gyrus, and left middle frontal gyrus, precentral gyrus and inferior frontal gyrus. However, notably, blind participants also demonstrated activations within the bilateral visual cortex and occipital fusiform gyrus. Bilateral occipital/fusiform clusters encompassed the left V1/V3/V4 and FG1/FG2/FG2, as well as the right V1/V2/V4 and FG1.

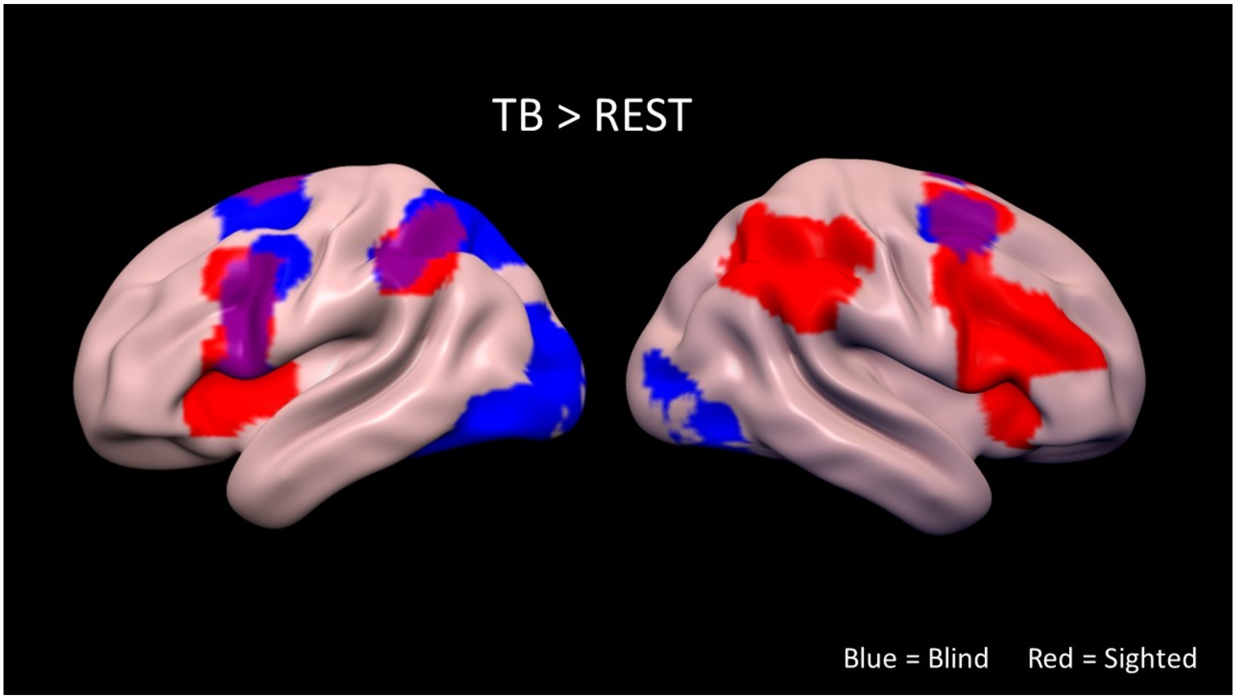

Figure 4.4: Whole brain activations of TB > Rest comparison within each group (blue = blind, red = sighted). Activation shown is significant clusters at a FWE correction threshold of $p < 0.05$, with a cluster threshold of 141 voxels. Purple represents areas of overlapping activation between groups

When comparing conditions (TB > OB, see Figure 4.5), higher verbal working memory demands were associated with activations within sighted participants in bilateral parietal clusters, including the right superior parietal lobe, supramarginal gyrus, superior occipital cortex and precuneus, and left superior parietal lobe and supramarginal gyrus. Significant bilateral clusters within the frontal lobe included the right frontal pole, middle frontal gyrus, superior frontal gyrus, frontal operculum and left inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, insula and frontal operculum. Bind participants demonstrated greater activity associated with higher verbal working memory demands in the left superior parietal lobe and superior occipital cortex.

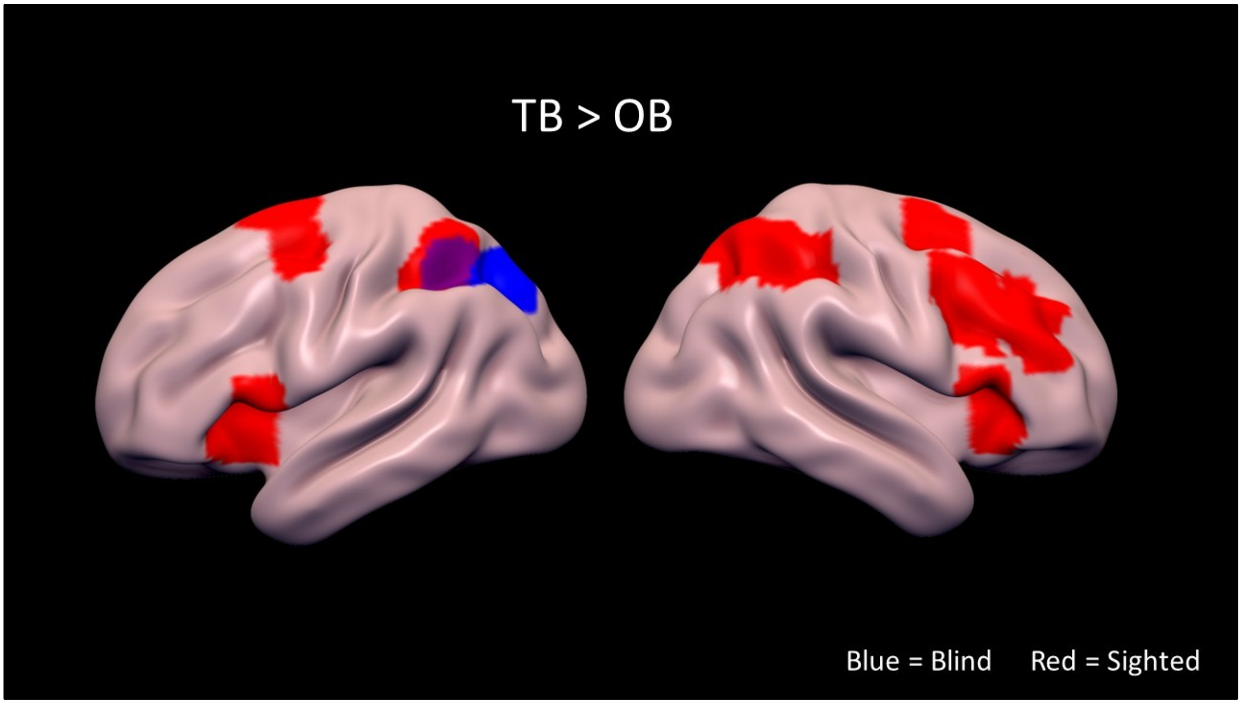

Figure 4.5: Whole brain activations of TB > OB comparison within each group (blue = blind, red = sighted). Activation shown is significant clusters at a FWE correction threshold of $p < 0.05$, with a cluster threshold of 113 voxels. Purple represents areas of overlapping activation between groups

Table 4.1: Whole-brain activation for each *N*-back condition compared to rest (OB > Rest, TB > Rest) and the between condition comparison (TB>OB), within each group. Coordinates represent the local maximum within each cluster.

Group	Contrast	Region	*t*	*z*	*k*	Coordinates (x, y, z)
Blind	OB > Rest	R pre SMA	16.97	5.72	2620	12 6 54
		L supramarginal gyrus	5.4	3.8	200	-34 -44 38
	TB > Rest	R pre SMA	10.71	4.93	1412	10 10 54
		R occipital fusiform gyrus (FG1)	7.79	4.33	499	32 -70 -6
		L occipital fusiform gyrus (FG2)	9.13	4.63	1530	-42 -70 -10
		L precentral gyrus	8.35	4.46	429	-46 8 32
		L superior parietal lobe, visual motor association area (BA 7)	7.09	4.15	963	-14 -66 50
	TB > OB	L superior parietal lobe	7.61	4.29	195	-36 -54 50
Sighted	OB > Rest	R opercular IFG	12	4.94	396	46 14 10
		R supramarginal gyrus	8.72	4.40	551	52 -38 54
		L opercular IFG	9.32	4.63	282	-54 8 2
		L supramarginal gyrus	6.65	3.91	198	-44 -40 42
	TB > Rest	R opercular IFG	15.51	5.36	1367	50 12 22
		R supramarginal gyrus	15.08	5.31	1360	52 -46 50
		R middle frontal gyrus	6.99	4.00	177	28 6 56
		L supramarginal gyrus	9.52	4.55	554	-46 -50 54
		L superior frontal gyrus	9.09	4.47	183	-14 0 64
		L paracingulate cortex	9.07	4.46	309	-10 18 46
	TB > OB	R superior parietal lobe	9.81	4.60	243	14 -68 52
		R superior parietal lobe	7.37	4.09	786	32 -62 54

Group	Contrast	Region	*t*	*z*	*k*	Coordinates (x, y, z)
		R paracingulate gyrus	8.03	4.25	285	8 24 40
Sighted		R middle frontal gyrus	7.82	4.20	564	40 38 36
		R superior frontal gyrus	6.31	3.81	127	24 0 68
		R inferior frontal gyrus	7.59	4.15	263	34 24 -4
		L opercular IFG	7.55	4.14	444	-44 16 8
		L middle frontal gyrus	6.95	3.99	155	-30 -2 58
		L superior frontal gyrus	7.60	4.15	159	-14 0 64
		L superior parietal lobe	3.39	3.83	244	-34 -50 52

4.3.2.2 GROUP COMPARISON

4.3.2.2.1 WHOLE-BRAIN

We then compared whole-brain activation between groups (blind > sighted, sighted > blind) for each condition compared to rest (OB > Rest, TB > Rest) and for the TB condition compared to the OB condition (TB > OB). Coordinates of local maximum within significant clusters are reported in Table. 4.2. For the OB condition compared to rest (see Figure 4.6), blind participants demonstrated greater activity than sighted participants within the left occipital fusiform gyrus/lateral occipital cortex, with a significant cluster encompassing regions including FG1/FG2 and V3/V4.

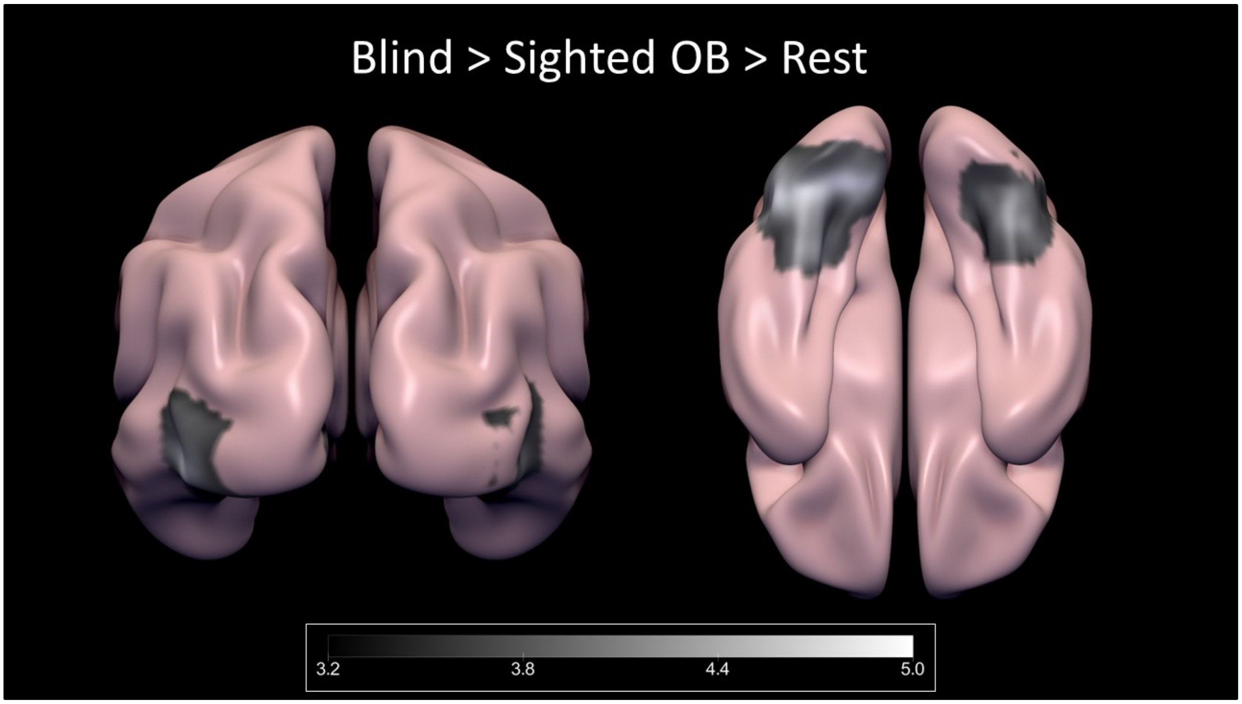

Figure 4.6: Between-group comparison (blind > sighted) of whole-brain activations for OB > Rest. Note that the sighted > blind comparison did not yield suprathreshold activation. Activation shown is significant clusters, FWE corrected p < .05, with a cluster threshold of 378 voxels. Colour bar represents *z*-values

For the TB condition compared to rest (Figure 4.7), blind participants demonstrated greater activity again within the bilateral occipital fusiform gyrus/lateral occipital cortex, with a significant cluster in the left hemisphere encompassing regions including V1/V3/V4 and FG1/FG3 and a significant cluster within the right hemisphere encompassing V3/V4, FG1/FG2/FG3. When comparing conditions directly (TB > OB), no significantly greater activity within the blind group compared to the sighted group was observed.

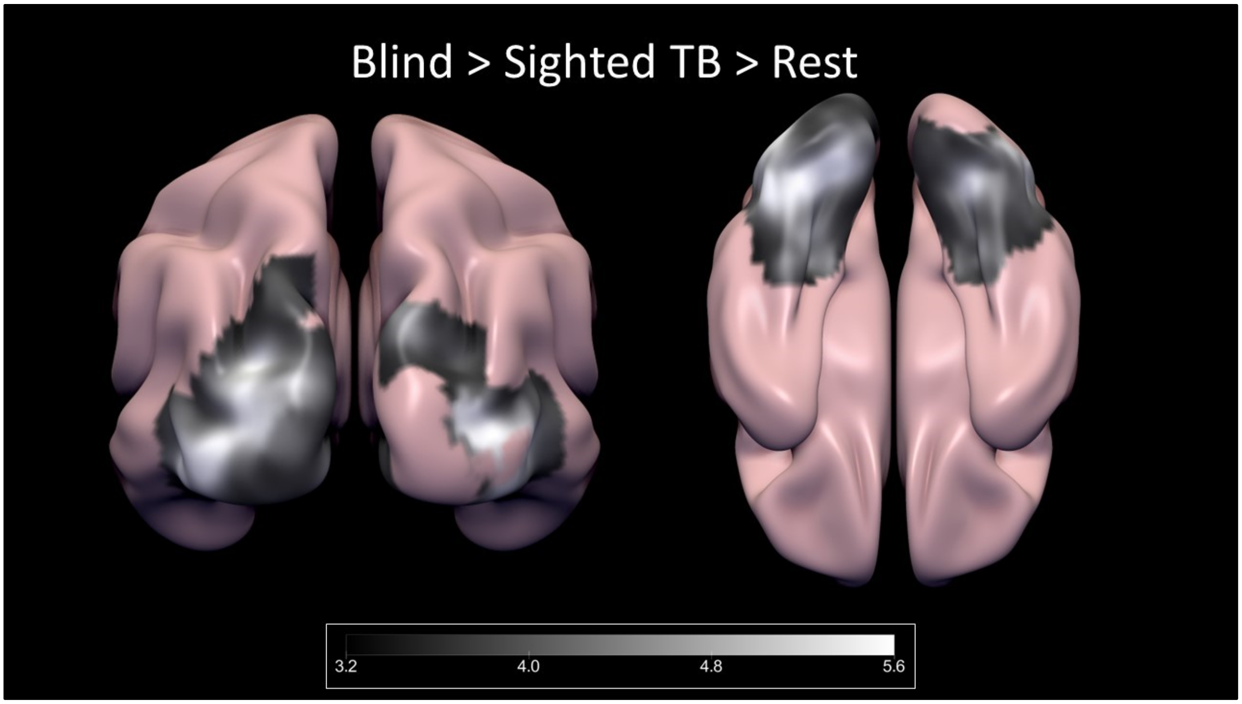

Figure 4.7: Between-group comparison (blind > sighted) of whole-brain activations for TB > Rest. Note that the sighted > blind comparison did not yield suprathreshold activation. Activation shown is significant clusters, FWE corrected $p < .05$, with a cluster threshold of 95 voxels. Colour bar represents *z*-values

When investigating regions with greater activation in sighted participants compared to blind participants, no significant difference in activity was observed for the OB > Rest contrast or the TB > Rest contrast. For the TB > OB contrast, greater activity was observed for sighted participants compared to blind participants in the right middle frontal gyrus, right nucleus accumbens, right insula and left hippocampus.

Table 4.2: Whole-brain group comparison of working memory conditions (blind > sighted, sighted > blind). Coordinates correspond to local maximum within significant clusters.

Difference	Condition	Region	*t*	*z*	*k*	Coordinates (x, y, z)
Blind > Sighted	OB	L V4v	5.99	4.43	1059	-40 -70 -10
		R FG1	5.79	4.34	378	36 -66 -8
	TB	L V3v	9.18	5.61	3058	-30 -74 -8
		R V4v	8.31	5.34	1945	32 -70 -6
	TB > OB	-				
Sighted > Blind	OB	-				
	TB	-				
	TB > OB	R middle frontal gyrus	5.09	3.99	360	32 12 36
		L insula	4.98	3.94	351	-36 16 -8
		L hippocampus	5.96	4.42	257	-14 -14 -16
		R nucleus accumbens	6.13	4.50	179	12 12 -8

4.3.2.2.2 VISUAL CORTEX ROI

We then performed an ROI investigation into group differences (blind > sighted) within the visual cortex specifically (see Figure 4.8). For the lower verbal working memory condition (OB > Rest), greater activation for blind participants compared to sighted participants was observed within the visual cortex, with a significant cluster including left extrastriate regions V2/V3/V4. Increasing verbal working memory demands (TB > Rest) again resulted in greater recruitment for blind participants compared to sighted participants within bilateral visual areas, including a cluster in the left primary visual cortex encompassing (V1) through to V4 and a right hemisphere cluster which included extrastriate regions V2/V3/V4. Although the between-group differences were more spatially extensive in the TB than OB condition, no significant differences were observed in blind participants compared to sighted participants when comparing the two verbal working memory conditions directly (TB > OB). Details of these results are provided in Table 4.3.

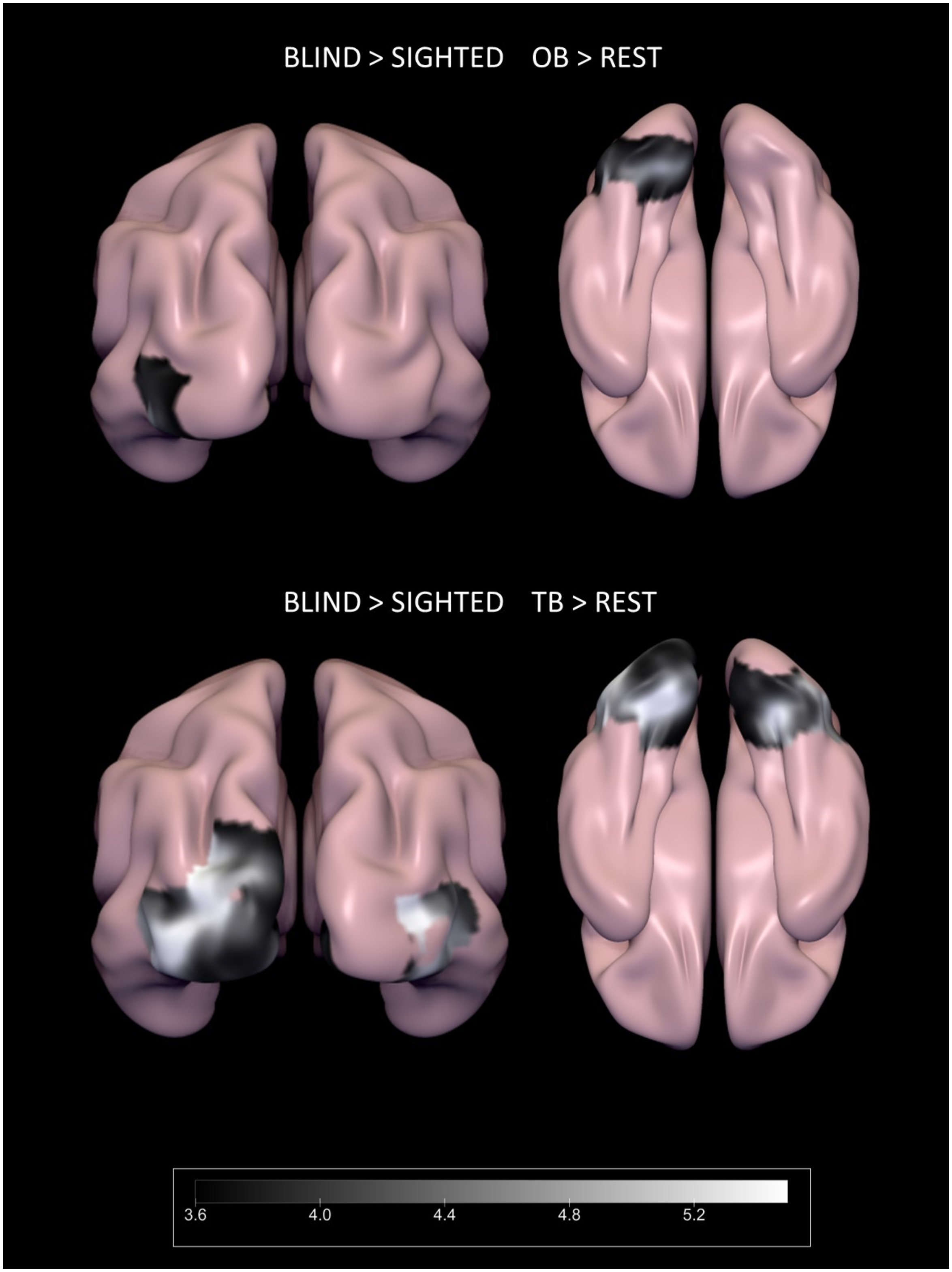

Figure 4.8: Group comparison (blind > sighted) in visual cortex ROI for both N-back conditions compared to rest. Activation shown is significant clusters, FWE $p < .05$, with a cluster threshold of 95 voxels. Colour bar represents z-values.

Table 4.3: Group comparison of working memory conditions (blind > sighted) within the visual cortex ROI. Coordinates correspond to local maximum within significant clusters

Condition	Region	*t*	*z*	*k*	Coordinates (x, y, z)
OB	L V3v	5.91	4.40	448	-16 -78 -8
TB	L V4v	7.86	5.18	1274	-28 -76 -8
	R V4v	7.84	5.18	627	28 -72 -6
TB > OB	N/A				

4.3.2.3 COVARIATE ANALYSIS

We investigated whether behavioural measures of verbal working memory ability, as measured by the Digit Span subcomponent of the WAIS and accuracy on the *N*-back task, was correlated with recruitment of visual cortex regions in the blind group. Overall accuracy on the Digit Span and *N*-back scores were not correlated to visual cortex recruitment in blind participants during tasks that involve low verbal working memory demands (OB > Rest) or higher verbal working memory demands (TB > Rest) within the visual cortex ROI, nor were scores related to the additional recruitment of visual regions when verbal working memory demands increased (TB > OB).

4.4 DISCUSSION

The purpose of the current study was to investigate verbal working memory abilities in early blind individuals and the functional relationship between visual cortex activity and verbal working memory in early blind adults. We compared early blind adults to sighted controls on a behavioural assessment of verbal working memory ability to determine if verbal working memory abilities differ between early blind and sighted individuals. As well, we investigated visual cortex recruitment during a verbal working memory task to determine if visual cortex recruitment increases with increased verbal working memory demands and if verbal working memory ability correlates to visual cortex recruitment. We found that blind and sighted participants did not differ on behavioural assessments of verbal working memory ability. We did however observe that the visual cortex is recruited in blind, but not sighted individuals during tasks that involve verbal working memory and increasing verbal working memory demands leads to more widespread involvement of the visual cortex, including recruitment of primary visual areas (V1). However, we did not observe a correlation between verbal working memory ability and visual cortex recruitment in blind participants.

While there is evidence showing advantages in verbal memory tasks for early blind individuals (Amedi et al., 2003; Arcos et al., 2022; Park et al., 2011; Raz et al., 2005, 2007), the evidence for verbal working memory is not entirely uniform. Many studies reporting a working memory advantage in the early blind come from studies involving children (Tillman & Bashaw 1968; Smits & Mommers 1976; Hull & Mason 1995; Withagen et al. 2013: Crollen et al., 2021), although not all studies report an advantage for short-term and working memory processing in blind children (Swanson & Luxenberg, 2009). The evidence in adults is mixed, with some studies showing a cognitive advantage on working memory tests (Dormal et al., 2016; Pigeon & Marin-Lamellet, 2015), while other studies report no difference between blind and sighted control groups (Park et al., 2011; Rokem & Ahissar, 2009; Wan et al., 2010), or a non-significant tendency towards advantages in blind participants (Castronovo & Delvenne, 2013). The failure to observe an advantage for blind participants in our case, and in previous cases (Park et al., 2011; Rokem & Ahissar, 2009; Wan et al., 2010), may be due to the fact that cognitive advantages within specific domains are not consistent across all early blind individuals due to natural variation in individual ability. It's also necessary to consider the potential effect of other factors associated with variability between individuals' working memory ability, such as age (Anders et al., 1972; Linden et al., 1994; Rypma & D'Esposito, 2000). Working memory capacity has been demonstrated to decline with increasing age (Dobbs & Rule, 1989). In the case of our data, the mean age of blind participants was 48 (median = 44, range = 33 - 65), whereas the mean age of sighted participants was 38 (median = 22, range = 18 - 73), although average age was not significantly different between groups ($p = 0.21$). Although we included a screen for mild cognitive impairment (MOCA/MOCA-Blind), and all participants scored within normal range, this does not rule out the possibility that age-related declines in working memory ability could have masked the supposed performance enhancements associated with blindness.

Taking into consideration the discrepancies in perceptual processing abilities between blind and sighted individuals is also necessary. Although group differences in perceptual processing cannot account for our results, it could potentially explain the considerable discrepancy regarding group differences in verbal working memory ability in the previous literature. When differences in perceptual processing skills are controlled for (by presenting stimuli at each individual participant's 80% speech-in-noise detection threshold), blind participants have been shown to perform similarly to sighted controls on a verbal *N*-back task (Rokem et al., 2009), whereas they outperform sighted participants under normal quiet conditions.

Finally, it's possible that task difficulty could account for the comparable performance between groups. Regarding the Digit Span test, each component (forward, backward, sequencing) of the Digit Span test has a maximum level of 8, i.e., the maximum span tested is 8 digits. For the forward component specifically, 5 of the 11 blind participants reached a forward span of 8, whereas only 2 of the sighted participants reached a forward span of 8. This suggests that although mean scores did not differ between groups, more blind than sighted participants were above normal range (6 +/- 1, according to (Miller, 1956; Peña-Casanova et al., 2009; Spitz, 1972), and because the test does not go beyond a span of 8 digits, we were unable to determine the true forward span maximum of almost half of the blind participants. As well, while *N*-back tasks are considered to involve more processing demands than Digit Span tasks (Scharinger et al., 2017), the *N*-back task used here involved two levels (1-back and 2-back), and could be considered relatively easy, as compared to more demanding tasks, such as the Operation Span (OSPAN, Turner & Engle, 1989) or Reading Span (RSPAN, Daneman & Carpenter, 1980). Increasing task demands on the *N*-back task by including additional levels (3-back+) or using a more demanding task (OSPAN, RSPAN) could result in greater variability in performance and allow for group differences to be elucidated.

Regarding brain activity, our primary finding of interest is that in early blind individuals but not sighted controls, the visual cortex is recruited during verbal working memory processing and increasing verbal working memory demands leads to a more widespread recruitment of the visual cortex, including recruitment of V1. This research extends previous work in blind individuals demonstrating visual cortex involvement in long-term and episodic verbal memory tasks (Amedi et al., 2003; Raz et al., 2005). As well, it extends previous findings demonstrating visual cortex activity in blind individuals during verbal working memory tasks (Park et al., 2011), by showing for the first time that the spatial extent of visual cortex recruitment is proportional to verbal working memory demands. Increases in verbal working memory demands are typically (as in sighted people) associated with increases in activation and increased bilaterality in the fronto-parietal working memory network (Braver et al., 1997; Höller-Wallscheid et al., 2017; Owen et al., 2005; Smith et al., 1998; Wager & Smith, 2003). In particular, incremental increases in working memory demands (i.e., on *N*-back tasks up to a 3rd level) are associated with incremental increases in activation in frontal regions including the dorsal-lateral prefrontal cortex (DL-PFC), middle frontal gyrus and IFG, and the posterior parietal cortex (Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000; Jonides et al., 1997). Here, both blind and sighted participants demonstrated typical activity within fronto-parietal working memory networks and increased activation and bilaterality as task demands increased (TB > Rest and TB > OB), although the increase in fronto-parietal activation was more pronounced in sighted participants. However, only blind participants showed increases in visual cortex activity as task demands increased, suggesting that the visual cortex is sensitive to verbal working memory load. As such, in addition to demonstrating the effects of working memory load in frontal-parietal regions, our results demonstrate that blind individuals also uniquely recruit the primary visual cortex when verbal working memory demands increase.

The observation of more widespread involvement of the visual cortex in blind individuals for the condition that involved higher working memory demands is in line with previous work showing increased complexity in other cognitive domains results in greater visual cortex recruitment. For example, larger visual cortex responses in blind individuals are observed for syntactically complex sentences (Bedny et al., 2011; Lane et al., 2015; Röder et al., 2001). The recruitment of an additional neural resource (i.e. the recruitment of the visual cortex) has been tied to increased behavioural abilities in blind individuals, including on sentence comprehension tasks (Lane et al., 2015) and on verbal memory tasks (Amedi et al., 2003; Raz et al., 2005). As well, previous demonstrations in sighted people have noted a correlation between verbal working memory performance and activity in frontal regions sensitive to working memory load (Braver et al., 1997). It is for this reason that we expected to observe a correlation between behavioural scores and visual cortex recruitment in blind participants. However, no relationship was found between overall performance on the Digit Span test and visual cortex recruitment, nor on *N*-back accuracy and visual cortex recruitment.

Of note with regards to the lack of correlation between Digit Span scores and visual cortex recruitment is that the tasks used (Digit Span as a behavioural measurement and an *N*-back task to assess visual cortex recruitment) are similar in that they both involve verbal working memory, but they are not identical in their working memory load. Working memory can be broken down into components consisting of a short-term memory storage component and a processing component, the central executive (Baddeley, 2003a, 2003b; Engle, 2002). Tasks that manipulate working memory load can be differentiated based on these components; demanding short-term memory tasks (storage-load) and demanding executive function tasks (processing-load) (Scharinger et al., 2017). The forward component of Digit Span tasks can be considered a storage-load task, given that it consists of memorization of a series of items (typically digits or letters) for later recall, without any additional processing (Richardson, 2007). In contrast, *N*-back tasks involve comparing a current stimulus to one seen *N*-steps back in the sequence. For *1*-step trials, stimuli have to be continuously updated in working memory storage and for

2-step trials and up, attention must be shifted between items for comparison, inhibition of stimuli no longer required to be maintained in working memory storage and response inhibition (Jonides et al., 1997; Smith et al., 1998). Thus, *N*-back tasks can be considered a demanding processing-load task. While the backward and sequencing components of the Digit Span task used here could minimally tax the executive functioning component of working memory, they would not do so to the extent characteristic of the *2*-step+ component of the *N*-back task. This discrepancy in the demands of each task could potentially account for the lack of relationship between the Digit Span measure of verbal working memory and neural responses observed here. In terms of the lack of relationship between *N*-back scores and visual cortex recruitment, this could potentially be related to task difficulty. Performance on the *N*-back task was high and comparable between groups. As well, prior evidence in sighted individuals demonstrating a relationship between *N*-back scores and frontal regions sensitive to working memory demands included an additional 3-back level (Braver et al., 1997). Increasing task demands by including a 3-back condition could potentially result in greater variability in *N*-back accuracy.

How might the visual cortex take on functioning related to verbal working memory in people who are blind? The adoption of cognitive function by the visual cortex in people who are blind has been suggested to be a result of an underlying potential of sensory cortical regions to take on a variety of specialisations, as proposed by Bedny (2017). According to this view, the function subserved by the visual cortex is the result of developmental experience and cortical-cortical connectivity profiles. If an individual is exposed to visual stimuli during development, visual regions develop typically and specialise for visual/sensory processing. In the absence of visual stimulation, input from higher-level cognitive networks, like those involved in memory and language, drive the development of the visual cortex so that it becomes involved in higher-level cognitive processing (Bedny, 2017). Evidence in support of this hypothesis includes research describing the connectivity profile of the visual cortex to higher-level cognitive regions. Instances of increased functional connectivity are typically between the visual cortex and regions within language (Abboud & Cohen, 2019; Bedny et al., 2011; Deen et al., 2015; Heine et al., 2015; Striem-Amit et al., 2015), memory (Abboud & Cohen, 2019; Harold Burton et al., 2014; Deen et al., 2015) or attention/executive control networks (Abboud & Cohen, 2019; Harold Burton et al., 2014; Kanjlia et al., 2021; Striem-Amit et al., 2015). Effective connectivity analyses (specifically, GC analyses) have shown that working memory actively engages the visual cortex in blind individuals and activity in visual regions can be explained by effective connections from regions in the fronto-parietal working memory network (Park et al., 2011). Further work could potentially involve DCM investigations into how modulations in verbal working memory demands affect the interregional interactions between the visual cortex and the fronto-parietal working memory network

4.5 CONCLUSION

Together, these results demonstrate that the visual cortex is involved in verbal working memory processing in the early blind. Increasing verbal working memory demands leads to more widespread recruitment of visual regions, including recruitment of the left primary visual cortex. When comparing blind participants to sighted controls, no differences in behavioural measures of verbal working memory abilities were observed, and no relationship between verbal working memory task performance and visual cortex recruitment in blind individuals was observed. This latter result could primarily be related to low task difficulty and a difference in underlying working memory components measured by the tasks employed. Further research could explore this structure/function relationship further by using more demanding and comparable verbal working memory measurement tools. Finally, the recruitment of the visual cortex related to verbal working memory is thought to be driven by integration of the visual cortex into higher-level memory networks. Investigations into the precise mechanisms governing this integration are warranted, including an exploration of modulatory connectivity associated with task demands, are necessary to further understand the neuroplastic changes associated with congenital blindness.

CHAPTER 5 - DISCUSSION

5.1 SUMMARY OF FINDINGS BY CHAPTER

This thesis sought to address gaps in the research on the impact of blindness on the function and development of cognition and involved investigations into the specifics of the integration of the visual cortex into existing language networks and the relationship between verbal working memory and visual cortex recruitment. We addressed four primary research questions through two studies of early blind individuals; 1) how does the visual cortex interact with the typical language network during auditory language processing 2) is visual cortex activity modulated by verbal working memory demands, 3) do verbal working memory abilities differ between early blind and sighted individuals and 4) does verbal working memory ability correlate to visual cortex recruitment during verbal working memory processing.

Chapter 3: The primary purpose of this chapter was to clarify the nature of visual cortex involvement in auditory language processing in people who are early blind. While previous research has demonstrated widespread involvement of the visual cortex during a variety of language tasks, and this activity was suggested to be the result of direct input from regions functionally specialised for language processing within an established left-lateralized fronto-temporal language network, evidence of an effective connection between the language network and the visual cortex had yet to be demonstrated. We replicated previous demonstrations of visual cortex involvement in both word-level semantic and phonological processing in early blind, but not sighted individuals. Results of the DCM analysis show that activity in the visual cortex during word level semantic and phonological processing is due to a cortico-cortical connection from the VWFA, i.e., word level semantic and phonological information reaches the visual cortex via the VWFA.

Chapter 4: The primary purpose of this chapter was to clarify the effect of early blindness on verbal working memory, specifically as it relates to ability and the underlying neural mechanisms. Similar to work demonstrating an involvement of the visual cortex in language processing, previous work has also demonstrated involvement of the visual cortex in verbal memory and a correlation between visual cortex recruitment and verbal memory performance in people who are blind. However, the evidence regarding the performance on verbal working memory tasks and how this may relate to visual cortex involvement was less clear. We replicated previous findings demonstrating an absence of enhanced verbal working memory ability in early blind adults, suggesting an increase in verbal memory function may be limited to certain tasks or memory subsystems, i.e., long-term or episodic verbal memory (Amedi et al., 2003; Raz et al., 2005). Early blind individuals, but not sighted individuals, demonstrated recruitment of the visual cortex during a verbal working memory task and crucially, activity was more widespread and included the primary visual cortex (V1) for conditions that involved greater verbal working memory demands. In early blind individuals, no relationship was observed between visual cortex recruitment and any of the measures of verbal working memory ability we used.

Overall, this work strengthens our understanding of the flexibility of cortical regions to take on new functions due to developmental sensory deprivation, provides new insight into the mechanisms driving this functional reorganisation of cortical regions, and clarifies what impact the reorganisation of the functional networks subserving cognitive functions can ultimately have on cognitive ability. These results are discussed below within the context of theories regarding the cross-modal reorganisation of visual regions as the result of blindness – namely that visual regions are inherently capable of performing a variety of cognitive computations and ultimately specialise for cognition due to information received during development – and within the broader literature on what, if any, impact blindness has on cognitive ability and function.

5.2 AUDITORY LANGUAGE PROCESSING IN THE VISUAL CORTEX

5.2.1 LANGUAGE ACTIVATIONS

The results reported in Chapter 3 replicate previous findings of auditory language processing in the visual cortex of blind individuals. The capacity of the visual cortex to take on auditory language function in people who are blind represents a marked deviation from the typical functions performed by visual cortical regions. It might be logical to expect that inherent physiological limitations constrain the functional specialisation of visual regions and 'new' functions (i.e., those observed as the result of visual deprivation) correspond closely to the functions that would be expected as the result of typical development. To put it more simply, visual regions may be limited to certain types of operations and will continue to perform those operations if they receive the necessary information from another sensory system. This has indeed been shown, for example, in the middle temporal visual motion complex, which is capable of processing auditory motion in blind individuals (Wolbers et al., 2011). However, the existing evidence, including our own, suggests that the visual cortex is capable of performing new operations specifically related to language, uniquely in blind individuals.

The auditory language tasks that activate the visual cortex in blind individuals are broad and encompass multiple levels of linguistic processing, including lexical-semantic, morphology, phonology and syntax (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002; Ofan & Zohary, 2007; Bedny et al., 2011; Burton et al., 2003; Noppeney et al., 2003; Deen et al., 2015; Röder et al., 2002; Lane et al., 2015; Pant et al., 2020). This activity is suggested to be language-specific, and not simply a reflection of perceptual processes or domain-general aspects of task performance (Bedny et al., 2011). Previous work has attempted to elucidate if the visual cortex is more selective for one type of language processing over another. Burton et al., (2003) attempted to determine if visual cortex activity in blind individuals is preferential for semantic or phonological information. Results indicated that in early blind individuals, both semantic and phonological processing activated the visual cortex, but activity was more widespread for semantic processing compared to phonological processing (Burton et al., 2003).

Here, we replicated previous findings of visual cortex recruitment for both semantic and phonological processing in people who are blind and replicated the finding of more widespread activation associated with semantic processing. We observed no difference in visual cortex activity when contrasting the two conditions directly (SEM > PHON and PHON > SEM). It seems likely that the more widespread activity associated with semantic processing does not reflect a functional specialisation for semantic processing per se, and instead reflects a more general sensitivity to linguistic complexity. In addition to involving basic speech sound identification (i.e., phonological processing) the semantic condition also involved lexical access. Prior evidence in blind individuals indeed shows a sensitivity of the visual cortex for linguistic complexity with greater activity observed for syntactically complex sentences compared to simpler sentences (Lane et al., 2015), semantically meaningful sentences compared to jabberwocky, and lists of unrelated real words compared to lists of unrelated pseudowords (Bedny et al., 2011). The suggestion that visual cortical regions may be more selective for one aspect of linguistic processing over another is not currently supported by much evidence and it is more likely that visual regions are responsive to linguistic information as a whole and are also sensitive to the level of complexity involved in the linguistic task.

Future work could explore, what, if any effect visual cortex recruitment has on language function in people who are blind. Does the recruitment of additional neural resources to accomplish language-based tasks result in altered language processing behaviours or enhanced language processing abilities in people who are blind? In terms of speech perception abilities more generally, blind individuals have been shown to outperform sighted individuals on speech-in-noise tasks (Muchnik et al., 2009; Niemeyer & Starlinger, 1981; Rokem & Ahissar, 2009). Other areas of performance enhancements for blind individuals with regards to speech perception include faster lexical decision times (Röder et al., 2003), improved ability to distinguish between vowels (Ménard et al., 2009), superior prosody detection (Klinge, Röder, et al., 2010) and better syllable parsing (Hugdahl et al., 2004). These results are typically interpreted as a reflection of blind individuals' superior perceptual processing abilities and not superior linguistic abilities, per se. However, with regards to higher-level language abilities, some work suggests that the recruitment of the visual cortex observed in blind individuals results in enhanced sentence processing abilities, particularly on sentences involving syntactic movement and garden-path sentences (Loiotile et al., 2020) and larger visual cortex responses are associated with better sentence comprehension performance (Lane et al., 2015). This does not necessarily rule out the possibility that sentence comprehension enhancements are not due to visual cortex involvement and may instead arise due to differences in how blind individuals attend to language in their day-to-day lives. Blind individuals must interpret language information in the absence of visual cues and may therefore become better at attending to and extracting information from language input that might typically come through nonverbal channels (Bedny et al., 2011). A better understanding of the potential relationship between visual cortex activity and language performance will come from more comprehensive analyses of the correlation between different language skills and activity in the visual cortex.

5.2.2 THE VISUAL WORD FORM AREA AS A ROUTE OF LINGUISTIC INFORMATION INTO THE VISUAL CORTEX

Chapter 3 presented the findings of a DCM analysis into the possible routes of semantic and phonological information into the visual cortex in early blind individuals. We were interested in further understanding the nature of the integration of the visual cortex into the existing language network in the brain. As well, we were interested in further understanding how visual cortex activity associated with language processing in people who are blind can be explained via direct input from other cortical regions specialised to perform language computations. The specialisation of the visual cortex for language processing - and other types of cognitive processes - in people who are blind is generally suggested to be the result of input received during development from the cortical networks typically subserving these processes, which is only made possible due to a lack of competing visual input (Bedny, 2017; Tomasello et al., 2019). This theory is partially supported by evidence including neurocomputational work demonstrating the capacity for simulated semantic networks to "grow into" visual regions, but only under visually deprived conditions (Tomasello et al., 2019), as well as evidence of increased resting-state functional connectivity in blind individuals between the visual cortex and regions within language (Abboud & Cohen, 2019; Bedny et al., 2011; Deen et al., 2015; Heine et al., 2015; Striem-Amit et al., 2015), memory (Abboud & Cohen, 2019; Burton et al., 2014; Deen et al., 2015) or attention/executive control networks (Abboud & Cohen, 2019; Burton et al., 2014; Kanjlia et al., 2021; Striem-Amit et al., 2015). However, functional connectivity only indicates a correlational relationship between neural activity within spatially distinct brain regions and cannot indicate the direction of the correlational relationship, or how the relationship may have arisen (Friston, 2011). As such, it cannot provide concrete evidence of the proposed direct, modulatory connection from established cognitive networks to the visual cortex. Effective connectivity, on the other hand, specifically estimates the effect one neural system has over another (Friston, 2011; Friston et al., 2003). This technique is particularly useful in understanding the temporal dynamics of interactions between distributed brain networks and provides information on how information may move through such networks (Friston, 2011; Friston et al., 2003). We therefore used DCM to investigate how semantic and phonological information may reach the visual cortex via possible connections from the IFG and/or the VWFA.

We hypothesised eight possible models of interregional connectivity between the IFG, VWFA and the visual cortex in order to explain how semantic and phonological information may reach the visual cortex via connections with regions in the fronto-temporal language network. In blind individuals, previous work has demonstrated an increased resting-state functional connection between the visual cortex and the IFG (Sabbah et al., 2016), therefore we included a model in which semantic and phonological information reach the visual cortex via input from the IFG. Other evidence has indicated an increased functional connection during speech processing between the visual cortex and the VWFA (Dzięgiel-Fivet et al., 2021), therefore we included a model in which semantic and phonological information reach the visual cortex via input from the VWFA. We also wanted to allow for the possibility that semantic and phonological information may reach the visual cortex via separate connections, therefore we included models in which semantic and phonological information reach the visual cortex via distinct inputs from the IFG and/or the VWFA. Finally, we iterated on these base models to test for the possibility that the connections between the IFG/VWFA and the visual cortex are bidirectional - i.e., that the visual cortex can exert an influence on the IFG and/or the VWFA.

Results indicated that, in people who are early blind, there is a significant endogenous connection from the VWFA to the visual cortex, indicating positive baseline connectivity from the VWFA to the visual cortex, irrespective of task demands (i.e., in the absence of semantic or phonological input). This result does not imply a directional anatomical connection, but it does indicate that at rest, activity in the VWFA leads to activity in the visual cortex. The reverse connection, from the visual cortex to the VWFA, was not significant. As well, we also observed a significant endogenous connection from the VWFA to the IFG, indicating positive baseline connectivity from the VWFA to the IFG, again irrespective of task demands. These endogenous connections should be considered within the context of the typical anatomical connections of the VWFA. In sighted individuals, the VWFA has direct anatomical connections to left hemispheric perisylvian language areas and ventral visual field regions, including V1 and V2 (Bouhali et al., 2014; Saygin et al., 2016; Yeatman et al., 2013). DCM studies in sighted individuals indicate the presence of a bidirectional endogenous connection between the VWFA and the IFG (Bitan et al., 2007; Booth et al., 2008; Perrone-Bertolotti et al., 2017) and a bidirectional endogenous connection between the VWFA and the visual cortex (Booth et al., 2008; Schurz et al., 2014). Our results indicate that in blind individuals, visual deprivation causes a novel organisation of this pathway, indicating a preservation of the underlying connection from the VWFA to higher-order language regions and a unidirectional connection from the VWFA to the visual cortex.

In addition to the above endogenous connections, our results indicate that both semantic and phonological processing positively modulate the connection from the VWFA to the visual cortex. These results add clarity to the possible direction of previous demonstrations of increased functional connectivity between the VWFA and the visual cortex (Dzięgiel-Fivet et al., 2021), and suggest that the connection is causal, such that activity in the VWFA leads to activity in the visual cortex. This is, to our knowledge, the first demonstration of a direct effective connection between a region in the typical language network and the visual cortex during auditory linguistic processing in early blind individuals. This finding is particularly interesting within the context of the original conceptualization of the functional specialisation of the VWFA in sighted individuals, as well as recent findings indicating how visual deprivation may affect its response profile. In sighted individuals, the VWFA is part of the distributed neural network for reading.

Located lateral to the middle section of the fusiform gyrus, it has been suggested to provide a direct connection between visual regions and other language regions involved in reading (Bouhali et al., 2014; Yeatman et al., 2013) and was originally suggested to serve a specific function, namely the decoding of visual written words (Cohen et al., 2000). However, results from both sighted and blind participants contradict the notion that this region exclusively functions to identify visual word forms. First, the VWFA has previously been demonstrated to be active during speech processing in sighted individuals (Planton et al., 2019) and may support modality-independent word identification/meaning-binding, which involves linking a written or auditory word to its associated meaning (Qin et al., 2021). In blind individuals, there is consistent evidence of VWFA activation during Braille reading (Rączy et al., 2019; Reich et al., 2011; N Sadato et al., 1998; Tian et al., 2021), during sentence-level semantic tasks and during verb generation (Abboud & Cohen, 2019) and it has been suggested to be the site of speech/reading convergence (Dzięgiel-Fivet et al., 2021). Other work has shown that the VWFA is uniquely sensitive to the grammatical complexity of sentences in blind individuals, which has not been demonstrated in sighted individuals (Kim et al., 2017). This suggests that, like the visual cortex, the VWFA in blind individuals is functionally reorganised and becomes involved in spoken- language and written- language processing more generally.

Taken together, this positions VWFA as the route of word level semantic and phonological information into the visual cortex in blind individuals. We have demonstrated that in blind individuals, the VWFA forms an endogenous connection to the visual cortex and that word level semantic and phonological processing modulates the connection from the VWFA to the visual cortex. However, whether the VWFA serves as the route of sentence-level linguistic information (e.g., sentence-level semantic and/or syntactic information) into the visual cortex remains to be seen. Recent work by Abboud & Cohen, (2019) and Kim et al. (2017) suggests that this may be possible. Abboud et al. (2019) observed activity within the VWFA in blind individuals associated with sentence-level semantic processing and during a verb generation task. Work by Kim et al., (2017) indicated that in blind braille readers and sighted readers of visual print, the visual cortex was sensitive to reading, but only blind participants demonstrated activity within the VWFA associated with the grammatical complexity of spoken sentences, i.e., responses in the VWFA were greater for sentences that included syntactic movement compared to those that did not (Kim et al., 2017). Given that the VWFA in blind individuals appears to be uniquely sensitive to sentence-level language information, it may serve as a hub for the routing of all linguistic information into the visual cortex. An alternative explanation is that sentence level information reaches the visual cortex directly from regions within the fronto-temporal language network that are more specialised for sentence-level semantic and syntactic processing, such as Broca's area or regions within the anterior temporal lobe, including the superior temporal gyrus and superior temporal sulcus (Friederici, 2011, 2012; Rogalsky & Hickok, 2011). Further work is necessary to properly delineate the potential pathways of all levels of linguistic information into the visual cortex of blind individuals, which could include DCM investigations into the effects of sentence-level linguistic tasks on the modulation of the connections between the visual cortex and regions with fronto-temporal language network.

The present study describes findings in a group of early blind individuals who were either totally blind from birth or who lost their sight completely prior to the age of two. It is also necessary to determine how the onset of blindness, particularly later blindness onset, impacts the route of linguistic information into the visual cortex. Crucially, it is also essential to determine how the development of visual literacy impacts the function of the VWFA as a route of linguistic information into the visual cortex of blind individuals who lose their sight later in life. In sighted individuals, the VWFA forms an important part of the reading-related neural network and serves as an intermediary between early visual areas and higher-order language regions involved in reading (Bouhali et al., 2014; Yeatman et al., 2013). DCM analyses have demonstrated that the connection between the visual cortex and the VWFA in sighted individuals is bidirectionally modulated by visual reading tasks (Booth et al., 2008; Richardson et al., 2011; Schurz et al., 2014). Our results indicate that this pathway may be reorganised in early blind individuals to support the transfer of auditory linguistic information into the visual cortex, compared to findings from previous studies of sighted individuals. However, the prior specialisation of this pathway to support visual reading may prevent it from being able to function as a hub for auditory linguistic information into the visual cortex in late-onset blind individuals. Relatedly, it’s possible that the VWFA only develops as a hub for linguistic information into the visual cortex in the absence of visual stimulation entirely, regardless of whether vision loss occurs pre- or post-visual literacy development. Further work is necessary to determine whether there is a sensitive period for the reorganisation of the function of the VWFA and its related connections to the perisylvian language network and the visual cortex. Given that the visual cortex had been demonstrated to be involved in auditory language processing in later blind individuals (Aguirre et al., 2016; Büchel et al., 1998; Büchel et al., 1998; H Burton et al., 2003; Burton, Snyder, Conturo, et al., 2002; Burton & McLaren, 2005; Pant et al., 2020), understanding how linguistic information reaches the visual cortex in that population is necessary to fully understand how blindness impacts the organisation of the functional networks subserving auditory linguistic processing.

5.3 VERBAL WORKING MEMORY IN THE VISUAL CORTEX

5.3.1 VERBAL WORKING MEMORY ABILITY

Chapter 4 presented the findings of an investigation into the effect of early blindness on verbal working memory ability. We were specifically interested in investigating if verbal working memory abilities, as measured by the Digit Span subcomponent of the WAIS and a verbal *N*-back task, differed between early blind and sighted individuals. This work was motivated by previous findings demonstrating an advantage for blind individuals on tasks assessing other measures of verbal memory ability, including long-term recall and episodic memory (Amedi et al., 2003; Pasqualotto et al., 2013; Amedi et al., 2003; Röder et al., 2001; Raz et al., 2007) and inconsistencies regarding the presence or absence of an advantage for blind individuals on tasks measuring working and short-term memory ability (Dormal et al., 2016; Loiotile et al., 2020; Pigeon & Marin-Lamellet, 2015; Arcos et al., 2022; Castronovo & Delvenne, 2013; Occelli et al., 2017; Park et al., 2011; Rokem & Ahissar, 2009; Wan et al., 2010).

Our results indicated that blind participants performed comparably to sighted controls on all subcomponents of the Digit Span test (forward, backward, sequencing, and overall) and performed comparably to sighted controls on both levels of the *N*-back task (1-back and 2-back conditions). Failure to observe a difference in blind and sighted participants on similar measurements of memory ability have been observed previously. Park et al., (2011) observed no difference between blind and sighted participants on a verbal *N*-back task, and Bliss et al., (2004) found that blind participants performed comparably on a tactile Braille discrimination *N*-back task to sighted participants on a homologous visual letter *N*-back task. Concerning Digit Span assessments, our results are similar to those of Rokem & Ahissar (2009), who observed no difference in performance between blind and sighted individuals on the backwards subcomponent, although they did observe a performance enhancement for blind participants on the forward subcomponent. Castronovo & Delvenne (2013) and Pigeon & Marin-Lamellet (2015) meanwhile observed no difference in group performance on either the forward or backward subcomponent and Castronovo & Delvenne (2013) also failed to report group differences on a word span task. Similarly, Rokem et al., (2009) eliminated blind participants' enhanced performance on a word span task by controlling for individual participants' perceptual abilities (i.e., signal-to-noise perception ratios). Using a non-verbal task of pitch working memory, Wan et al. (2010) reported similar performance between blind and sighted participants, although they did note a slight performance enhancement for congenitally blind individuals compared to blind individuals who lost their sight later in life.

These results are in contrast to those reporting a significant advantage on similar tasks for blind participants as compared to sighted participants. Dormal et al., (2016) compared early blind, late blind and sighted controls on a complex letter span task with intervening pitch discrimination and observed significantly higher performance in the early blind group as compared to the late blind and sighted control groups. Arcos et al., (2002) used a similar complex letter span task with intervening math operations and similarly observed superior performance in blind participants compared to sighted controls. Arcos et al. (2022) and Loiotile et al. (2020) both demonstrated superior performance for blind participants on the forward and backward components of the Digit Span test, and Occelli et al. (2017) observed superior performance on the backwards component, but no difference on the forward component (note that this is the opposite result of Rokem et al. (2009), above).

What could potentially account for these mixed results? One potential explanation that has been proposed is that blind individuals have an advantage specifically for verbal materials and not a domain general memory enhancement, and thus only show an advantage for memory tasks involving verbal stimuli. When directly comparing performance on tasks assessing verbal, spatial and auditory abilities, including verbal, spatial and auditory memory, blind participants have been shown to only outperform sighted controls on verbal tasks (Arcos et al., 2022; Occelli et al., 2017). Blindness might confer a memory advantage specific to verbal materials due to blind individual's greater reliance on verbal and linguistic cues to extract information about the environment in their day-to-day lives and a greater reliance on linguistically encoded information retained in memory more generally (Arcos et al., 2022; Occelli et al., 2017). This could potentially account for the failure to observe a blindness-related advantage on memory tasks involving non-linguistic auditory material (i.e., Wan et al., (2010)), however it cannot account for the results obtained in our study, as both memory assessments used involved verbal materials, and many of the aforementioned studies also showing comparable performance between blind and sighted participants also involved verbal or linguistic information.

A more plausible explanation for the mixed results concerning the so-called performance enhancement for blind individuals on tasks measuring verbal working memory is that other factors associated with variability between individuals' working memory ability, such as age (Anders et al., 1972; Linden et al., 1994; Rypma & D'Esposito, 2000) and fluid intelligence (Engle et al., 1999; Shelton et al., 2010; Unsworth & Engle, 2005) may not be controlled for between groups. Working memory capacity has been demonstrated to decline with increasing age (Dobbs & Rule, 1989), indicating the importance of age-matching blind and sighted participants. In the case of our data, the average age of blind participants was 48 (median = 44, range = 33 - 65), whereas the mean age of sighted participants was 38 (median = 22, range = 18 - 73), although average age did not differ between groups ($p = 0.21$). We anticipated recruiting participants from older age groups and therefore included a screen for mild cognitive impairment (MOCA/MOCA-Blind), and all participants scored within normal range, however this does not rule out the possibility that age-related declines in working memory ability may mask any performance enhancements associated with blindness. Assessing intelligence of blind and sighted participants is also necessary, given that some aspects of intelligence, particularly fluid intelligence (Ackerman et al., 2002), have been shown to be closely related to working memory function. Another important factor to consider when comparing scores on tasks assessing verbal working memory between blind and sighted participants is that blind individuals have been shown to have better perceptual processing abilities, including those related to speech processing. For example, blind individuals outperform sighted individuals on speech-in-noise tasks (Muchnik et al., 2009; Niemeyer & Starlinger, 1981; Rokem & Ahissar, 2009). The importance of controlling for differences in perceptual processing skills is highlighted by the results of Rokem et al., (2009), who eliminated blind participants' advantage over sighted participants on a complex word span task by presenting stimuli at each individual participant's 80% speech-in-noise detection threshold. This is particularly important to consider when assessing verbal working memory skills within noisy environments, such as within an fMRI scanner. While a discrepancy in perceptual processing skills is not immediately relevant to our results, given that we did not observe group differences in verbal working memory performance, it could potentially account for the considerable discrepancy in the previous literature.

Another possible explanation for the comparable results obtained specifically on the Digit Span test is that blind participants may have been exhibiting ceiling effects. Each component (forward, backward, sequencing) of the Digit Span test has a maximum level of 8, i.e., the maximum span tested is 8 digits. Regarding the forward component specifically, five of the 11 blind participants reached a forward span of 8, whereas only two of the sighted participants reached a forward span of 8. Given that the normal range for forward digits is 6 +/- 1 (Peña-Casanova et al., 2009), this suggests that although group level average scores did not differ between groups, more blind participants than sighted participants were above normal range on the forward component. As well, because the test does not go beyond a span of 8 digits, we were unable to determine the true forward span maximum of almost half of the blind participants.

Taken together, the inconsistency in results concerning differences in blind and sighted individuals' verbal working memory abilities suggests that blindness does not impart a specific or universal advantage with regards to verbal working memory skills. Individual differences in verbal working memory in both blind and sighted individuals' verbal working memory scores could potentially be explained by other variables including age, intelligence, and perceptual processing skills. When these factors are properly controlled for, it may be that blind individuals' do show enhancements related to verbal working memory, suggesting that visual deprivation can impact this ability, potentially through practice-related effects due a greater reliance on linguistic information and memory in day-to-day life. It may also be that when other variables are controlled for, blind individuals perform comparably to sighted individuals on tasks assessing verbal working memory. Clearly, further work is necessary in order to isolate what, if any, effect blindness has on the development of verbal working memory capacity.

5.3.2 VERBAL WORKING MEMORY AND THE ROLE OF THE VISUAL CORTEX

In addition to working memory performance, we were specifically interested in determining whether the visual cortex is sensitive to verbal working memory load in early blind individuals. This work was motivated by previous demonstrations of visual cortex involvement during verbal memory tasks in people who are blind (Amedi et al., 2003; Park et al., 2011; Raz et al., 2005), but a lack of information regarding the potential involvement of the visual cortex in tasks assessing verbal working memory and how this may be related to verbal working memory function.

Our results indicated that early blind individuals, but not sighted controls, recruit the visual cortex during a verbal *N*-back task. Crucially, when verbal working memory demands were increased (as in the 2-back condition), we observed more widespread recruitment of the visual cortex, including the recruitment of the primary visual cortex, V1. In contrast, sighted participants showed increases in activation in the fronto-parietal working memory network as verbal working memory increased. These results replicate previous findings of visual cortex involvement during the 2-back level of a verbal *N*-back task in people who are blind (Park et al., 2011), and add to previous findings by also demonstrating visual cortex involvement at a less demanding level (1-back). As well, they complement previous findings of visual cortex involvement, including V1, during other types of verbal memory tasks, including long-term recall (Amedi et al., 2003) and episodic retrieval (Raz et al., 2005). Finally, they provide new insight into the involvement of the visual cortex in verbal working memory in people who are blind, by demonstrating that the visual cortex is sensitive to verbal working memory demands.

What does visual cortex activity in the blind during verbal working memory processing reflect? One suggestion is that visual cortex activation during verbal memory tasks is a reflection of auditory processing more generally, and not a reflection of memory processes, per se. This is unlikely given that the two verbal working memory conditions were equal in terms of auditory stimulation, however the TB condition resulted in more widespread recruitment of the visual cortex. As well, previous demonstrations of visual cortex involvement during verbal memory tasks indicate that the visual cortex is active in blind individuals during the covert retrieval of previously learned word lists, indicating activity is present even in the absence of any sensory stimulation (Amedi et al., 2003). Another suggestion is that the activity observed in the visual cortex during verbal memory tasks actually reflects the processing of the semantic content of stimuli, given that visual cortex activity has previously been associated with semantic processing (Amedi et al., 2003; H Burton et al., 2003), including in our own data, reported in Chapter 3. However, the semantic content of the OB and TB conditions was equal (i.e., each condition contained the same number of unique real words, and words within each condition were counterbalanced across participants), and again, visual cortex activity was more widespread in the TB condition. This is in line with previous work indicating that visual cortex activity is different across verbal memory conditions with comparable semantic content, indicating that activity is related to memory processes and not simply a reflection of semantic processing (Raz et al., 2005). Finally, it may be that visual cortex involvement is limited to working memory processes involving verbal material (Arcos et al., 2022; Occelli et al., 2017). While our data cannot speak to this specific point, given that we did not include non-verbal working memory tasks, previous work has found similar visual cortex recruitment in blind individuals for verbal working memory tasks involving verbal, auditory and spatial information (Park et al., 2011). Taken together, this suggests that the visual cortex in blind individuals is involved in the core aspects of working memory processing, across modalities.

We also observed more widespread activity of the visual cortex in blind participants during the TB condition, including the recruitment of V1, which suggests that the primary visual cortex is sensitive to verbal working memory load. In sighted individuals, there is evidence of increased activation in frontal-parietal working memory networks as working memory task demands increase (Braver et al., 1997; Höller-

Wallscheid et al., 2017; Owen et al., 2005; E. E. Smith et al., 1998; Wager & Smith, 2003). For example, incremental increases in working memory demands are associated with incremental increases in activation in the dorsal-lateral prefrontal cortex (DL-PFC) and posterior parietal cortex (Braver et al., 1997; Callicott et al., 1999). Tasks requiring executive processes (i.e., updating/manipulation of information, as in *N*-back tasks) typically result in more prefrontal cortex activity when compared to storage-only tasks (Wager & Smith, 2003). These working memory networks are typically left-lateralized (Reuter-Lorenz et al., 2000), but the additional recruitment of cross-hemisphere resources (bilaterality) has been associated with increases in working memory task demands (Höller-Wallscheid et al., 2017; Wager & Smith, 2003). This increased activation and recruitment of additional resources within frontal-parietal networks is thought to reflect a compensatory mechanism that is activated when a working memory task becomes sufficiently demanding (Höller-Wallscheid et al., 2017; Reuter-Lorenz & Cappell, 2008). In both blind and sighted participants, we observed increased activation and increased bilaterality in frontal-parietal networks for the TB condition, both compared to rest and compared to the OB condition, although for blind participants increased activation for the TB condition compared to the OB condition was limited to the parietal cortex.

Only blind participants demonstrated the additional recruitment of V1 as working memory demands increased. As such, in addition to demonstrating the typical effects of working memory load in frontal-parietal regions, our results demonstrate that blind individuals also uniquely recruit the primary visual cortex when verbal working memory demands increase.

It should be noted that the activity in V1 was observed when comparing blind individuals to sighted controls for the TB > Rest contrast, but a when comparing the TB condition to the OB condition directly (TB > OB), no difference in activation within V1, or elsewhere in the visual cortex, was observed. It's possible that differences in activation between working memory conditions do not arise until there's a substantial discrepancy in working memory load between them. Previous work demonstrating incremental increases in DLPFC activity in sighted individuals associated with incremental increases in working memory load included a 1-, 2- and 3-back levels of an *N*-back task (Braver et al., 1997). Here, if we had included an additional 3-back condition, we may have observed significant differences in activation in V1 associated with differences in lower vs. higher levels of working memory load. The relationship between V1 activity and verbal working memory load could also be evaluated with tasks that require more executive processes, including OSPAN or RSPAN. This latter suggestion could also shed light on whether V1 is primarily involved in the storage vs executive-processing aspects of verbal working memory. Our results indicate that V1 may be involved in the executive-processing aspects of verbal working memory, given that we only observed activity in V1 during the TB condition. The TB condition (and all *N*-back levels 2+) requires updating items in storage, shifting attention between items for comparison, inhibiting stimuli no longer required to be maintained in working memory storage and inhibiting responses for non-repeated stimuli (Jonides et al., 1997; Smith et al., 1998), and is thus considered to be a condition requiring more executive processes than a 1-level *N*-back, or storage-only tasks. However, specific comparisons between executive-load tasks and storage-load tasks are necessary in order to disambiguate the potential role of V1 in the different aspects of working memory.

5.3.3 THE RELATIONSHIP BETWEEN VERBAL WORKING MEMORY ABILITY AND THE VISUAL CORTEX

Chapter 4 presents the findings of an investigation into the relationship between behavioural measurements of verbal working memory ability and visual cortex activity associated with verbal working memory processing. This work was motivated by previous findings suggesting a relationship enhanced long-term and episodic verbal memory abilities and visual cortex recruitment in blind individuals such that blind individuals who demonstrate better verbal memory skills demonstrate increased visual cortex recruitment. However, there is a lack of information regarding the relationship between verbal *working* memory ability and visual cortex recruitment. While we did observe recruitment of the visual cortex associated with verbal working memory processing, we observed no relationship between behavioural performance on tasks assessing verbal working memory ability and the recruitment of the visual cortex.

We entered blind participants' accuracy on the *N*-back task as a within-group second-level covariate to test for a correlation between behavioural scores and signal change in the visual cortex for specific contrasts of interest (OB > Rest, TB > Rest, TB > OB). No relationship between *N*-back performance and visual cortex recruitment was observed, for any contrast. This is again not entirely unsurprising, given that blind participants performed comparably to sighted controls and sighted controls did not demonstrate visual cortex during verbal working memory processing. The lack of correlation between *N*-back scores and visual cortex recruitment could also potentially be related to task difficulty, or rather the lack thereof. The *N*-back task used here was only moderately challenging, and behavioural performance was high. Previous demonstrations of a correlation between *N*-back performance and activity within brain regions specialised for working memory (DLPFC) in sighted individuals included an additional 3-back level (Braver et al., 1997). Increasing task difficulty, by including an additional *N*-back level, or by using more complex span tasks such as OSPAN or RSPAN, could result in greater variability in behavioural performance and thus allow for a potential relationship between behavioural performance and visual cortex activity to be revealed.

We also entered blind participants' overall score on the Digit Span test (i.e., the combined score of the forward, backward and sequencing component) as a within group second-level covariate to test for a correlation between behavioural performance and signal change in the visual cortex for specific contrasts of interest (OB > Rest, TB > Rest, TB > OB). No relationship between behavioural scores and visual cortex recruitment was observed, for any contrast. This result is not entirely unsurprising, again given that blind participants performed comparably to sighted controls on the Digit Span test, and sighted participants did not demonstrate visual cortex involvement in verbal working memory processing. Previous demonstrations of a relationship between verbal memory abilities and visual cortex recruitment in blind individuals were specific to instances in which blind participants outperformed sighted controls on behavioural tests (Amedi et al., 2003; Raz et al., 2005). As well, it is worth noting that measurements of brain activity were taken only during the *N*-back task. Although the *N*-back and Digit Span tasks are both used to assess working memory, the Digit Span task (especially the forward component) is considered to be more of a reflection of the short-term storage component of working memory, whereas the *N*-back engages executive processes to a greater extent (Jonides et al., 1997; Smith et al., 1998). Thus, failing to see a correlation between behavioural scores and brain activity associated with tasks that are not identical in terms of their working load is also not entirely unsurprising. Finally, although some previous demonstrations of an association between verbal memory abilities and visual cortex recruitment have reported significant correlations between V1 activity associated with long-term retrieval and performance on standardised verbal memory assessments (Amedi et al., 2003), other work has only demonstrated a correlation between brain activity and measurements of verbal memory task performance taken during the fMRI scan (Raz et al., 2005). Thus, we considered it more likely that we would observe a correlation between *N*-back performance and brain activity within the visual cortex, and failing to do so, a correlation between Digit Span scores and visual cortex recruitment was unlikely.

Separate from explanations related to specifics of the experimental design, another important thing to consider when interpreting the results obtained here is that sample size can affect the detectability of brain–behaviour correlations in task-based fMRI data (Grady et al., 2020; Yarkoni, 2009). The data reported here comes from a small sample of 11 blind participants. Recent work by Grady et al., (2020) has investigated the effect of sample size on correlations between brain activity and task performance in a large data set of a working memory *N*-back task using both univariate and multivariate approaches. Grady et al., (2020) observed that low sample sizes can lead to both type I and type II errors, as well as inflated correlation values, consistent with similar work on simulated data (Cremers et al., 2017; Yarkoni, 2009). Regardless of approach (univariate or multivariate), typical fMRI sample sizes (20-30 participants, much larger than the sample here) are unlikely to be sufficient to demonstrate stable correlations in behavioural performance and brain activity (Grady et al., 2020). Given this, a much larger sample size is likely necessary in order to obtain a reliable estimation of the correlation between visual cortex activity and verbal working memory performance, if such a relationship does exist.

It's also worth mentioning that this is not the first instance of a lack of relationship between visual cortex activity associated with a high-level cognitive function and cognitive abilities in people who are blind. For instance, Crollen et al. (2019) and Kanjlia et al. (2016) reported visual cortex activity associated with mathematical processing in blind individuals, but neither demonstrated any difference between blind and sighted individuals in mathematical ability. Comparable performance on tests of mathematical abilities between blind and sighted individuals have also separately been reported by Kanjlia, Feigenson, et al. (2018) and Loiotile et al. (2020). This demonstrates that the recruitment of the visual cortex during cognitive tasks doesn't always translate to enhanced cognitive abilities. Further research is necessary to fully describe the relationship between verbal working abilities and the involvement of the visual cortex in verbal working memory processing.

5.4 COGNITIVE FUNCTIONS IN THE VISUAL CORTEX

The overarching goal of this dissertation was to better understand the functional specialisation of the visual cortex in blind individuals, particularly as it relates to cognition, including auditory language processing and memory. Here, we observed activity within the visual cortex of blind individuals associated with both linguistic and verbal working memory tasks. This functionality is suggested to develop due to input from higher-level cognitive networks during development (Bedny, 2017). Within this context, the visual cortex is considered to be “pluripotent”, or capable of supporting a range of cognitive functions (Bedny, 2017). Developmental constraints and long-range connectivity profiles ultimately drive the type of representation and processing that occurs within a cortical region (Bedny, 2017; Passingham et al., 2002). Our own data demonstrating an effective connection between the VWFA and the visual cortex provides direct evidence that visual cortex activity associated with linguistic processing can be explained by driving input from a typical language region. The extensive neuroplastic changes observed in individuals with developmental visual deprivation, including the involvement of the visual cortex cognitive processing, is therefore likely due to an unmasking of top-down inputs from existing cognitive networks.

Having established that the visual cortex is involved in a broad range of cognitive functions in blind individuals, it is also necessary to determine if cognitive functions are segregated or dissociable within visual regions. Our own data cannot speak to this point directly, as the activations we observed within the visual cortex associated with both linguistic processing and verbal working memory were broad, with local maximum within significant clusters typically found within V3, and both semantic processing and higher verbal working memory demands were associated with bilateral recruitment of the visual cortex. However, previous work by Abboud et al., (2009) has found distinct activations within visual regions associated with sentence-level semantics, verb generation, non-linguistic executive control, and long-term memory, seen in Figure 5.1, which suggests that some regions could be specialised for specific cognitive computations.

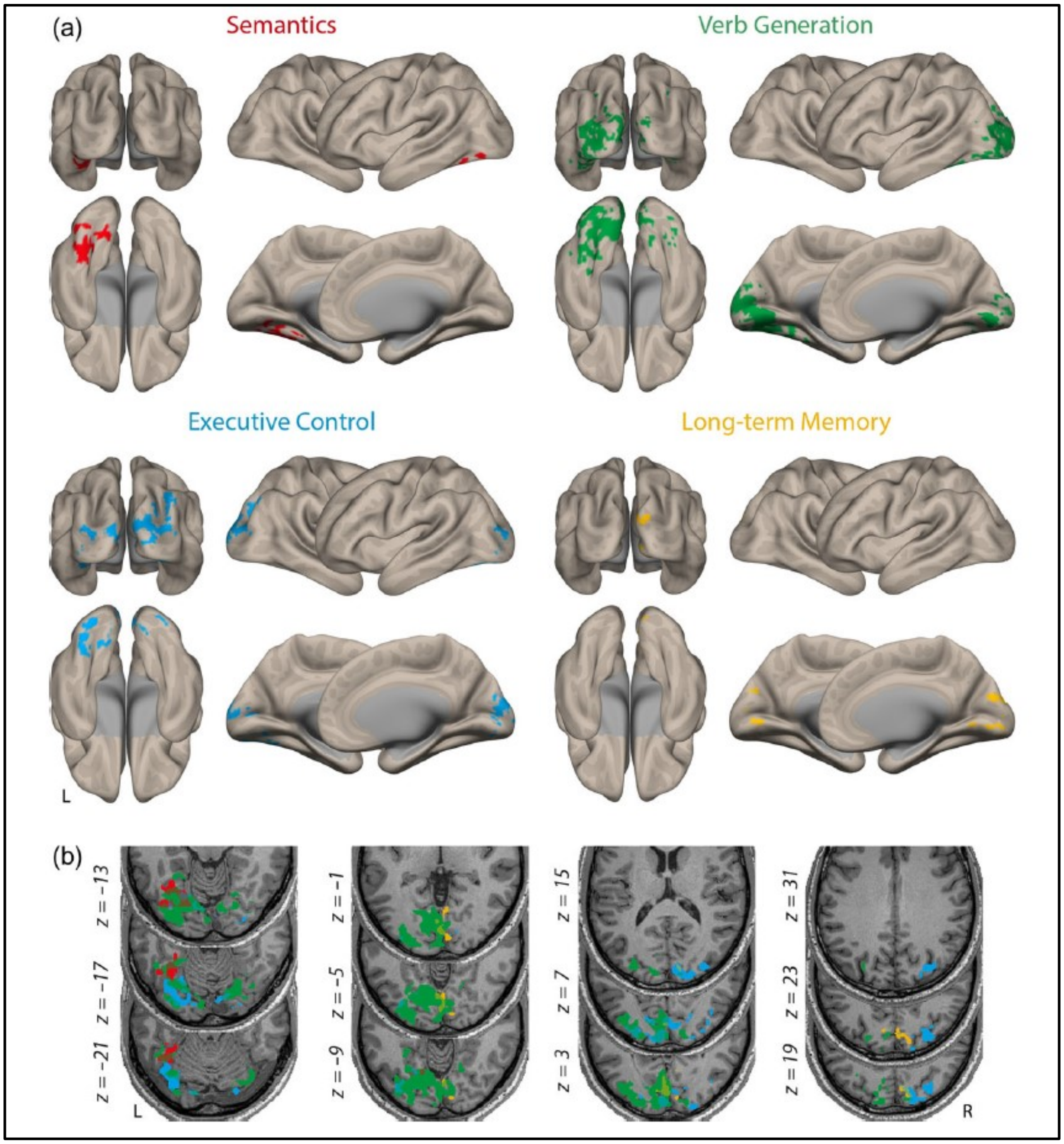

Figure 5.1: Visual cortex activations associated with semantics, verb-generation, executive control, and long-term memory, reprinted from (Abboud & Cohen, 2019)

Other work has demonstrated that the region within the right occipital lobe in blind individuals that is sensitive to non-linguistic response selection demands is not similarly activated by sentence processing or mathematical operations (Kanjlia et al., 2021). Crucially, visual regions that show cognitive task selectivity also demonstrate unique resting state functional connectivity profiles - i.e., language-related visual regions are functionally connected to language network regions (e.g. IFG), whereas executive control visual regions are functionally connected to regions in the fronto-parietal executive control network (e.g. prefrontal cortex), (Abboud & Cohen, 2019; Kanjlia et al., 2021). As such, task selectivity within the visual cortex seems to be driven by unique patterns of functional integration into existing cognitive networks.

It should also be noted that the cognitive functions associated with visual cortex activity are highly related in some instances. For example, the processing of sentences, particularly syntactically complex sentences, requires verbal working memory resources (Caplan & Waters, 1999b). The primary visual cortex in blind individuals has previously been shown to be sensitive to syntactic complexity, particularly syntactic movement (Lane et al., 2015), and our results demonstrate that the primary visual cortex is selectively recruited in blind individuals as verbal working memory demands increase. In sighted individuals, the processing of syntactic structure and working memory both occur within the LIFG, however syntactic structure selectively recruits the left pars opercularis, whereas working memory operations are performed by the left inferior frontal sulcus (Makuuchi et al., 2009). While these functions appear to be carried out by neuroanatomically distinct frontal regions, the regions are highly interconnected both functionally and anatomically (Makuuchi et al., 2009). Whether there is similar segregation of function within the visual cortex in blind individuals associated with the computational aspects of linguistic processing and the activations associated with increased working memory load has yet to be determined.

Finally, understanding the relative contribution of visual and non-visual regions to cognitive processing in blind individuals is an important open question. Blind individuals show typical activations within fronto-temporal and fronto-parietal cognitive task related networks but additionally recruit the visual cortex. How are functional roles distributed across cognitive networks that involve the visual cortex in blind individuals? Our data showed a shift towards visual cortex activation when verbal working memory demands increase, instead of the typical increase in activation within the fronto-parietal network observed in sighted participants. It's possible that in blind individuals, working memory resources are uniquely re-allocated to the visual cortex and the visual cortex may replace or supplement fronto-parietal regions as load increases. Further work is necessary to better understand the functional significance of visual cortex involvement in cognition in people who are blind, particularly how cognitive processes are distributed across reorganised functional networks.

5.5 LIMITATIONS AND CHALLENGES

The following sections deal with an examination of the limitations and challenges associated with the research described above, including a discussion of how sample size could affect the veracity and reliability of reported activations and subsequent DCM analysis.

5.5.1 SAMPLE SIZE

It is important to note the sample size of the studies presented in Chapters 3 & 4, specifically that the blind group had an *n* = 11 and the sighted control group had an *n* = 10. The issues with small sample sizes in research in general and in fMRI studies specifically has been discussed previously (Button et al., 2013; Cremers et al., 2017; Grady et al., 2020; Ioannidis, 2005; Lohmann et al., 2017; Turner et al., 2018). In general, low sample sizes in fMRI studies can result in insufficient or low statistical power (i.e., the ability to detect an effect, if one is present) and result in failure to detect small effects, the overestimation of effect sizes, reduce reproducibility of findings and reduce the chances of observing a significant correlation between behavioural responses and brain activity (Button et al., 2013; Cremers et al., 2017; Grady et al., 2020). This could potentially account for the lack of within-groups differences in our fMRI data that reached statistical significance, specifically with regards to within-group differences in activation associated with linguistic vs. perceptual processing in the blind group. As well, we did not observe a significant correlation between behavioural performance on tests of verbal working memory ability and brain activity in the visual cortex in blind participants. As discussed previously, low statistical power resulting from small sample sizes greatly reduces the chances of observing statistically significant brain-behaviour correlations (Cremers et al., 2017; Grady et al., 2020; Yarkoni, 2009).

Although our low sample size may have contributed to low statistical power, results converge with past published studies, bolstering our confidence in the veracity and reliability of the pattern of brain activity we report. We replicated effects documented previously in terms of the regions within the typical language network associated with speech processing in general and with semantic/phonological processing (Dzięgiel-Fivet et al., 2021; Friederici, 2011, 2012; Hagoort, 2005; Heim et al., 2005, 2009; Katzev et al., 2013; Planton et al., 2019; Qin et al., 2021; Tate et al., 2014), activations within the frontal-parietal network associated with working memory (Cabeza & Nyberg, 2000; Emch et al., 2019; Narayanan et al., 2005) and the consistently demonstrated effect in the visual cortex of blind individuals associated with linguistic processing (Amedi et al., 2003; Burton, Snyder, Diamond, et al., 2002; Ofan & Zohary, 2007; Bedny et al., 2011;

Burton et al., 2003; Noppeney et al., 2003; Deen et al., 2015; Röder et al., 2002; Lane et al., 2015; Pant et al., 2020).

Looking across the literature on visual cortex activation in blind individuals, these studies typically have small samples, due to the fact that fully blind individuals make up a small proportion of the general population, and this group must be further segmented, for example between early and late blind, as well as considering MRI inclusion criteria, age, cognitive status, and other factors. The consistency with which these studies demonstrate language-related activity within the visual cortex within small samples makes it unlikely that the activations we do report reflect spurious or unreplicable effects.

5.5.2 LIMITATIONS OF DCM

We were interested in how inter-regional interactions between visual cortical regions and regions within the typical left-lateralized frontotemporal language network can explain the observation of functionally significant visual cortex recruitment during speech processing in early blind individuals. We relied on the implementation of deterministic DCM, which is designed to test specific hypotheses about the underlying neuronal states that may give rise to experimentally observed brain responses and model data that comes from controlled external stimuli (Friston, 2009; Stephan et al., 2010). In deterministic DCM, regions are typically those that show an experimental effect, i.e., demonstrated task-related activity as determined by the general linear model (GLM) implemented in SPM (Seghier et al., 2010; Stephan et al., 2007, 2010). The activity within a region, as identified by an appropriate contrast, can then be explained by either one or many afferent connections with other regions of interest or by self-connectivity (Allen et al., 2008; Stephan et al., 2007).

However, this means that factors that can impact the detectability of an experimental effect as determined by GLM can ultimately affect the makeup of models that are evaluated using DCM. For example, low sample sizes can reduce statistical power and ultimately result in the failure to detect small but meaningful effects within a region (Cremers et al., 2017). If experimental effects within a region are not detected due to low statistical power, that region is not included as part of the network to be modelled and evaluated with DCM. Ultimately, this could potentially result in the failure to include regions within a modelled network that exert significant control with other regions of interest (Seghier et al., 2010; Stephan et al., 2007, 2010). Since each group in our study was relatively small (blind participants n =11, sighted controls n = 10), in order to increase statistical power, we chose to determine which regions within the typical language network to use as VOIs in the DCM analysis at a whole group level (n = 21). In this analysis, we observed significant activity associated with semantic and phonological processing in the IFG and VWFA, which is consistent with prior literature investigating the functional profile of those regions (Dzięgiel-Fivet et al., 2021; Friederici, 2011, 2012; Hagoort, 2005; Heim et al., 2005, 2009; Katzev et al., 2013; Planton et al., 2019; L. Qin et al., 2021; Tate et al., 2014). Given this, it is reasonable to conclude that these regions constitute crucial nodes with the network of brain regions supporting semantic and phonological processing. Thus, we are confident that the models ultimately tested can be considered simple but plausible explanations of the underlying neural states resulting in the observation of visual cortex activity during auditory language processing in blind individuals.

5.6 CONCLUSION

The purpose of the research reported here was to understand the nature of the involvement of visual cortical regions in cognitive processing in blind individuals, particularly language and memory, how the shift from perceptual to cognitive processing may occur and what, if any, impact this ultimately has on cognitive function and ability. The capacity for the visual cortex to process linguistic information has been suggested to be the result of input from the typical frontal-temporal language network. To that end, we demonstrate for the first time in blind individuals a direct modulatory connection between the VWFA and the visual cortex during linguistic processing, suggesting that activity in the visual cortex during linguistic processing can be indeed explained by driving input from the typical frontal-temporal language network. As well, we demonstrate evidence of visual cortex involvement in blind individuals associated with verbal working memory and demonstrate that the visual cortex is sensitive to verbal working memory load. However, visual cortex activity associated with verbal working memory in blind individuals was not associated with superior verbal working abilities, nor did it correlate with behavioural performance on verbal working memory tasks. Stemming from the current work, a critical line of questioning pertaining to the potential pathways of all levels of linguistic information into the visual cortex of blind individuals and how blindness onset could potentially impact the integration of the visual cortex into the existing language network in the brain has emerged. As well, it suggests that to understand the effect the marked reorganisation of cognitive networks in blind individuals may ultimately have on cognitive ability, careful consideration must be placed on task selection and task complexity. Collectively, this work represents an important step forward in understanding the flexibility of the human brain and the nature and extent of neural changes that can occur as the result of atypical developmental experience.

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