
Investigating the function of the ventral visual reading pathway and its involvement in acquired reading disorders

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Statement of originality

I declare that the work contained in this thesis is my own and conforms to the rules and guidelines set out for PhD theses by Imperial College London.

Abbreviations

ANOVA	Analysis of variance
aTL	Anterior temporal lobe
B ₀	Longitudinal magnetic field in the MRI scanner
BOLD	Blood-oxygen level dependent
COPE	Contrast of parameter estimate
Cpd	Cycles per (visual) degree
DG	¹⁴ C-2-deoxy- <i>d</i> -glucose
EC	Euler characteristic
EPI	Echo-planar image
EV	Explanatory variable
FEAT	fMRI Expert Analysis Tool
FFA	Fusiform face area
FLAME	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's Linear Image Registration Tool
FNIRT	FMRIB's Non-linear Image Registration Tool
fMRI	Functional magnetic resonance imaging
fMRI-RA	Functional magnetic resonance imaging – rapid adaptation
FMRIB	Oxford Centre for Functional Magnetic Resonance Imaging of the brain
FSL	FMRIB's Software Library
FWHM	Full width at half maximum
GA	Global alexia
GLM	General linear model
HA	Hemianopic alexia
HRF	Haemodynamic response function
HRP	Horseradish peroxidase
IFG	Inferior frontal gyrus
IPS	Intraparietal sulcus
ISI	Inter-stimulus interval
ITG	Inferior temporal gyrus
LCD	Local combination detector
LGN	Lateral geniculate nucleus

LVF/RH	Right hemisphere / left visual field
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
OKN	Optokinetic nystagmus
OVP	Optimal viewing position
PA	Pure alexia
PCA	Posterior cerebral artery
PET	Positron emission tomography
PPA	Parahippocampal place area
PPC	Posterior parietal cortex
RF	Radio frequency
RHH	Right homonymous hemianopia
ROI	Region of interest
RSVP	Rapid serial visual presentation
RVF/LH	Left hemisphere / right visual field
SF	Spatial frequency
SMA	Supplementary motor area
SMG	Supramarginal gyrus
STS	Superior temporal sulcus
T1	T1-weighted structural MRI scan
TE	Echo time
TR	Repetition time
V1	Primary visual cortex
V2, V4 etc.	Visual area V2, V4 etc.
vOT	Ventral occipitotemporal
VWFA	Visual Word Form Area
WLE	Word length effect

Table of contents

List of figures

List of tables

Abstract

1 Introduction

1.1 The visual input system for reading

- 1.1.1 From the eye to primary visual cortex
- 1.1.2 Left hemisphere dominance for reading
- 1.1.3 Word preferential activity in the left ventral visual stream: the case for the Visual Word Form Area
- 1.1.4 Alternative interpretations of the role of the left ventral occipitotemporal cortex in reading
- 1.1.5 Beyond the Visual Word Form Area

1.2 Reading disorders

- 1.2.1 The neurological basis of the peripheral alexias
- 1.2.2 Functional imaging studies of the peripheral alexias
- 1.2.3 Cognitive models of pure alexia
- 1.2.4 Treatment of acquired peripheral reading disorders

1.3 Aims and predictions

2 Methods

2.1 The Physics of Magnetic Resonance Imaging

- 2.1.1 The MRI scanner
- 2.1.2 Nuclear magnetic resonance
- 2.1.3 Spin-echo imaging sequences
- 2.1.4 Signal localisation
- 2.1.5 Echo planar imaging

2.2 The physiological basis of functional MRI

- 2.2.1 Neurovascular coupling
- 2.2.2 Blood-oxygen level dependent fMRI
- 2.2.3 Temporal and spatial specificity of the haemodynamic response

2.3 The Analysis of fMRI data

- 2.3.1 Experimental design
- 2.3.2 Preprocessing
- 2.3.3 Statistical analysis
- 2.3.4 Special considerations for analysing patient data

3 Results

- 3.1 Investigating the reading-related networks in healthy volunteers using narrative texts
- 3.2 Investigating the effect of sentence coherence in healthy volunteers
- 3.3 Evaluation of a novel technique for improving single word reading in patients with acquired reading disorders
- 3.4 Investigating the effects of reading training on the reading networks of patients with acquired reading disorders
- 3.5 Investigating whether perceptual features could cause lateralisation in the ventral visual stream

4 Discussion

Appendix FEAT design matrices

List of figures

Figure 1.1	Anatomy of the visual system
Figure 1.2	The Local Combination Detector Model
Figure 1.3	The connectionist 'triangle' model of reading
Figure 1.4	The posterior cerebral artery
Figure 2.1	The MRI scanner
Figure 2.2	The MRI gradient coils
Figure 3.1.1	Experimental stimuli
Figure 3.1.2	Contrast of reading versus false font
Figure 3.1.3	Contrasts of reading versus false font in the left and right visual hemifields
Figure 3.2.1	Main effect of stimulus type, words versus numbers
Figure 3.2.2	Contrast of reading sentences versus unconnected words and activity plots of lateral temporal and vOT ROI
Figure 3.3.1	Word reading speed as a function of word length
Figure 3.3.2	Lesion overlay map and lesion-symptom mapping
Figure 3.3.3	Word reading speed over time for trained and untrained words
Figure 3.4.1	Test-retest effects in patients and volunteers
Figure 3.4.2	Contrast of reading versus rest in healthy volunteers
Figure 3.4.3	Effect of reading three word sentences versus unconnected words in healthy volunteers
Figure 3.4.4	Contrast of reading-related activity in patients versus volunteers
Figure 3.5.1	Experimental stimuli
Figure 3.5.2	Functional localiser results
Figure 3.5.3	Contrasts of high and low spatial frequencies
Figure 3.5.4	Spatial frequency sensitivity mapping results

List of tables

Table 3.1.1	Eye-tracking data
Table 3.1.2	Region of interest data, reading and false font in the left and right visual hemifields
Table 3.3.1	Demographic information of participants with acquired peripheral reading disorders
Table 3.3.2	Behavioural neuropsychological assessment scores
Table 3.3.3	Reading ability comparison of patients and volunteers

Abstract

This thesis investigated the role of the left ventral occipitotemporal (vOT) cortex and how damage to this area causes peripheral reading disorders.

Functional magnetic resonance imaging (fMRI) studies in volunteers demonstrated that the left vOT is activated by written words over numbers or perceptually-matched baselines, irrespective of the word's location on the visual field. Mixed results were observed for the comparison of words versus false font stimuli. This response profile suggests that the left vOT is preferentially activated by words or word-like stimuli, due to either: (1) bottom-up specialisation for processing familiar word-forms; (2) top-down task-dependent modulation, or (3) a combination of the two. Further studies are proposed to discriminate between these possibilities.

Thirteen patients with left occipitotemporal damage participated in the rehabilitation and fMRI studies. The patients were impaired on word, text and letter reading. A structural analysis showed that damage to the left occipitotemporal white matter, in the vicinity of the inferior longitudinal fasciculus, was associated with slow word reading speed. The fMRI study showed that the patients had reduced activation of the bilateral posterior superior temporal sulci relative to controls. Activity in this area correlated with reading speed.

The efficacy of intensive whole-word recognition training was tested. Immediately after the training, trained words were read faster than untrained words, but the effects did not persist until the follow-up assessment. Hence, damage to the left vOT white matter impairs rapid whole-word recognition and is resistant to rehabilitation.

The final study investigated the role of spatial frequency (SF) in the lateralisation of vOT function. Lateralisation of high and low SF processing was demonstrated, concordant with the lateralisation for words and faces to the left and right vOT respectively. A perceptual basis for the organisation of vOT cortex might explain why left vOT damage is resistant to treatment.

1. Introduction

This thesis examines the neural networks involved in reading, using behavioural methods and functional neuroimaging of healthy volunteers and patients with a form of acquired reading disorder following left occipital focal injury.

This ease with which a skilled reader can read a paragraph of text belies the complexity of the cognitive processes involved. Attention has to be directed towards the text and maintained. Eye movements have to be carefully coordinated to allow sequential fixations across the line of text. Visual information from the left and right visual fields have to be integrated, and the integrated visual pattern has to be recognised as familiar letters and words, ignoring variation in luminance conditions, retinal locations, fonts or cases. Syntactic, phonological and semantic knowledge have to be accessed rapidly enough to allow text comprehension to occur in real time in order to influence future eye movements and predict forthcoming words.

In addition to improving our understanding of the brain, research into reading is critical for developing effective treatments for reading disorders. The processes that seem so effortless for a skilled reader are thrown into sharp relief when observing a child struggling to learn to read, or an adult who has lost the ability to read following brain injury.

Acquired reading disorders, or 'alexias', are most commonly caused by stroke but can occur as a result of other types of focal brain damage such as traumatic brain injury, brain tumours or arteriovenous malformation; or in the context of a neurodegenerative disorder such as posterior cortical atrophy. Acquired reading disorders can be classified into two broad types: central alexia, where the reading disorder is part of a generalised language disorder; or peripheral alexia, where the central ability to use and understand language is intact, but the ability to access it via the visual modality is lost (Shallice, 1988; Leff, 2004).

Peripheral alexia, the subject of this thesis, can be further sub-classified into a number of distinct disorders. The most common is hemianopic alexia (HA), where damage to the left occipital cortex causes a right homonymous hemianopia (RHH) – blindness in the right visual hemifield. This visual disturbance is tolerated surprisingly well, and in some cases the patient may not even be aware of it (Pambakian & Kennard, 1997). As well as an increased tendency to bump into objects on their right-hand side, the most common complaint of patients with an RHH is impaired reading speed, if the defect encroaches on right parafoveal vision and, especially, right foveal vision. Formal testing reveals spared letter and word reading ability, but slow text reading. This is mainly due to the difficulty that patients encounter in planning and executing reading saccades along the line of text, as upcoming words lie in the blind hemifield (Leff et al. 2000). The reading of individual words is mostly accurate, except for an occasional tendency to omit suffixes at the end of long words extending into the blind hemifield.

A second type of peripheral alexia is pure alexia (PA), which is a more severe reading disorder than HA. Like HA, it is normally caused by occlusion of the posterior cerebral artery, which supplies blood to the occipital lobe and medial temporal lobe. However, in PA the damage extends beyond the occipital lobe, towards the left ventral occipitotemporal cortex (vOT). Patients with pure alexia usually have an RHH plus additional problems with single word reading that cannot be accounted for by the field defect alone. Their reading speed on single word reading tests can be extremely slow, with some patients reported to take up to ten seconds to read a six-letter word (Cohen et al. 2004). Most notably, they exhibit a 'word length effect' (WLE) whereby reading speed increases monotonically with word length. The ability to spell and write words accurately indicates that the patient's word knowledge is intact, but the ability to access that knowledge from the visual modality is damaged. Letter reading is usually relatively spared, allowing the patient to resort to a 'reverse-spelling' strategy, whereby they read the constituent letters of the word sequentially, and combine them to form the whole word. This process is effortful and slow.

This thesis concentrates on cases of HA and PA, but three further types of the disorder have been documented. Global alexia (GA) is the most extreme version of peripheral alexia, where even single letter reading is impaired. Patients may experience GA immediately after their stroke or brain injury, but it tends to resolve spontaneously to a milder version of alexia. Attentional alexia and neglect alexia are caused by parietal or occipitoparietal damage and are characterised respectively by an inability to read words when flanked by distracting stimuli or other words, and an inability to direct attention to the whole word (Leff, 2004).

Peripheral reading disorders such as HA and PA have been intensively studied as a way of understanding the visual input system for reading and for investigating neural specialisation for reading. HA offers an insight into why coordinated activity in the left and right visual cortices is essential for efficient reading. Studying HA allows us to test hypotheses about the nature of the callosal transfer of visual information in the right occipital lobe to the left (language dominant) hemisphere. In PA, the occurrence of an isolated word recognition deficit strongly suggests that there are left-lateralised cortical areas or networks that are specialised (at least to some degree) for processing written words and not other visual stimuli. Over and above the theoretical motivations for studying peripheral reading disorders is a practical motivation: a good understanding of the disorder will allow more targeted interventions to improve reading ability.

The aims of this thesis are:

- (1) to address questions about the normal reading system that are key to understanding the nature of acquired reading disorders
- (2) to identify what reading disorders can tell us about the intact reading system
- (3) to test the efficacy of a reading training programme for patients with acquired reading disorders.

This introduction will review the literature on the neural networks involved in reading, paying particular attention to the visual input system and the

evidence for neural specialisation for reading. It will then outline models of how damage to the reading network causes HA and PA, and the types of reading intervention that have previously been used to treat these disorders.

1.1 The visual input system for reading

1.1.1 From the eye to primary visual cortex

A brief review of the anatomy of the visual system is required to understand how written words are processed.

As depicted in Figure 1.1, photoreceptors lining the surface of the retina are stimulated by light coming through the pupil from the opposite side of the visual field. Axons from the photoreceptors project through the optic nerve, via the optic chiasm and the optic tract to terminate (predominantly) in the lateral geniculate nucleus (LGN) of the thalamus. 'Hemidecussation' occurs at the optic chiasm, where axons from photoreceptors on the nasal half of both retinas decussate to join the optic tract of the opposite hemisphere. Axons from photoreceptors on the temporal half of both retinas do not decussate, but proceed to the optic tract of the ipsilateral hemisphere. Hence, axons that reach the left LGN represent the temporal half of the left eye and the nasal half of the right eye, both of which are stimulated by light from the right visual field; similarly the right LGN receives axons representing the left visual field.

In the LGN, the retinogeniculate axons synapse with geniculostriate neurons that proceed via the optic radiations to primary visual cortex (V1) within the banks of the calcarine sulcus. In this way, V1 of the left hemisphere receives inputs from the right visual field (RVF/LH), and V1 of the right hemisphere receives input from the left visual field (LVF/RH).

The spatial organisation of photoreceptors on the retina is preserved throughout the pathway from the retina to striate cortex. Methods such as single cell recording (e.g. Hubel & Weisel, 1968; Van Essen et al. 1984) and deoxyglucose (DG) mapping (e.g. Tootell et al. 1988) in non-human primates, and phase-encoded retinotopic mapping using fMRI in humans (Sereno et al. 1995; Tootell et al. 1998) have allowed detailed mapping of the retinotopic spatial organisation of neurons in primary visual cortex (see Figure 1.1b).

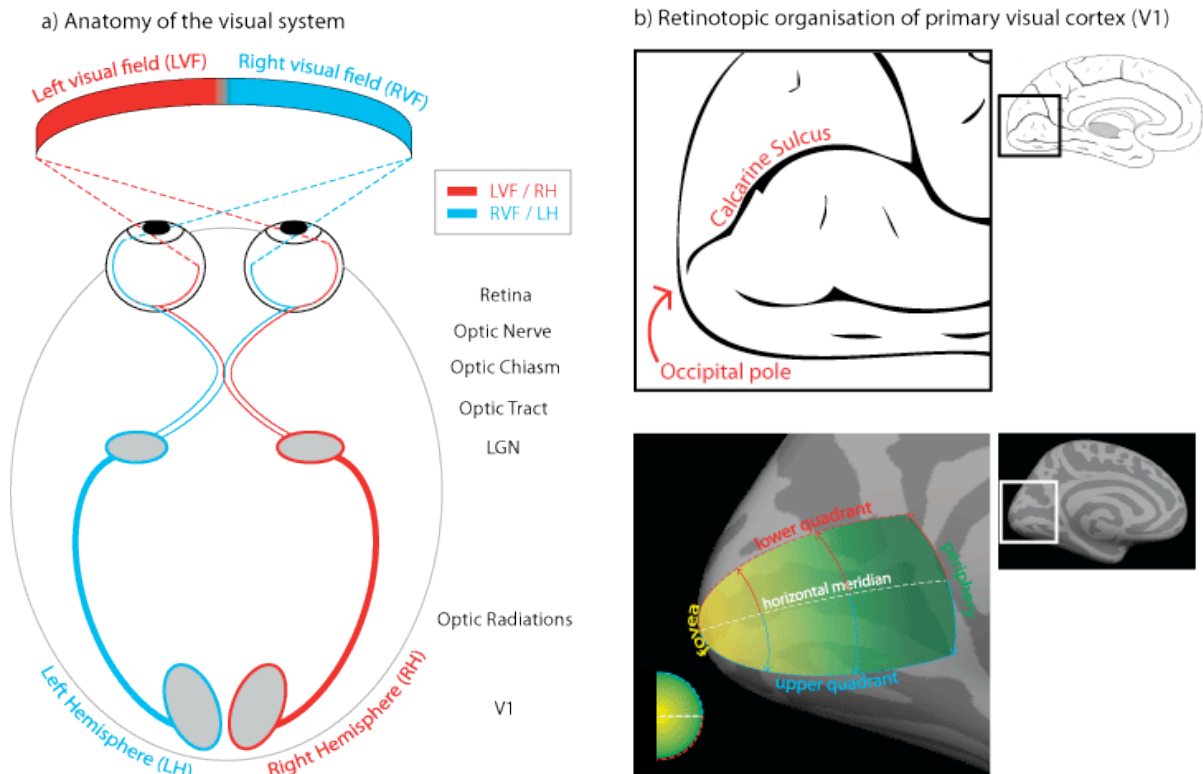


Figure 1.1. (a) Schematic diagram of the anatomy of the visual system, from retina to primary visual cortex (V1). (b) Upper panel depicts the location of the calcarine sulcus on the medial surface of the occipital lobe. Lower panel depicts the approximate retinotopic organisation of primary visual cortex along the banks of the calcarine sulcus on an inflated brain. Illustrations by Zoe Woodhead.

A contentious issue in the study of retinotopy in primary visual cortex is whether there is a clear division between the RVF/LH and the LVF/RH (the 'split fovea' theory); or whether there is an area of overlap along the vertical meridian of the visual field that is represented in both hemispheres (the 'bilateral projection' theory). This has clear implications for reading, as an overlap of just one visual degree would allow a single word to be initially represented in both hemispheres without the need for callosal transfer.

Early anatomical studies of non-human primates using horseradish peroxidase (HRP) to stain ganglion cells in the LGN showed that both left and right V1 contained a thin strip of cells along the vertical meridian that originated in the ipsilateral visual field, supporting the bilateral projection theory (Stone et al. 1973; Bunt & Minckler, 1977; Bunt et al. 1977). However, contradictory results were observed in studies using the DG method, whereby the monkey's eyes are stabilised, an infusion of DG is

given, visual stimuli are presented, and the visual cortex is sectioned to examine which areas were activated by the visual stimuli (Tootell et al. 1988). This (arguably more precise) method showed no evidence for a hemispheric overlap, suggesting that the results using HRP were either erroneous, or that the crossed fibres they identified play no functional role.

The occurrence of macular-sparing hemianopia – instances where unilateral damage to primary visual cortex results in blindness in the contralateral visual field, but sparing a one to four millimetre strip adjacent to the vertical meridian – has been cited as support for the bilateral projection theory (Huber, 1962). However, the observation that 36% of patients with unilateral V1 damage exhibit macular splitting hemianopia (Celesia et al. 1983) cannot be accounted for by the bilateral projection theory. It seems more parsimonious that the cases of macular-sparing hemianopia could be accounted for by the split-fovea theory, but with partial preservation of cortex in V1. Additional evidence in favour of the split fovea hypothesis comes from behavioural studies following commissurotomy (surgery to sever the corpus callosum in order to treat severe epilepsy). Fendrich and Gazzaniga (1989) showed that a commissurotomy patient was unable to perform a visual matching task when the two stimuli to be matched appeared in different visual hemifields, even if one of the stimuli appeared within one degree of the vertical meridian.

The evidence described above has led to the split fovea hypothesis being held as the prevailing view today (Lavidor & Walsh, 2004). This raises an interesting problem for models of written word processing: if a word is fixated centrally, the first half will be processed by primary visual cortex in the right hemisphere, and the second half by the left hemisphere. Information must be shared between the hemispheres via callosal transfer in order to form a unified percept of the whole word. Interhemispheric fibres from the right occipital cortex proceed via the splenium of the corpus callosum and along the forceps major to terminate in various locations in the left hemisphere visual association cortex (Damasio & Damasio, 1983; Schmahmann & Pandya, 2006). The question of how the information from

the two hemispheres is integrated in order for whole word perception to occur may be key to understanding the causes of, and potential treatments for, disorders like HA and PA.

1.1.2 Left hemisphere dominance for reading

Despite the fact that the initial visual processing of a word is shared by both hemispheres, patients with HA, who have damage restricted to unimodal visual cortex in the left occipital lobe, are able to read single words with a high level of accuracy and a relatively normal reading speed (Leff et al. 2006). By contrast, unilateral damage to the left vOT causes pure alexia (PA), a much more severe whole-word recognition deficit (Damasio & Damasio, 1983; Binder & Mohr, 1992; Cohen et al. 2003; Leff et al. 2006).

The importance of the left hemisphere for reading is very likely to be due to its dominance in language tasks, particularly for speech production. Studies have shown that ~95% of right-handed participants have left hemisphere language dominance, compared to ~70% of left-handed participants (Rasmussen & Milner, 1975; Knecht et al. 2000; Szaflarsky et al. 2002; Lindell, 2006). The remaining participants have either bilateral or right lateralized language dominance. The influence of language dominance on reading was confirmed by Cai and colleagues (2008), who observed that subjects with atypical right hemisphere dominance for speech production tasks also showed right-lateralized vOT cortex activations during reading.

Three assumptions can be drawn from observations of the symptoms exhibited by patients with HA or PA:

- 1) the mechanisms for integrating information from the left and right visual cortices can tolerate substantial unilateral damage to visual cortex (as in HA), perhaps through behavioural changes in eye movements
- 2) there is hemispheric asymmetry in word recognition processes: cortex in the language dominant hemisphere plays a critical role in word

recognition that, if damaged, cannot be compensated for by the non-language dominant hemisphere following damage

- 3) in order for word recognition to occur, visual processing of words presented to the LVF/RH, or the left half of centrally presented words, must be transmitted to the language dominant left hemisphere via callosal transfer.

These assumptions can be tested in behavioural studies of healthy controls; for example, by manipulating the location of stimulus presentation relative to fixation, words can be directed exclusively to the left or right visual fields. In this way, it is possible to test the relative reading abilities of the LVF/RH and the RVF/LH and the impact of callosal transfer on reading speed. This is normally achieved by asking participants to fixate on a central point and to present words to the left or right of fixation using presentation durations that are too brief to allow eye movements. Using this technique, experimenters have been able to compare reading speeds or lexical decision times for words presented to the LVF/RH and RVF/LH. Mishkin and Forgays (1952) first observed that RVF/LH words were read marginally (but significantly) more rapidly and accurately than LVF/RH words, a finding that was later explored in depth by Young and Ellis (1985). They found that, in addition to the main effect of hemifield, there was a hemifield by length interaction: reading speed increased monotonically with word length (known as the word length effect, or WLE) for words presented to the LVF, but not for words presented to the RVF (see also Ellis et al. 1988; Bub & Lewine, 1988).

The RVF advantage is afforded by the direct connection between the RVF and the left (language dominant) hemisphere. By comparison, words presented to the LVF incur a processing 'cost' due to the time taken to transfer information from the right visual cortex to the left hemisphere via the corpus callosum.

An alternative explanation for the RVF advantage, raised by Kirsner and Schwartz (1986), is that RVF presentation places the initial letters of the word in high acuity foveal vision. It is recognised that the initial letters of the

word tend to be the most informative, perhaps because of their temporal precedence in spoken language. The importance of initial letters has also been observed in priming studies, where the word 'judge', or letter transpositions such as 'jugde' will prime the target word 'COURT', but the word 'ujdge' will not (Perea & Lupker, 2003). Young and Ellis rejected the hypothesis of initial letter acuity on the basis that the RVF advantage was unaffected by letter size manipulations that kept the acuity of the initial letters constant across LVF and RVF conditions.

It has been suggested that the word length effect (WLE) observed during LVF reading indicates that callosal transfer of letter information occurs in a serial, rather than parallel, fashion, causing an incremental increase in reading speed per letter (Bub & Lewine, 1988). However, this cannot explain the complementary observation that plausible non-words ('pseudowords') presented in either visual field also incur a WLE (Young & Ellis, 1985). An alternative hypothesis, raised by Ellis and colleagues (2009) is that WLEs occur when letter identification and word recognition are separate, sequential processing stages: for example, when the two stages occur in opposite hemispheres (as is the case for the LVF/RH reading), or when a word is unknown. By comparison, when familiar words are presented to the RVF/LH, the letter and word processing stages "enter into a state of mutually interactive activation", driven as much by bottom-up letter identification as by top-down prior knowledge of orthographic forms.

Hemispheric asymmetry for reading has also been observed in the optimal viewing position (OVP) paradigm, where the position of a word relative to the fixation point is manipulated in order to identify the fixation point within a word that affords the optimal reading speed. Studies using this technique have shown that the OVP falls to the left of centre of a word (O'Regan et al. 1984; Nazir et al. 1992), with reading speeds increasing monotonically to the left or right of this position. Again, an asymmetrical effect has been observed, with a more severe cost for fixation positions towards the end of the word than towards the beginning of the word.

As noted by Brysbaert and Nazir (2005), the left-of-centre fixation bias may be caused by a number of factors, including visual acuity, informational load, reading direction and hemispheric asymmetry. Given that visual acuity decreases as a function of eccentricity (distance from fixation), the left-of-centre fixation may be designed to position the initial letters, which tend to be most informative for predicting the word (Shillcock et al. 2000; Perea & Lupker, 2003), in high-acuity vision. Alternatively, the bias may be reflective of the hemispheric asymmetry for word recognition, as leftward fixations mean that more letters are projected directly to the left hemisphere. To discriminate between these two possibilities, Brysbaert and colleagues (1996) compared the OVP for words with informative beginnings with that for words with informative endings, with the prediction that if fixation is directed towards the most informative part of the word, words with informative endings should be right-of-centre, the mirror image of the standard OVP finding. If the OVP is predicted solely by hemispheric dominance, it should be unaffected by the informational load. Surprisingly, neither hypothesis proved to be entirely correct: the OVP for words with informative endings was symmetrical, with no bias in either direction. This finding suggests that both factors, information bias and hemispheric dominance, influence fixation position simultaneously.

It has also been proposed that the OVP and RVF advantage could be due to reading direction. If this was the case, it would be predicted that native Hebrew speakers, who read in a right-to-left direction, would show a reversed OVP curve and a LVF (rather than RVF) advantage. However, the results in this field are mixed. Whilst Farid and Grainger (1996) showed that the OVP curve for Arabic readers is symmetrical, rather than having a bias towards one side of the word, Nazir and colleagues (2004) showed that Hebrew readers show a reversed OVP curve. Lavidor and colleagues (2002) showed that Hebrew readers show the same RVF advantage as English readers on a lexical decision task, whereas Nazir and colleagues (2004) found that they showed no advantage in either hemifield. It appears that perceptual learning can influence reading behaviour, but that, in certain

tasks at least, the effect of left hemispheric dominance can over-ride this influence (Brysbaert & Nazir, 2005).

Finally, data supporting the role of hemispheric asymmetry have been provided by Brysbaert (1994), who showed that participants with atypical, right hemisphere language dominance show a weakened initial-letter advantage than participants with left hemisphere language dominance (Brysbaert, 1994).

The studies of healthy volunteers reviewed here suggest some modifications to the assumptions drawn about HA and PA pathology. The relatively spared word recognition abilities of patients with HA demonstrate that the mechanisms of visual hemifield integration are flexible, and words can be read comfortably when presented entirely to one hemifield. However, behavioural studies in healthy volunteers have indicated that word presentation in the LVF/RH incurs a processing cost, and it should be anticipated that patients with HA will have slightly slower word reading speeds than normal, and slightly elevated WLEs.

The deficits observed in PA are due to asymmetric word-related processing in the left vOT cortex that cannot be compensated for by analogous regions of the right hemisphere. The behavioural studies described above have confirmed the importance of this lateralization, in its causal role in the determining the OVP, and the occurrence of WLEs. However, these studies have not been able to identify the nature of the word recognition specialization in the left hemisphere. To explore this issue further, we must turn to the extensive literature from functional neuroimaging.

1.1.3 Word preferential activity in the left ventral visual stream: the case for the Visual Word Form Area

The study of patients with PA has contributed greatly to our understanding of word processing in the brain. Lesion overlap studies have been used to identify the critical lesion site for PA, with the assumption that this area must

play a critical role in word recognition. These studies (which will be reviewed in detail in Section 1.2.1) have shown that the left ventral occipitotemporal cortex is the most common area of damage in patients with PA (Damasio & Damasio, 1983; Binder & Mohr, 1992; Cohen et al. 2003; Leff et al. 2006). Patients with hemianopic alexia (HA), by comparison, have occipital damage that does not extend towards the occipitotemporal junction. Patients with global alexia, who have deficits in letter recognition as well as word recognition, tend to have additional damage to more dorsal occipital cortex or to the splenium of the corpus callosum (Binder & Mohr, 1992).

In the early 1980s, ablation studies on non-human primates led to the conceptualisation of two visual 'streams' that process different properties of the visual scene in parallel (Ungerleider & Mishkin, 1982; Ungerleider & Haxby, 1994). The ventral stream, which runs from V1 via area V4 to the inferior temporal lobe, was conceptualised as a 'what' stream, processing the visual form and colour of a percept in high spatial resolution. Damage to the ventral stream in monkeys caused selective impairment on visual discrimination tasks (Gaffan et al. 1986). By comparison, the dorsal stream, from V1 via area V5/MT to posterior parietal cortex, was thought to be responsible for processing 'where' a stimulus was, and whether it was moving. Damage to the dorsal stream caused impairments in visuospatial tasks (Ungerleider & Mishkin, 1982). A later refinement of this model by Goodale and Milner (1992) proposed that, rather than a dissociation of 'what' versus 'where', these pathways were better described as underlying visual processing for perception (ventral) and for action (dorsal).

Within this conceptual framework, the occipitotemporal lesion site for PA belongs to the ventral visual stream of the left hemisphere: it is in the posterior fusiform gyrus, which runs along the ventral surface of the brain from the occipital lobe at its posterior extent to the anterior temporal lobe. It has been proposed that, while the ventral stream is responsible for perception of visual form in general, it contains areas that are specialised for processing certain categories of visual objects. Thus, damage to a localised area of the left posterior fusiform gyrus causes pure alexia and damage to

the analogous area in the right hemisphere, known as the fusiform face area (FFA, Kanwisher et al. 1997), causes prosopagnosia, an inability to recognise faces (Meadows et al. 1974; Damasio et al. 1982; Barton, 2008b). Other areas in this hypothetical 'category map' include the extrastriate body area (Downing et al. 2001) and the parahippocampal place area (Epstein & Kanwisher, 1998).

Evidence for word-specific processing in the left posterior fusiform gyrus of healthy control participants began to accumulate in the early 1990s. Positron emission tomography (PET) studies using radioactively-labelled water ($\text{H}_2^{[15]\text{O}}$) to demonstrate small changes in local blood flow during reading tasks showed stronger activation in this region for words or plausible non-words ('pseudowords', such as *tweal*) than for letter strings or false font stimuli (Petersen et al. 1990; Beauregard et al. 1997). Studies using surface-based electrodes in patients with medically intractable epilepsy identified locations in the posterior fusiform gyrus that showed strong negative deflections in the event related potential at 200ms post-stimulus onset (N200) for words but not checkerboards, faces or objects (Nobre et al. 1994). Some patients also showed face-preferential N200s at locations immediately lateral to the word-preferential recording sites. Nobre's study did not assess lateralisation directly, as they were unable to test symmetrical areas within the same patients, but there were indications from a later fMRI study suggested that the response was left-lateralised for words and bilateral for faces (Puce et al. 1996).

The case for a word-preferential area within the left posterior fusiform gyrus was cemented by a series of influential studies by Laurent Cohen and Stanislas Dehaene (Cohen et al. 2000; Cohen et al. 2002; Cohen et al. 2004). Using electroencephalography they showed a left lateralised N200 response for words, irrespective of the visual hemifield to which the word was presented (Cohen et al. 2000). They were able to accurately localise the source of this response to the left vOT using fMRI, and demonstrated that it was stronger for words than for consonant strings (Cohen et al. 2002). Activity in this region, which they named the Visual Word Form Area (VWFA),

was shown to be insensitive to variations in letter case (*UPPER* or *lower*), and as such they suggested that it was involved in processing abstract orthographic representations of words (Dehaene et al. 2001). A response in this region was seen even when words were presented very briefly and followed immediately with a visual mask to prevent conscious perception of the word, although the response was significantly weaker than that for words presented in the conventional manner (Dehaene et al. 2001).

Dehaene and colleagues (2005) summarised their interpretation of the VWFA's role within the ventral visual route for reading in the Local Combination Detector (LCD) model (Figure 1.2). This model proposes that groups of neurons in V1 and V2 encode simple bars and contours, and that this information is combined in V4 to activate representations of letter shapes that are specific to a particular location on the retina. These location-specific letter representations map directly onto a bank of abstract letter detectors in area V8, which lies immediately anterior to area V4 in the ventral occipitotemporal cortex (Hadjikhani et al. 1998). The letter detectors feed forward to a group of open bigram detectors in the left posterior occipitotemporal cortex, at coordinates equivalent to the proposed location of the VWFA (Jobard et al. 2003), and from there to quadrigram or small word units in the anterior left occipitotemporal cortex. In summary, this model predicts that word recognition is achieved by neural processing in a feed-forward hierarchy of regions with strictly localised functions. In 2007, the same group presented complementary fMRI data (Vinckier et al. 2007) that systematically compared activation for a range of stimuli that increased in lexicality: strings of false font characters, infrequent letters, frequent letters, bigrams, quadrigrams and whole words. They showed that the ventral visual stream exhibited a gradient of activation, which was general to all stimuli at the posterior end, and became more word-preferential as it progressed further forward. This strongly supported the notion of hierarchical processing proposed by the LCD model.

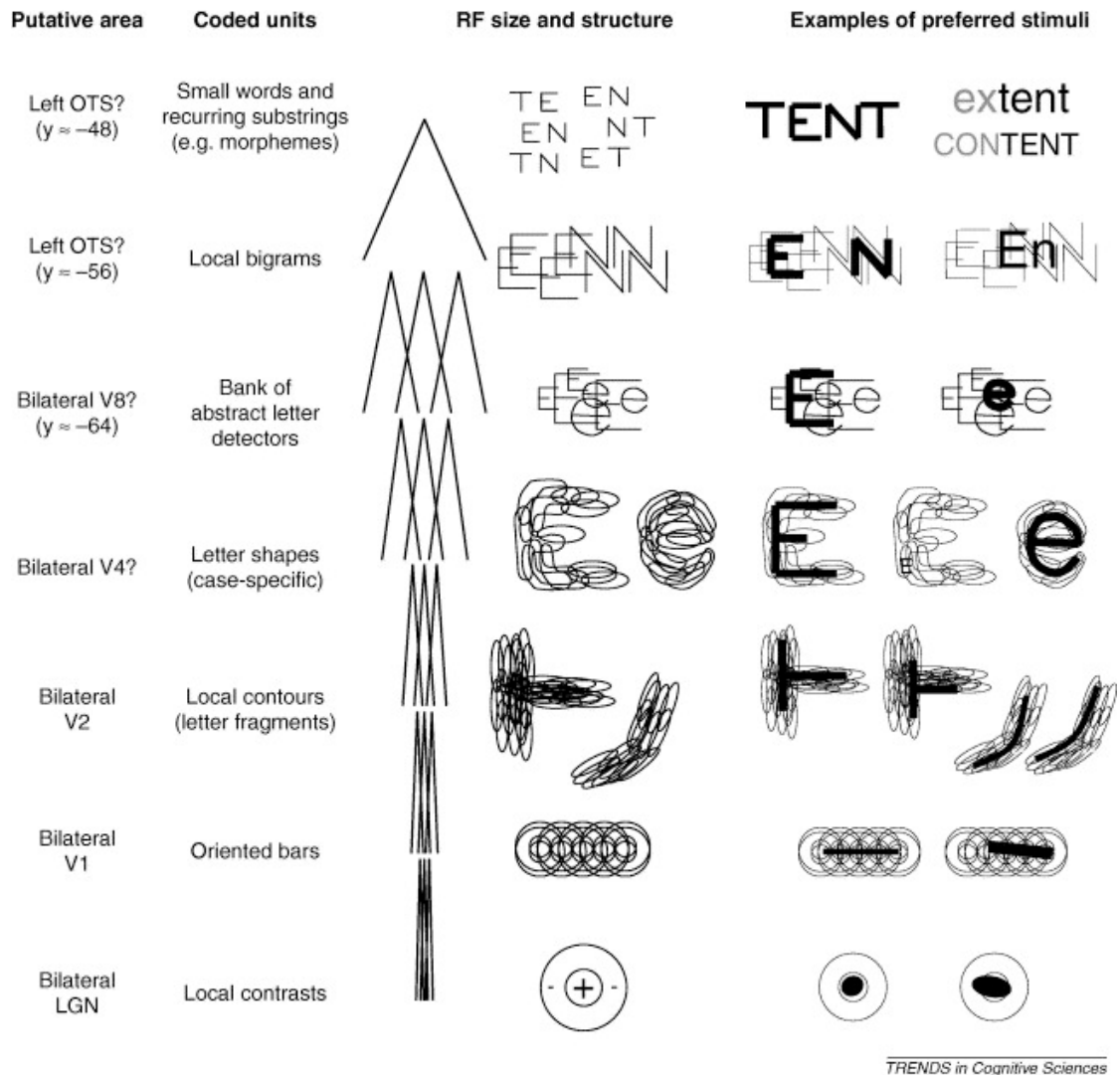


Figure 1.2. The Local Combination Detector Model of word recognition. Figure reproduced with permission from Dehaene S. Cohen L. Sigman M. Vinckier F. 2005. The neural code for written words: A proposal. *Trends Cogn Sci.* 9:335-341, courtesy of Elsevier.

Within this framework, other studies have focused on whether the VWFA stores representations of real words (i.e. an orthographic lexicon) or whether its role is pre-lexical. There appears to be evidence for both sides of the argument. A number of papers have reported that the VWFA is equally activated by real words and pseudowords, suggesting that it has a pre-lexical role (Petersen et al. 1990; Tagamets et al. 2000; Cohen et al. 2002). Similarly, Binder and colleagues (2006) showed that activation in the VWFA during presentation of pseudowords varied according to bigram frequency – i.e. the frequency with which letter pairings occur in real words – with stronger activation for more familiar bigrams. This suggests that processing in the VWFA becomes tuned to familiar sub-lexical forms through experience.

Contradictory evidence has been presented by Kronbichler and colleagues (2004), who showed a negative correlation between activity in the VWFA and lexical frequency – with the strongest activation for pseudowords, followed by low frequency words, then high frequency words. Evidence comes also from Devlin and colleagues (2006) using an fMRI rapid adaptation (fMRI-RA) paradigm. fMRI-RA is a priming technique, whereby a prime is presented very briefly (e.g. for 33ms), followed by a target word. It is known that if the prime and target are the same there will be a weaker blood-oxygen level dependent (BOLD) response to the target stimulus than if no prime (or an unrelated prime) had been used – this is known as repetition suppression. It is believed that repetition suppression occurs because the initial activation of neurons to the prime makes them respond more rapidly and efficiently to the target stimulus (Henson, 2003). Hence, fMRI-RA is used to detect whether the prime and target stimuli activate the same populations of neurons. Devlin and colleagues (2006) showed that although the VWFA showed strong repetition suppression for words, there was no repetition effect for pseudowords. This suggests that even though the overall activation of the VWFA for words and for pseudowords are similar, the neurons underlying these activations are different.

Glezer and colleagues (2009) took this work one step further, and found evidence for word-specific representations in the VWFA. They hypothesised that if activity in the VWFA is pre-lexical, it must contain assemblies of neurons that respond equally to stimuli with similar orthographic forms, so repetition suppression in these neuronal assemblies would occur for orthographically similar word pairs, irrespective of lexicality (such as *farm/form* and *soat/poat*). If the VWFA's role were lexical, neurons that responded to *farm* would not also respond to *form*, so there would be less repetition suppression for real words. Their results supported a lexical role for the VWFA – repetition priming was observed for repeated words and orthographically similar non-words, but not for orthographically similar words. This suggests that, through experience, assemblies of neurons in the VWFA become tightly tuned to familiar words.

In summary, there is strong evidence in favour of both lexical (Kronbichler et al. 2004; Devlin et al. 2006; Glezer et al. 2009) and pre-lexical (Petersen et al. 1990; Tagamets et al. 2000; Cohen et al. 2002; Binder et al. 2006) theories of VWFA function in reading. An attempt to reconcile these contradictory findings was made by Schurz and colleagues (2009). They argued that if the VWFA had a pre-lexical function, it would necessarily encode letter strings serially, as it would not have access to whole-word representations that support parallel letter recognition. Hence, it would show a WLE, with stronger activation for longer words. Conversely, if it has a lexical function, it would not show a WLE, but there would be a lexicality effect whereby activation would differ for words and non-words. In fact, their fMRI data showed an interaction in VWFA activity between word length and lexicality – there was no WLE for real words, but there was for pseudowords. They argued that the VWFA has a dual function, of pre-lexical, serial letter processing of non-words, and rapid whole-word recognition for familiar words.

1.1.4 Alternative interpretations of the role of the left ventral occipitotemporal cortex in reading

The conceptualisation of the VWFA as the seat of an orthographic lexicon has been attacked on a number of grounds. Firstly, it has been questioned whether activity in the VWFA is truly word-specific, or even word-preferential. In a review paper entitled 'The Myth of the Visual Word Form Area', Price and Devlin (2003) argued that this area of cortex is activated by various tasks that are unrelated to orthographic processing, such as "naming colours, naming pictures, reading Braille, repeating auditory words, and making manual action responses to pictures of meaningless objects". Studies by Moore and Price (1999) and Wright and colleagues (2008) failed to find reliable word-preferential activation in the VWFA when compared to object pictures.

A second pertinent question is whether word recognition is localised to a single cortical region or whether this process is distributed amongst multiple

regions. Price and Devlin (2003) maintained that it is impossible to ascribe word recognition processing to one region alone, but rather that this is achieved by the combined activity of a set of interacting regions. They propose that the changing connectivity of the network as a whole allows the cortex in the posterior fusiform gyrus to have varying functions depending on the task demands. For these reasons, they noted that the very name 'Visual Word Form Area' is misleading. In order to remain neutral on this point, this thesis will refer to this area according to its anatomical location, the left ventral occipitotemporal (vOT) cortex.

A number of studies have found evidence for this 'interactionist' view of left vOT function. Using an fMRI-RA protocol, Kherif and colleagues (2011) showed repetition suppression in the left vOT for prime-target pairs of written object names and object line drawings, indicating that the same assemblies of neurons that responded to words also responded to objects pictures. As the stimulus types had very different visual characteristics, they argued that this effect was driven by top-down connections from higher-order semantic or phonological areas back onto the left vOT. The fMRI-RA study by Devlin and colleagues (2006) demonstrated a similar effect. They showed that repetition suppression in the left vOT was modulated not only by orthographic similarity between the prime and target words, but also by phonological and semantic similarity. This implies that activity in the left vOT is not just affected by visual and lexical characteristics (that could reasonably be explained by the feedforward LCD model of word recognition), but by higher-order properties that are typically ascribed to the left temporal and inferior frontal lobes. In light of this, Devlin and colleagues reinterpreted the role of the left vOT as bridging orthographic processing in the ventral visual stream and phonological and semantic processing further forward in the brain. Orthographic processing in the left vOT is constrained by the parallel phonological and semantic processing in an interactive manner until activity in the network resolves onto a stable representation of the word. This process is not specific to words - it should be the same for any other visual object.

This description of word recognition as a domain-general, interactive process is similar to the connectionist 'triangle' model of reading developed by Plaut and colleagues (Seidenberg & McClelland, 1989; Plaut et al. 1996; Plaut, 1997; Patterson & Lambon-Ralph, 1999). As depicted in Figure 1.3, the model is represented as three interconnected domains of processing units. The orthographic, phonological and semantic domains in this triangle are connected via banks of hidden units. To perform a certain task (e.g. orthographic to phonological transformation for word naming), the patterns connect to the next domain via 'cooperative and competitive interactions among units....[which] are governed by weighted connections' (Plaut et al. 1996). There is no written word lexicon – rather, familiar words are represented by distributed activity across units in the three domains.

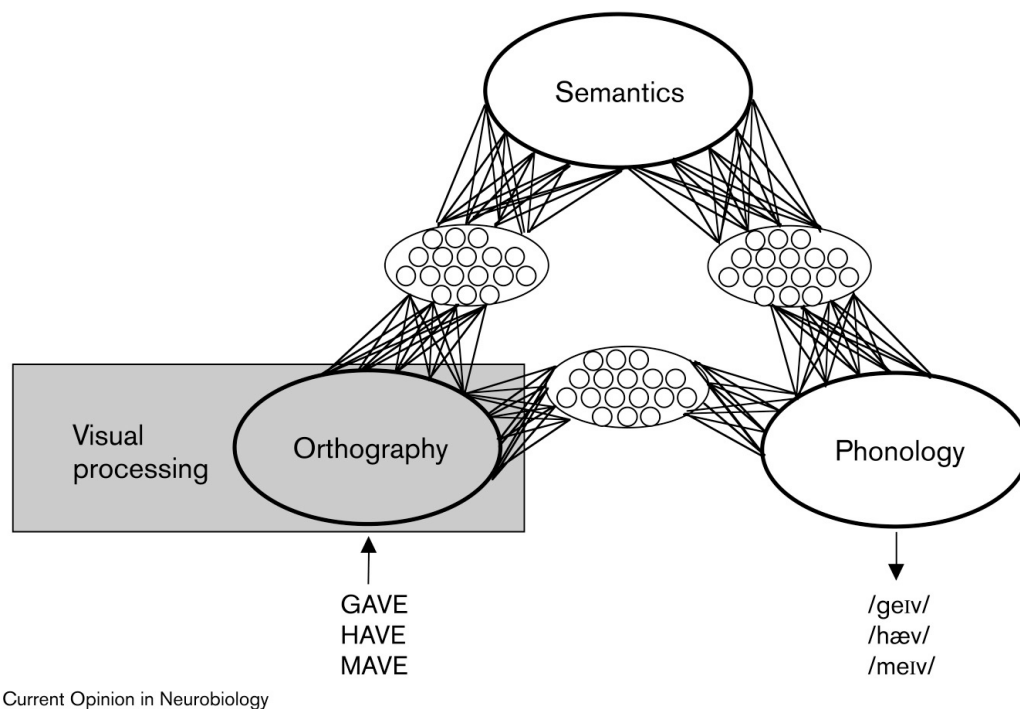


Figure 1.3. The connectionist 'triangle' model of reading by Plaut (1997) reproduced with permission from Patterson K. Lambon Ralph MA. 1999. Selective disorders of reading? Curr Op Neurobiol. 9:235-239, courtesy of Elsevier.

Orthographic experience modulates the connections between units in an interactive way, with back-propagation and attractor networks strengthening connection weightings that are used frequently. Hence, networks that represent words with higher lexical frequency will develop stronger connections due to more frequent activations. Similarly, words with high

orthographic similarity will activate partially overlapping networks, so that more common letter combinations will have stronger connections. Computer simulations of the model have shown that it can replicate classic effects of human reading performance, such as the observation that more frequent words or words with larger orthographic neighbourhoods are read faster.

Within this model, the left vOT is part of the orthographic domain, but its role is not functionally localised – it is heavily dependent on its functional connections. This model is able to explain the inverse relationship described by Kronbichler and colleagues (2004) between left vOT activity and lexical frequency. When a word is encountered, activity spreads through the orthographic domain and interacts with the phonological and semantic units. If the word has never been processed before, the activity will not resolve onto a stable network representing a familiar word, but will gradually dissipate. This will result in higher activation than that for a highly familiar word, which will rapidly engage the specific orthographic, phonological and semantic units associated with that word. The model also offers an explanation for why activity in the left vOT is modulated by semantic and phonological priming effects, as observed by Devlin and colleagues (2006). For example, for a semantically-related prime-target pair such as *flower/plant*, the network of semantic units that represent the prime will partially overlap with the semantic units for the target. Hence, presentation of the prime will facilitate activation to the target word, resulting in reduced activation. As the three domains operate interactively, facilitation in one domain will spread to facilitate activity in the other domains – so a smaller amount of repetition suppression is likely to be observed in both phonological and orthographic domains.

In such an interactive, distributed model of reading it is evident that top-down, context-dependent modulation has to be considered as well as bottom-up perceptual processing when interpreting findings from neuroimaging. This means that the choice of task in an experimental design is as important as the stimuli themselves. Some of the discrepancies between different studies of left vOT activation may be explained by

differences in task demands. For example, perceptual tasks such as the 1-back paradigm (e.g. Tagamets et al. 2000) or feature detection tasks (Binder et al. 2006) place a heavy emphasis on orthographic processing, and down-weight the interactions with the phonological and semantic domains. Conversely, overt naming tasks or lexical decision tasks (Devlin et al. 2006) may increase the influence of semantic or phonological modulation back onto the orthographic units. The influence of task demands on left vOT activity was tested by Starrfelt and Gerlach (2007). They used an fMRI design where both the type of stimulus (words or object pictures) and the task demands (colour decision or semantic decision) were varied. They showed that the left vOT was activated more strongly by the semantic task than the colour task. During the colour task, this area was more strongly activated by words than by objects, but there was no difference in the semantic task. This shows that the choice of task can determine whether the left vOT shows a stimulus-preferential response or not.

Reinke and colleagues (2008) present functional connectivity data that support this interactive view of the left vOT. They presented participants with words, strings of meaningful symbols (such as '????'), number strings, words in Hebrew script and simple geometric shapes. A 1-back task was used to maintain attention throughout the scan. A conventional fMRI subtraction analysis showed a response profile in the left vOT of Hebrew words > words / symbols > numbers, suggesting that the left vOT was not preferentially activated by words at all. However, they also analysed the data using a partial least squares approach, which identifies brain regions that are reliably co-activated by a particular condition in the experimental design. They showed that a left lateralised network of brain regions, including the vOT, the hippocampus, the lateral temporal lobe and prefrontal cortex, was uniquely co-activated during reading words and not by the other stimuli. Hence, although no single brain region showed reading-preferential activity, activity at the network level did.

In summary, there is considerable evidence for the view that word recognition is the result of activity over a distributed set of interactive

regions, and cannot be ascribed to one area alone. Within this network, the left vOT is involved in orthographic processing, but its function is domain-general and not specific to reading.

1.1.5 Beyond the Visual Word Form Area

Regardless of whether a distributed or localised view of word recognition is taken, it is clear that the ventral visual stream does not perform the entire act of reading in isolation – multiple areas of the brain operate together as reading networks. The following section presents a very abbreviated review of the roles that other regions may play in reading.

The first area under consideration is the dorsal visual stream. Although the ventral visual stream is optimised for the fine-acuity required for orthographic processing, the dorsal stream is also involved in reading. The dorsal stream runs from primary visual cortex via area V5 to posterior parietal cortex (PPC) and is involved in the visual control of action (Ungerleider & Mishkin, 1982; Goodale & Milner, 1992; Ungerleider & Haxby, 1994). The dorsal stream has been proposed to play a role in directing the spotlight of visual attention, by feeding back to primary visual cortex and forwards to the ventral visual stream to direct the more detailed visual analysis in this area (Vidyasagar, 1999). Furthermore, a deficit in dorsal visual stream activity has been implicated as a possible cause of developmental reading disorders (Vidyasagar & Pammer, 2010).

In a magnetoencephalography (MEG) study of reading, Pammer and colleagues (2006) showed that the right PPC is activated soon after word presentation (in the 100-300ms time window), consistent with the hypothesis that it is involved in pre-conscious direction of attention. This activity was stronger when words were presented in an unusual format, with letters located above or below the horizontal midline at random. Studies using fMRI have also shown dorsal stream involvement in reading when words are presented atypically, for example using “mIXed CaSe” presentation, “l e t t e r s p a c i n g”, vertical or angled word presentation

or presentation in the LVF (Mayall et al. 2001; Cohen et al. 2008). These manipulations are also known to cause an effect of word length on reading speed, indicating that they are not supported by the normal system of parallel letter encoding in the ventral visual stream. Vinckier and colleagues (2006) presented data from a patient with simultanagnosia following bilateral parietal atrophy. This patient performed well when reading words presented normally, but was severely impaired for atypical word presentations. Hence, the dorsal visual stream has been interpreted as playing a role in serial letter-by-letter reading in difficult reading conditions (Cohen et al. 2008).

In addition to the modality-specific visual areas of the brain, reading activates many modality-general language areas. The triangle model of reading places a particular emphasis on semantic and phonological processing. One influential opinion on semantic processing suggests that whilst modality-specific semantic knowledge is distributed across multiple brain regions, there is a modality-general semantic hub in the bilateral anterior temporal lobes (Patterson et al. 2007) – although this view is not without its detractors (e.g. Martin, 2007; Simmons et al. 2010). This view is supported by studies of patients with semantic dementia, the temporal lobe variant of frontotemporal dementia, which is characterised by a relatively isolated loss of semantic knowledge (Hodges & Patterson, 2007). Structural (Mummery et al. 2000) and functional (Nestor et al. 2006) imaging studies suggest that atrophy of the bilateral anterior temporal lobes causes semantic dementia. A recent analysis of the distribution of atrophy in patients with semantic dementia indicated that it is specifically pathology of the anterior fusiform gyrus that results in profound loss of semantic knowledge (Mion et al. 2010). The anterior temporal lobes are also observed in neuroimaging studies of semantic processing in healthy controls, but this literature is more variable, perhaps due to issues of fMRI susceptibility artefact in the ventral temporal lobes (Visser et al. 2010).

Metanalyses of functional imaging studies of language (Jobard et al. 2003; Vigneau et al. 2006; Binder et al. 2009) have also highlighted semantic processing in a left-lateralised network of regions including the middle and

inferior temporal gyri (MTG and ITG) extending back as far as the angular gyrus, and inferior frontal cortex extending back into pre-motor cortex. By comparison, phonological processing was localised to more superior areas of the lateral temporal lobes extending back into the supramarginal gyrus (SMG), and the pars opercularis of the inferior frontal gyrus (IFG). Pre-motor areas have also been shown to be involved in phonological tasks, and it has been proposed that this represents pre-articulatory motor activation (Price & Mechelli, 2005). Price and Mechelli (2005) propose a distinction in the IFG between anterior-ventral areas (lateral orbitofrontal cortex, pars orbitalis and pars triangularis) that are involved in semantic processing, and posterior-dorsal areas (pars opercularis and pre-motor cortex) that are involved in phonological processing.

1.2 Reading disorders

1.2.1 The neurological basis of the peripheral alexias

As described in the previous section, acquired peripheral deficits of word reading are usually caused by damage to the left vOT, which is critically involved in orthographic processing. This can be caused by any type of focal lesion, but it is most commonly due to cerebral infarction within the territory of the posterior cerebral artery (PCA). As shown in Figure 1.4, the PCA branches from the basilar artery on the ventral surface of the brainstem. It divides into multiple central branches that supply blood to parts of the thalamus including the LGN, plus cortical branches that supply the occipital and the ventromedial temporal lobes. The splenium of the corpus callosum lies on the border between the PCA and anterior cerebral artery territories and is sometimes involved in more extensive PCA lesions.

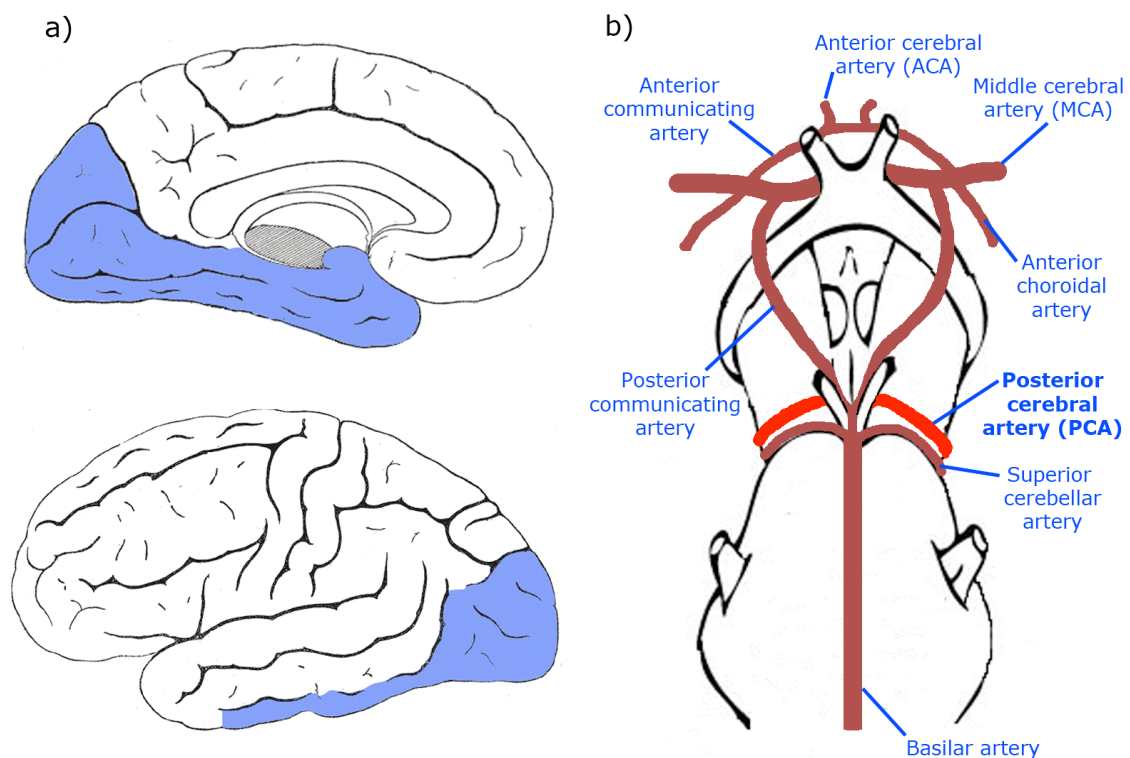


Figure 1.4. (a) Outline of the territory of the Posterior Cerebral Artery (PCA), encompassing the occipital and ventral temporal lobes. (b) Schematic drawing of the arterial vessels on the ventral surface of the brain stem including the PCA. Illustration by Zoe Woodhead.

The distribution of the cortical branches of the PCA explains why acquired peripheral reading disorders tend to be associated with visual field defects:

the branches which supply the fusiform gyrus (the anterior and posterior temporal arteries) are the first to divide from the PCA; the branches supplying the occipital lobe (the lateral and medial occipital arteries) are further downstream (Smith & Richardson, 1966; Leff et al. 2006). As such, if occlusion of the PCA affects blood supply to the fusiform gyrus, it will normally also affect the occipital lobe. However, PA can present with no visual field defect at all, particularly if the damage is caused by a primary cerebral haemorrhage or a non-vascular insult, such as a tumour or traumatic injury (Greenblatt et al. 1973; Leff et al. 2001). This implies that the relationship between the visual and word-recognition deficits observed in patients with PA is coincidental, not causal.

Damage that is restricted to the left occipital lobe or the optic radiations will result in a right homonymous hemianopia (RHH). If the hemianopia is macular splitting (i.e. affects the whole visual hemifield up to the vertical meridian) it can cause severe HA, where text reading is slow but word recognition is not substantially impaired. It has been inferred that this is because the commissural fibres from the right occipital cortex can still feed visual information to the ventral visual stream prior to the processing stage that is critical for word processing (Leff et al. 2006). Word reading is fast relative to patients with PA, but still slightly impaired relative to controls (Leff et al. 2001). As they are forced to use the LVF for reading, they show a small WLE due to the inter-hemispheric transfer from right to left occipital cortex (Ellis et al. 2009). Text reading is more dramatically impaired, because the RHH hinders their ability to make accurate saccades. They tend to fixate to the left of the OVP of each word, and have a higher frequency of 're-fixations' (fixating more than once on a single word) than normal readers (Leff et al. 2000; McDonald et al. 2006). Sparing of parafoveal vision within the blind right hemifield is sufficient to prevent HA.

Lesion overlap studies have shown that damage extending into the word processing areas of the left vOT cortex will result in the more severe disorder of PA (Damasio & Damasio, 1983; Binder & Mohr, 1992; Leff et al. 2006). When the left posterior fusiform gyrus is destroyed, word recognition cannot

occur in the normal manner even if the commissural fibres from the right occipital lobe to the left hemisphere remain intact. As a result, patients with PA have severely impaired single word reading, even for short words that can be read entirely within the fovea of the intact left visual field. Patients with very slow reading speeds have been known to rely on a letter-by-letter reading strategy, whereby individual letters are read and a reverse spelling procedure is employed to re-build the whole word (Shallice, 1988). As the central aspects of word semantics and phonology are preserved, patients with PA are still able to produce and understand speech, and to write and spell words as normal. For this reason, a distinction should be drawn between *alexia without agraphia* (i.e. a reading disorder without a spelling disorder as is the case in pure alexia) and *alexia with agraphia*, which normally indicates more extensive damage affecting the territory of the middle cerebral artery (Benson & Geschwind, 1969).

Reading disorders can be caused by damage to the interhemispheric fibres from the right occipital cortex, either in the splenium itself or portions of the forceps major. For example, global alexia (GA) may occur when there is damage to both the left occipital cortex and the interhemispheric white matter tracts. The left occipital damage prevents visual processing of the RVF/LH, and the white matter damage prevents visual information from the LVF/RH being communicated to the opposite hemisphere. This causes a visuo-verbal disconnection whereby even single letter naming is slow and inaccurate (Binder & Mohr, 1992).

A condition known as hemialexia can arise following partial commissurotomy for intractable epilepsy, or in stroke cases where the damage is restricted to the splenium or adjacent white matter tracts (Gazzaniga & Sperry, 1967; Benson & Geschwind, 1969; Cohen et al. 2003). As visual information cannot be communicated from the right occipital lobe to the language-dominant left hemisphere, this results in impaired reading ability when words are presented to the LVF/RH. This is another example of visuo-verbal disconnection. Interestingly, close examination using tachistoscopic presentation of words and objects in the LVF shows that some patients retain

certain reading abilities even when overt naming is abolished – for instance, they may be able to point at the object to which the word refers (Gazzaniga & Sperry, 1967). This suggests that although the left hemisphere connection is critical for verbal responses, the right hemisphere orthographic processing may be sufficient to support word recognition for non-verbal functions. The fact that hemialexia does not occur in all patients following disconnection of the splenium may be due to an increased rate of bilateral dominance for language functions in patients with life-long epilepsy (Benson & Geschwind, 1969). It is problematic inferring normal brain-function relationships from studies on patients whose cognitive architecture may have been altered by their epilepsy.

Deficits of colour vision have been shown to co-occur with PA or GA. The ventral visual stream is specialised for processing both visual form and colour. Cone photoreceptors on the retina (which are sensitive to different colours of the visual spectrum) project to the parvocellular laminae of the LGN, and thence to the colour sensitive 'blobs' of V1 in the striate cortex (Livingstone & Hubel, 1984). Colour processing proceeds through the ventral areas of the extrastriate cortex, with particular involvement of visual area V4 (Zeki, 1993; Zeki & Marini, 1998) and its connections to inferotemporal cortex. Damage to the occipitotemporal cortex in the vicinity of V4 can cause hemiachromatopsia – a complete loss of colour vision in the visual field contralateral to the lesion. Alternatively, left occipitotemporal damage plus damage to the splenium can prevent the transfer of colour information from the right hemisphere, causing a visuo-verbal disconnection that prevents the patient from naming colours, a condition known as colour anomia (Geschwind & Fusillo, 1966; Damasio & Damasio, 1983).

Finally, it should be noted that there are a small number of case studies that demonstrate the symptoms of pure alexia following damage to other areas of the left hemisphere than the left vOT cortex (e.g. Warrington & Shallice, 1980), or from right hemisphere damage. In most cases, this appears to arise due to atypical language lateralisation to the right hemisphere (Hirose et al. 1977; Winkelman & Glasson, 1984; Pillon et al. 1987). However,

Erkylvrawatr (1978) described a left handed patient with a right PCA territory lesion who showed left hemisphere dominance for speech production (using the Wada technique), but who demonstrated the classical signs of pure alexia. This case is an exception to the accepted visuo-verbal disconnection model of pure alexia, but is clearly in the minority when viewed in context of the total clinical literature.

1.2.2 Functional imaging studies of the peripheral alexias

There have been few reported studies of the consequences of peripheral alexia on functional activations during reading. Functional imaging studies have the potential to identify whether, following damage to the critical left ventral visual route, alternative routes to reading are brought to bear, and whether certain compensatory activations co-occur with reading rehabilitation or spontaneous recovery. If such compensatory routes were identified, this knowledge might be used to design ways of facilitating recovery through stimulation methods, such as transcranial magnetic stimulation (Miniussi et al. 2008).

A literature survey identified six functional imaging studies of patients with HA or PA, all using case reports (Cohen et al. 2004; Henry et al. 2005; Pyun et al. 2007; Ino et al. 2008) or case series with small numbers of patients (Leff et al. 2001; Cohen et al. 2003). The paucity of group studies in this field reflects how infrequently such cases arise. Functional imaging studies typically require between 12 and 20 participants, all with similar lesions and diagnoses in order to create a neurologically homogenous group.

Leff and colleagues (2001) presented data from a PET study of reading, comparing five alexic patients (four with HA and one with PA but no hemianopia) to control participants. Relative to the controls the HA group showed normal reading activations except for an unsurprising lack of activity in the (damaged) left occipital cortex. Activation was present in the left occipital cortex anterior to the lesioned area, which was attributed to the interhemispheric transfer of visual information from the right occipital lobe.

By comparison, the patient with PA showed intact visual responses in both hemispheres, but his left occipitotemporal damage prevented the visual activation from proceeding further forwards into higher-order areas of the left temporal lobe.

Cohen and colleagues (2003) reported an fMRI study of reading in healthy controls and three patients with acquired reading disorders: patients D, M and F. Patient D suffered inter-hemispheric disconnection due to a PCA lesion in the splenium and forceps major of the left hemisphere. As a result, he demonstrated the symptoms of hemialexia, with poor reading speed and accuracy for words presented in the LVF, but normal reading for words presented in the RVF. He did not experience any subjective impairment in his day-to-day reading ability. This was reflected in his fMRI data, where activations in the left ventral visual stream were normal for LVF words but absent for RVF words.

Patient M had a RHH caused by a left occipital PCA territory infarct. He exhibited the signs of HA, with accurate but slow text reading and relatively normal word reading. Similarly to the HA patients described by Leff and colleagues (2001), patient M had intact cortex in the left vOT region that was preferentially activated by words relative to consonant strings, despite the damage to left primary visual cortex. The authors inferred that the presence of word-preferential activity in this region explained Patient M's preserved word reading ability.

Patient F had a similar left PCA territory lesion to Patient M, but it extended further forward into the ventromedial temporal lobe. As a result, his word reading speed was considerably slower than Patient M, and he exhibited a more substantial effect of word length on reading speed. Curiously, the word-preferential activation in Patient F was displaced to the right vOT cortex. Additional activations for the contrast of words relative to consonant strings were observed in a bilateral fronto-parietal network including the IFG, dorsolateral prefrontal cortex and the left supramarginal gyrus.

Cohen and colleagues describe two functional imaging studies of patient CZ six months after surgical resection of a left occipital tumour (Cohen et al. 2004) and a follow-up report 8 months later (Henry et al. 2005). The operation removed the entire left striate cortex and part of the splenium of the corpus callosum, extending forwards into the ventral and medial temporal lobe. CZ was left with very slow word and letter reading, and a substantial WLE, while spoken language comprehension and expression were unimpaired. The patient resorted to a letter-by-letter reading strategy, as letter reading ability was largely spared. At the initial fMRI session CZ showed stronger activation than control subjects (for the contrast of reading words relative to consonant strings) in right occipital cortex, right parahippocampal gyrus and left pre-motor cortex, extending into the inferior frontal gyrus. Substantial activation of the right ventral visual stream was observed, which was significantly stronger than in the control participants. This area showed stronger activity for alphabetic strings than checkerboards, but with no preference for real words over consonant strings. The authors inferred that this region was involved in processing letter identity, and that whole-word recognition was achieved by transferring this information to the left hemisphere, where a fronto-parietal network effortfully re-constructed the word as a whole.

By the follow-up study eight months later (Henry et al. 2005), CZ showed improved (but still impaired) word reading and a reduced WLE. Comparing the contrast of alphabetic stimuli versus checkerboards at the two time points showed a general decrease in activity across most of the reading network, including the bilateral ventral visual streams and left hemisphere pre-motor cortex and intraparietal sulcus. Comparing the patient's activity to a group of healthy controls showed that the activation in the right ventral visual stream had returned to normal levels. Focal increases in activation between the two time points were restricted to the posterior portion of the left middle frontal gyrus and a small cluster in the anterior of the superior parietal lobule. Two explanations were suggested for the widespread decreases in activation: firstly, that as the patient became more proficient at reading there was less top-down attentional enhancement of visual

processing; or secondly, that longer reading latencies translate into increased activity simply because the orthographic processing takes longer (Price & Friston, 1997).

Pyun and colleagues (2007) described patient MH, who developed PA with an RHH following an intracerebral hemorrhage in the left occipitotemporal cortex. They performed fMRI at one month post-stroke and at a follow-up session around six months later. At the initial session patient MH exhibited the symptoms of GA, which resolved by the time of the second session to the point where he was able to perform letter-by-letter reading. Reading speed was not reported, but reading accuracy had improved from 27-81%. Interestingly, the functional imaging data showed increased activation of the right occipitotemporal cortex at the second session, along with additional bilateral activations of the frontal lobe and the SMG. This suggests that the patient's spontaneous recovery was due to recruitment of the right ventral visual stream for reading to compensate for the damage in the left hemisphere. The additional frontal activations may indicate the increased attentional and executive control required for letter-by-letter reading.

A similar picture was described by Ino and colleagues (2008). They reported a patient who suffered a haemorrhage in the left ventral occipitotemporal cortex following traumatic injury. The patient was scanned seven days after admission to the hospital, when he exhibited clear signs of PA and letter-by-letter reading, and again fifty days later when his reading ability had returned to normal levels. Comparing reading-related activation at the initial scan relative with the post-recovery scan identified significantly heightened activity in the right vOT cortex and a frontal network (comprising bilateral pre-motor cortex, bilateral IFG and the supplementary motor area (SMA)) that reduced as reading ability recovered. Conversely, stronger activation was observed at the post-recovery scan in the perilesional area of the left occipitotemporal cortex and the left superior parietal lobule.

These case studies provide rare insights into the effects of damage on the reading networks, but it should be noted that single-case reports are

anecdotal, and may not be representative of the wider patient population. There is also an issue of the statistical sensitivity of single case studies. However, some commonalities between cases can be identified. The studies by Leff et al. (2001) and Cohen et al. (2003) strongly support the hypothesis that patients with HA rather than PA have an intact pathway from the right occipital cortex to the left hemisphere language areas via the left vOT that is sufficient to allow rapid whole-word reading. These patients demonstrate visual activations in the right occipital cortex and word-preferential activations in the left vOT.

In all of the cases reported, damage to or disconnection of the left vOT resulted in impaired word reading ability. Ino and colleagues (2008) showed that spontaneous recovery of the word reading deficits (due to the cessation of the acute effects of haemorrhagic stroke) coincided with recovery of activity in the left vOT.

These studies offer some indications relating to the role of the right vOT cortex in reading disorders. In the patient reported by Pyun et al. (2007), *inactivation* of the right vOT was related to the presentation of GA, and recovery of function in this region was inferred to underlie improvements in letter reading ability. Similarly, Patient CZ (Cohen et al. 2004) showed activity in the right vOT that was preferential for alphabetic stimuli in general, but not for real words. This suggests that the right ventral visual stream can support letter reading, but not whole-word recognition. The only evidence against this hypothesis was the observation that Patient F (Cohen et al. 2003) showed stronger right vOT activity for words than alphabetic stimuli. However, this activity clearly did not support overt word naming, as his mean reading latencies were over two seconds per word, with a strong effect of word length. It would have been interesting to test whether these right hemisphere activations were sufficient to support covert reading abilities such as lexical decision.

These studies reliably showed an increase in fronto-parietal activations that appear to be associated with letter-by-letter reading. This network variously

comprised the inferior or middle frontal gyri extending into pre-motor cortex, and areas of the inferior or superior parietal lobules (Cohen et al. 2003; Cohen et al. 2004; Ino et al. 2008; Pyun et al. 2007). In patient CZ (Henry et al. 2005) this activity could be divided into areas that decreased as letter-by-letter proficiency increased (bilateral precentral gyrus, left IFG and intraparietal sulcus) and focal areas of increased activity (the posterior portion of the left middle frontal gyrus, and the anterior part of the superior parietal lobule). It is likely that these regions are involved in a combination phonological processing and attention control that are taxed by the effortful task of letter-by-letter reading. As described previously, phonological processing is generally localised to a left-lateralised network of pre-motor cortex, dorsal IFG and the SMG (Jobard et al. 2003; Price & Mechelli, 2005; Vigneau et al. 2006). The bilateral intraparietal sulci and superior frontal cortices are known to be part of a dorsal attention network that is involved in the control of goal-directed, voluntary attention (Corbetta & Shulman, 2002).

1.2.3 Cognitive models of pure alexia

Like the literature on normal reading, cognitive descriptions of pure alexia fall into two main categories: the domain-specific word form view, and the domain-general perceptual view. Those ascribing to the word form view hold that damage to the left vOT causes a domain-specific deficit in orthographic processing that prevents rapid recognition of whole words. Alternatively, the perceptual view proposes that patients with pure alexia have a domain-general deficit that is most evident during reading because of the particular balance of cognitive processes involved in reading relative to other visual tasks.

Cohen and colleagues (2003; 2004) are proponents of the word form view. They describe PA as being caused by damage or disconnection to the VWFA, which, according to the LCD model (Dehaene et al. 2005), houses representations of familiar letter combinations or whole words. This damage prevents recognition of whole words, forcing the patient to use a compensatory letter-by-letter strategy instead. Abstract letter identity can be

processed in the posterior ventral visual stream of either hemisphere and combined to form whole words using frontoparietal networks for phonological processing and executive control of attention. The WLE is accounted for by the serial nature of this letter-by-letter processing. The authors do not claim that the VWFA is only activated by words – it may well be the case that the VWFA contains neurons that process other visual objects. Rather, the modality-specificity of pure alexia reflects the left lateralised anatomical location of the orthographic lexicon. Whereas redundancy in the system means that most visual objects can be processed by left or right ventral visual streams interchangeably, the constraint of language lateralisation to the left hemisphere means that word recognition is restricted to the left vOT and damage to this area is necessary and sufficient to cause pure alexia.

In conflict with the word form view, a number of studies have demonstrated that patients with PA have a more general perceptual deficit that causes (as opposed to being a coincidental to) their word recognition deficit. Farah and Wallace (1991) demonstrated that patients with PA show larger WLEs when the stimuli are degraded by adding visual noise. According to the 'additive factors' logic (Sternberg, 1969) this interaction implies that the WLE is caused by a deficit at the same processing level that is affected by the visual noise – that is, that the WLE is caused by a deficit at an early, perceptual stage.

A number of alternative propositions have been raised regarding which perceptual process might be at fault in patients with PA. Farah (2004) and Kinsbourne and Warrington (1962) describe PA as a mild form of simultanagnosia – an inability to process multiple visual stimuli, such as the component letters of a word, in parallel. The simultanagnostic view is supported by data from Sekuler and Behrmann (1996), who demonstrated that a group of four patients with PA performed significantly worse than controls on tasks of 'perceptual fluency' - identifying multiple targets within a visual array. Interestingly, they performed poorly on this task even when numbers or shapes were used instead of letters. However, data from Starrfelt and colleagues (2009) conflicted with this view. Using brief

presentations and backward-masking to control exposure duration, they too demonstrated a domain-general perceptual impairment that affected both numbers and letters; however, the patients were impaired at naming single stimuli as well as identifying targets within arrays of multiple stimuli. The simultanagnostic view cannot account for a deficit in identifying isolated stimuli.

Behrmann and colleagues (Behrmann et al. 1998a; Behrmann et al. 1998b; Mycroft et al. 2009) proposed an alternative locus of the perceptual deficit in PA. They showed that patients with PA performed worse than controls on picture identification tasks (Behrmann et al. 1998a) and checkerboard matching tasks (Mycroft et al. 2009), and were more adversely affected by stimulus complexity than controls. They hypothesised that the deficit is due to an inability to perceive complex stimuli, perhaps due to poor visual acuity for high spatial frequencies.

A series of behavioural studies by Arguin and colleagues (Arguin et al. 2002; Arguin & Bub, 2005) shed more light on the nature of the perceptual deficit in PA. They demonstrated that, unlike healthy controls, patients with PA showed an effect of letter 'confusability' on word reading speed. Letter confusability is a measure of the visual similarity of a particular letter to other letters of the alphabet, and can be quantified as the probability that a normal participant will read a letter inaccurately. Letters like *L* and *I* both have high confusability ratings as they share features with a number of other letters, whereas *M* and *B* have low confusability ratings. Arguin and colleagues showed that patients with PA are better able to read words containing low confusability letters than high confusability letters. Furthermore, when the sum confusability rating of all of the letters in a word was matched across word with varying lengths, patients with PA no longer showed a WLE (Fiset et al. 2005; Fiset et al. 2006b). This suggests that parallel letter processing is fully functional in patients with PA, but can only be utilised when the letters are visually distinct and can be easily encoded. Interestingly, healthy volunteers have been shown to demonstrate a similar interaction of confusability and word length on reading speed when stimuli

were degraded by filtering out the high spatial frequency information (Fiset et al. 2006a).

As well as the issue of domain-specificity versus domain-generalizability, descriptions of PA differ in terms of whether they ascribe to a hierarchical or interactive model of word reading. As described previously, the LCD model describes reading as a hierarchical process, in which context PA is caused by damage at the level of the abstract orthographic processing of letter-strings or words. However, this cannot account for the frequently observed effects of lexical or semantic variables on reading ability. For example, some patients (but not all) exhibit the 'Saffran effect' – an ability to make accurate lexical or semantic decisions even when the words are presented too briefly to support overt naming (Shallice & Saffran, 1986; Coslett & Saffran, 1989). Similarly, it has been demonstrated that some patients with PA show a word superiority effect whereby they are quicker at identifying target letters presented within real words than within nonwords (Bub et al. 1989; Behrmann et al. 1998b). Effects of word frequency or imageability on reading speed have also been reported (Behrmann et al. 1998b).

Saffran and Coslett (1998) argued that the influence of higher-order effects on word recognition in patients with PA is due to the preserved functions of the right hemisphere. According to this model, both left and right hemispheres have access to visual word form and semantic systems, but the right hemisphere only supports implicit reading. Explicit reading requires access to the phonological system of the left hemisphere.

Behrmann and colleagues (1998b) proposed an alternative explanation for these findings, based on an interactive model of reading. They suggested that patients with PA suffer from a low-level perceptual deficit that effectively weakens activity in the orthographic processing system. This attenuated activity continues to spread throughout the reading network, causing weak activity in assemblies of neurons in higher-order areas that are compatible with the incomplete orthographic information. This higher-order activity will give rise to the semantic or lexical effects observed in patients with PA, even

in the absence of overt reading. A similar explanation has been raised by Patterson and Lambon-Ralph (1999), who couch the orthographic deficit in terms of the distributed triangle model of reading. Computational models of reading using this unthresholded, interactive approach are able to successfully simulate the behaviour of a low-level sensory impairment causing higher-order effects (Plaut et al. 1995; Mayall & Humphreys, 1996).

Behrmann and colleagues (1998b) argued that whilst Saffran and Coslett's right hemisphere model of reading may be plausible, the invocation of two symmetrical reading networks performing implicit and explicit processing separately is a less parsimonious account than having one left hemisphere network that performs both functions depending on the level of activation. Furthermore, if Saffran and Coslett are correct, it should be possible to demonstrate a dissociation between left and right hemisphere activation in explicit and implicit reading tasks – to my knowledge, this has not been described in the neuroimaging literature to date.

In summary, my preferred model of PA is that damage to the left vOT causes a domain-general, low-level perceptual deficit, perhaps related to high spatial frequency processing. Due to the visual characteristics of written words, letter recognition is particularly affected by this impairment, and the deficit prevents parallel letter encoding from occurring in the normal way. Number recognition is also impaired, but this deficit is less evident, perhaps because numbers are typically read in series rather than in parallel. Although the deficit is at an early level in the reading process, the interactive nature of the network means that the attenuated orthographic activity can spread to higher-order areas and in some patients may be sufficient to support implicit reading abilities such as lexical or semantic decision.

1.2.4 Treatment of acquired peripheral reading disorders

Reading rehabilitation aims to improve speed and accuracy of word and text reading. In order to result in a noticeable improvement in day-to-day reading ability, the treatment must either apply to a large corpus of trained words, or

generalise to novel, untrained items. Although there is no generally accepted method of rehabilitating peripheral reading disorders, a number of approaches have been tested with varying success. Rehabilitation approaches can be divided into restitutive therapies that aim to improve the damaged function, and compensatory therapies that aim to replace the damaged function with an alternative strategy. Rothi (1995) suggested that restitutive therapies are likely to work by strengthening the neuronal connections that underlie the original reading pathways and encouraging the use of perilesional cortex. For this reason they may be most effective if employed soon after the brain damage has occurred. Compensatory therapies are likely to use alternative neural routes to reading, therefore may have a longer time-window but are less likely to be as efficient as the original reading strategy.

Attempts have been made to ameliorate the hemianopic component of HA or PA using oculomotor training to restore efficient eye movement strategies during text reading. When reading a line of text, the patient's RHH prevents them from planning their next fixation target and as a result they tend to make small, cautious saccades with frequent re-fixations to correct errors (Leff et al. 2000; McDonald et al. 2006). Optokinetic nystagmus (OKN) training has been shown to help the patients adopt a more efficient eye movement strategy (Kerkhoff et al. 1992; Zihl et al. 1995; Spitzyna et al. 2007). In this approach, patients are trained to read text that scrolls smoothly from right-to-left across a screen. This movement induces a nystagmus, an involuntary saccade against the direction of the movement. Spitzyna and colleagues (2007) showed that following the training, the patients with HA made larger rightwards saccades in normal text reading, resulting in faster average reading speeds.

Whilst OKN therapy appears to be a promising form of rehabilitation for HA, it does not address the key word reading deficit of PA. A number of word reading rehabilitation case-studies have been described in the literature. Kinaesthetic reading – using the intact tactile modality as an alternative form of orthographic input – has been shown to be effective at improving word

reading speed and accuracy in a way that generalises to novel stimuli (Lott et al. 1994; Seki et al. 1995; Maher et al. 1998; Lott & Friedman, 1999; Sage et al. 2005). In this compensatory letter-by-letter reading approach, the patients are taught to trace out the words, either on the page or on the palm of their hand, so that the familiarity of the motor sequence cues word recognition. It has been suggested that this technique selectively engages the intact dorsal visual stream (which is involved in vision for action), thus bypassing the impaired ventral visual route (Farah, 2004). Interestingly, some patients adopt this strategy spontaneously during natural recovery (Benson & Geschwind, 1969). These methods have resulted in impressive improvements in reading speed, but the patient's kinaesthetic reading can only ever be as fast as their natural writing speed, which is approximately thirty words per minute in healthy adults. Hence, this type of training is only suitable for patients with reasonably severe PA, with word reading speeds in excess of two seconds per word.

Multiple Oral Reading (MOR) rehabilitation is perhaps the most widely used approach. This simple technique, devised by Moyer (1979), requires the patient to repeatedly read a single passage of text out loud over the course of a week. In some cases this has had the surprising effect of improving reading speed for novel texts as well as improving single word reading speed and accuracy (Beeson, 1998; Beeson et al. 2005). Two possible reasons have been proposed for the efficacy of MOR training: firstly, repeated presentation of the same words may strengthen orthographic processing in a bottom-up manner; or secondly, familiarity with the text may strengthen orthographic processing through top-down support from semantic areas (Moyer, 1979). By carefully controlling the texts used in training and testing, Lacey and colleagues (2010) showed that MOR training effects only generalised to novel texts if they shared a critical mass of the common words. This suggests that the efficacy of MOR training is because repeated presentation of words strengthens their orthographic representations and not because of top-down effects.

The word-specific effects of the MOR approach led to the hypothesis that patients may benefit from a training strategy that uses repetitive presentation of single words. This type of approach has not received a great deal of attention in the literature despite its simplicity. Some studies have attempted to enhance implicit word reading skills by training patients on covert lexical or semantic decision tasks, with mixed effects. Maher and colleagues (1998) reported that their patient could not tolerate the implicit training protocol and it was soon abandoned. Rothi and colleagues (1998) noted that the training improved performance on the decision task itself, but translated to a worsening of overt reading ability. Friedman and Lott (2000) describe a more successful approach whereby the patient showed improved reading speed, accuracy and a reduced word length effect after training with a semantic decision task.

Friedman and Lott (2000) posited that the success of their approach was, like the results of Lacey and colleagues (2010), due simply to the intensive, repetitive presentation of the same words. They tested this by devising a simple oral naming protocol, where the patient was shown briefly-presented (30ms) written words, which he read aloud, then received auditory feedback in the form of the correct spoken word. This training successfully improved reading accuracy, but unfortunately reading speed after the training was not reported. The training was more effective for functor words with high lexical frequency than for common nouns, and was least effective for pseudowords. The authors suggested that this frequency effect indicated that the training worked by strengthening the connections to the existing orthographic lexical representations in the left hemisphere.

In summary, the literature on the rehabilitation of peripheral reading disorders suggests that oculomotor training can be effective at improving text reading speed in patients with HA, and compensatory reading strategies such as kinaesthetic reading can be effective at improving reading speed and accuracy for patient with severe forms of PA. What is less obvious is how patients with a milder single word reading deficit can be treated. The studies by Friedman and Lott (2000) and Lacey and colleagues (2010) suggest that

intensive, repetitive training of single word naming may be effective at improving reading ability by strengthening the orthographic input system, although training effects may be item-specific.

1.3 Aims and predictions

As stated previously, this thesis has three overarching aims, which can now be considered in more detail:

- (1) to address questions about the normal reading system that are key to understanding the nature of acquired reading disorders

Specifically, this thesis will address questions relating to the role of the left vOT cortex in reading in healthy volunteers: does it support domain-specific 'word form' processing, or is its role more likely to be domain-general? Is the orthographic processing in the left vOT localised or distributed? And finally, does the orthographic processing in the left vOT cortex occur in a feedforward manner as predicted by the LCD model (Dehaene et al. 2005) or does it occur interactively?

These questions are addressed in Results Chapter 3.1, which investigated whether a left-lateralised word-preferential response was observed in the vOT cortex, and secondly whether this system was also activated by numbers or by visually-matched false font stimuli. Additionally, this study explored the effects of stimulus presentation to the left or right visual fields, to gain an insight into how callosal transfer of information from the right hemisphere visual cortex to the left hemisphere verbal areas may occur in patients with an RHH.

Results Chapter 3.2 aimed to replicate the findings of Chapter 3.1 using central rather than parafoveal presentation, and using more closely matched reading and number processing conditions. It also examined how the higher-order semantic processes involved in sentence reading affects activity in the reading network.

Finally, results Chapter 3.5 investigated whether the word-preferentiality apparent in the left vOT might be driven by the low-level perceptual characteristics of written words (namely high spatial frequency) rather than

higher-order properties such as lexicality. High spatial frequency perception has been proposed by Fiset and colleagues (2006a) and Mycroft and colleagues (2009) as a potential locus of the perceptual deficit in patients with PA. If this prediction is correct, it should be possible to observe preferential activity in the left vOT for high rather than low spatial frequency stimuli. This was tested in Chapter 3.5 by mapping vOT activity in response to simple sine-wave gratings varying in spatial frequency.

- (2) to identify what reading disorders can tell us about the intact reading system

Results Chapter 3.3 investigated the behavioural effects of structural damage to the left vOT cortex, in order to better understand its role in orthographic processing. It was predicted that PA is caused by damage to the left vOT or the white matter tracts connecting the left and right occipital cortices. The behavioural effects of PA were predicted to be a deficit in word reading speed and accuracy, with a significant WLE on reading speed, and a corresponding deficit in text reading ability. The results from Starrfelt and colleagues (2009) predict that patients with PA will also demonstrate a substantial deficit in letter reading ability.

The literature reviewed above demonstrates a paucity of functional imaging studies of patients with HA or PA. Results Chapter 3.4 presents an fMRI study of eleven patients with mild PA, aimed at investigating how damage to the left vOT disrupts the normal reading networks, and identifying whether any compensatory networks are activated instead. An attempt was made to test whether activity in key regions such as the perilesional cortex of the left vOT, the symmetrical region in the right vOT or the alternative dorsal visual route to reading predicted reading ability.

- (3) to test the efficacy of a reading training programme for patients with acquired reading disorders.

The results of Friedman and Lott (2000) and Lacey and colleagues (2010) suggest that intensive, repetitive whole-word reading training may be effective at improving word reading ability in patients with PA. However, these studies reported case-study results from one and two patients respectively – clearly a larger group study is required to make valid inferences. Chapter 3.3 presents the results of a pilot study of twelve patients that tested whether intensive word reading training can improve reading speed in patients with mild-to-moderate acquired peripheral reading disorders. A computer-based rehabilitation programme was employed, using repetitive presentation of written words, presented simultaneously with their spoken forms. Brief presentation latencies were used to prevent a letter-by-letter reading strategy and to increase reliance on whole-word recognition. The behavioural results of this training programme are reported in Results Chapter 3.3.

If improvements in whole-word recognition after intensive training are possible, it will be very informative to investigate which areas underlie these changes – can the perilesional cortex in the left vOT be recruited, or are compensatory activations observed in the dorsal visual streams or the right vOT? These questions are explored in Chapter 3.4 by comparing fMRI activations during reading before and after rehabilitation.

2. Methods

2.1. The physics of Magnetic Resonance Imaging

2.1.1. The MRI scanner

A Magnetic Resonance Imaging (MRI) scanner has four essential components, as depicted in Figure 2.1:

- a high field strength, superconducting electromagnet
- radio-frequency transmitter and receiver coils (a single coil usually performs both functions)
- a set of gradient coils
- a set of shimming coils.

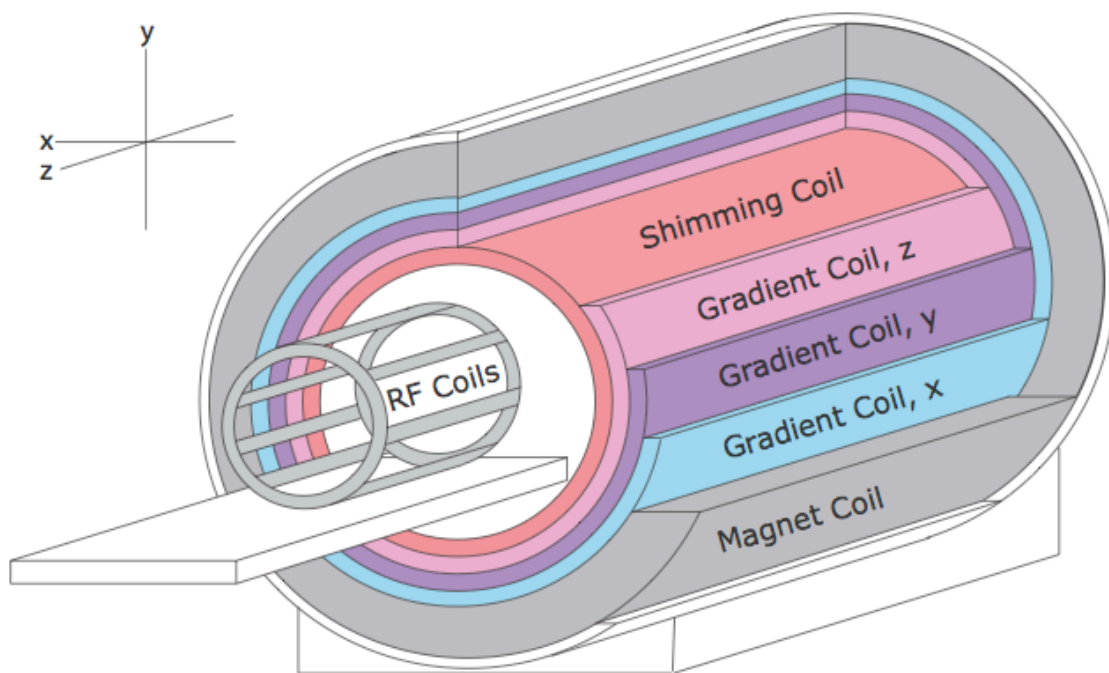


Figure 2.1. Cut-away diagram of the different parts of the MRI scanner.

The main magnetic field is supplied by the superconducting electromagnet in the bore of the scanner. This field is known as the B_0 , and is aligned with the z-axis or 'longitudinal' plane of the scanner. The magnet is a coil immersed in liquid helium to cool it to near absolute zero, so that there is minimal electrical resistance, meaning that a strong electric current can be maintained with minimal power requirements.

The radio-frequency coils are aligned orthogonally to the B_0 field, in the x-y or 'transverse' plane. They are responsible for transmitting pulses of radio frequency (RF) energy at the resonant frequency of protons in the tissue, which absorb the energy. When the pulse ceases, the tissue re-emits the RF energy, and the RF coils receive this signal. Specialised arrays of RF coils with overlapping fields are used for functional or structural MRI of the brain to provide good coverage of the whole head.

Gradient coils are used to localise the MR signal. Three sets of gradient coils are used to modify the strength of the B_0 field linearly over x, y and z dimensions. For example, in the z-axis, a pair of conducting loops are arranged to make the B_0 field stronger at one end of the bore and weaker at the other end. In the centre of the bore, the gradient field will be zero and the B_0 field will be its normal strength. By modifying the three sets of gradient coils rapidly over the course of a scanning sequence, slices through the brain can be targeted sequentially, and the source of the signal emitted from the brain can be identified.

The final essential components of the MRI scanner are the shimming coils. Shimming coils are used to adjust the magnetic fields to correct for any inhomogeneities in the main magnetic field, such as the distortions caused by the participant's head in the scanner. The shimming coils produce additional fields to bring the main field as close to being homogenous across the field of view as possible.

2.1.2. Nuclear magnetic resonance

Hydrogen ions are present in abundance in human tissue, for example in water and in hydrocarbon molecules. A hydrogen ion consists of a lone proton in the nucleus and no orbiting electron. A proton carries a very small positive electrical charge, equivalent to 1.6×10^{-19} coulombs. All isotopes with odd numbers of nucleons (protons or neutrons), including hydrogen ions, have the property of nuclear spin. Nuclear spin, first proposed by

Wolfgang Pauli in the 1920s, can be conceived of as a self-rotation of a particle around its own central axis.

Movement of an electric field creates a magnetic field perpendicular to it. Thus, the spin of the positively-charged proton generates a very small magnetic field. In normal conditions, the magnetic fields of all the protons in a tissue will be randomly aligned, so the net magnetisation vector will be zero. By comparison, in the large magnetic field of the MRI scanner the spinning nuclei tend to align so that their tiny magnetic fields are either parallel or antiparallel with the longitudinal axis of the B_0 field. The parallel state is the most energetically favourable, but some protons will always be antiparallel, i.e. opposite to the B_0 . The relative proportion of parallel and antiparallel spins depends on the strength of the B_0 and the temperature – at stronger field strengths, more spins will be parallel, and at lower temperatures more spins will be parallel as it is energetically favourable. At rest, there is a small majority of parallel spins meaning that the net magnetisation vector of the tissue will be positive.

The manner in which the spins align with the main B_0 field is complex – as they are rotating around their axes, when they align with the field they take on a motion known as 'precession', which is akin to the way a spinning top gyrates around its main axis. The frequency of the precession can be calculated by the following formula:

$$\omega_0 = \gamma B_0$$

where ω_0 is the precessional frequency, γ is the gyromagnetic ratio (a known constant for a particular nucleus) and B_0 is the field strength. This is the Larmor Equation, and the specific precessional frequency of protons in the MRI scanner is known as the Larmor Frequency.

The precessing hydrogen nuclei can only absorb energy that is supplied at their resonant frequency. The Larmor Frequency at the field strength used in MRI is in the RF range of the electromagnetic spectrum. The transmitter coils

emit pulses of RF energy, which are absorbed by the nuclei. This excitation causes some nuclei to tip into the anti-parallel state. In terms of the net magnetisation vector, this can be visualised as a movement of the vector away from the longitudinal axis. The angle between the net magnetisation vector and the longitudinal axis is proportional to the amount of energy absorbed, so 'flip angles' of 90° or 180° can be achieved if the RF pulse transmits sufficient energy. In a 90° flip, enough energy is absorbed so that there are equal numbers of parallel and anti-parallel spins, and the net magnetisation vector moves to be at right angles to the longitudinal axis and aligned instead with the transverse plane. In addition to this change in the direction of the magnetisation vector, the application of the RF pulse causes the protons' precession cycles to move into phase with each other, which further strengthens the magnetisation vector in the transverse plane.

When the RF pulse ceases, the protons re-radiate the absorbed RF energy into their surroundings, which is detected by the scanner's receiver coils. This relaxation back to a low-energy state occurs in two ways: precession moves back towards the B_0 , increasing energy in the longitudinal plane (T_1 recovery); and the spins rapidly lose phase coherence, resulting in a loss of energy in the transverse plane (T_2 decay).

Different tissue types have different T_1 and T_2 characteristics, enabling us to create high contrast images of brain structure. The rate at which the protons release their absorbed energy depends on the tissue's composition. Molecules are never still, but constantly tumbling around each other. If the rate of this molecular tumbling is close to the Larmor frequency, such as in lipids, the energy release from the proton to its surroundings can occur rapidly, resulting in fast T_1 recovery. If the tumbling rate is either faster or slower than the Larmor frequency, such as in cerebrospinal fluid or solid tissues respectively, the T_1 recovery is slow.

Compared to T_1 recovery, the T_2 decay process is very rapid. This dephasing process also depends on the molecular tumbling frequency: protons in slow tumbling molecules, such as fats or solids, dephase more rapidly than

protons in fast tumbling molecules, such as water. Hence, fatty and solid tissues have shorter T2 times than cerebrospinal fluid.

There are two causes of dephasing: one caused by inhomogeneities in the B_0 field itself (external magnetic effects), which are constant throughout the scan; and one caused by inhomogeneities due to interactions between neighbouring molecules of the tissue (internal magnetic effects). The external magnetic effects cause very rapid decay, known as $T2^*$ decay, which reduces the available amount of signal to be detected. However, as these effects are constant and predictable, they can be corrected for in a process known as spin-echo imaging, so that the received signal will decay at the true T2 rate.

2.1.3. Spin-echo imaging sequences

In a spin-echo imaging sequence, an RF pulse is emitted, causing a 90° flip. After the cessation of the pulse, dephasing due to external and internal inhomogeneities in the magnetic field cause the spin vectors to fan out away from the transverse plane, and the signal rapidly dissipates. To reduce the rapid $T2^*$ dephasing and make it possible to detect the T2 decay, a second pulse (known as the refocusing pulse) is emitted, causing a full 180° flip. This reverses the magnetisation vector into the opposite direction along the transverse plane. After this refocusing pulse, dephasing will occur again, but in the reversed direction – so spins that had begun to fan out from the x-y axis will swing back into alignment with it. In effect, this reverses the T2 decay so that the signal intensity gradually builds up and generates an echo as all the vectors move back into phase. The rate of signal increase will be dependent on the tissue type, allowing an image to be formed of the tissue.

The scanner operator is able to manipulate two key timing parameters in the spin echo sequence – the echo time (TE), which is the time between the application of the initial RF pulse and the measurement of the signal; and the repetition time (TR), which is the time between repeated applications of the

RF pulse. Variations in these parameters will affect whether signal intensity is primarily due to T1, T2 or T2* relaxation.

A sequence with a very short TE will minimise the time available for the spins to move out of phase before the refocusing pulse – so when they are refocused, there will be less T2 decay and signal will be primarily be due to T1 effects. The length of the TR is also critical – if a short TR is used there will not be enough time for all of the spins to relax back into the z-plane. When the pulse sequence begins again, fewer protons will be flipped into the transverse plane, creating a weaker signal.

This is what happens in a T1-weighted image – a short TE and a short TR are used to ensure that the signal intensity is mostly driven by T1 relaxation. A T2-weighted image uses the opposite parameters (a long TE and a long TR) to maximise the T2 decay, which will dominate the acquired signal.

2.1.4. Signal localisation

The gradient coils (shown in Figure 2.2) are used to localise the source of the radio-frequency signal. Slice selection, for example to acquire a sequence of axial slices that cover the whole brain, occurs by varying the magnetic field in the z-dimension. The gradient coil in the z-axis emit a magnetic field that is negative at one end of the bore, positive at the other end, and zero in the middle. This field sums with the B₀ field, strengthening it or weakening at opposite ends of the z-axis.

As stated in the Larmor Equation, the precession frequency is proportional to the field strength – so changing the field strength will also change the rate of precession. Only protons located at the z-coordinate where the gradient field is zero will precess at the precise frequency required to absorb enough radio-frequency energy to flip the magnetisation vector. Hence, by changing the gradient field, the slice of tissue in the z-axis that will be excited by the RF pulse can be manipulated. When acquiring a series of slices, there will be a degree of cross-talk as excitation 'bleeds' across slices. The noise caused by

this cross-talk can be reduced by acquiring slices in an interleaved order, or using a gap between adjacent slices.

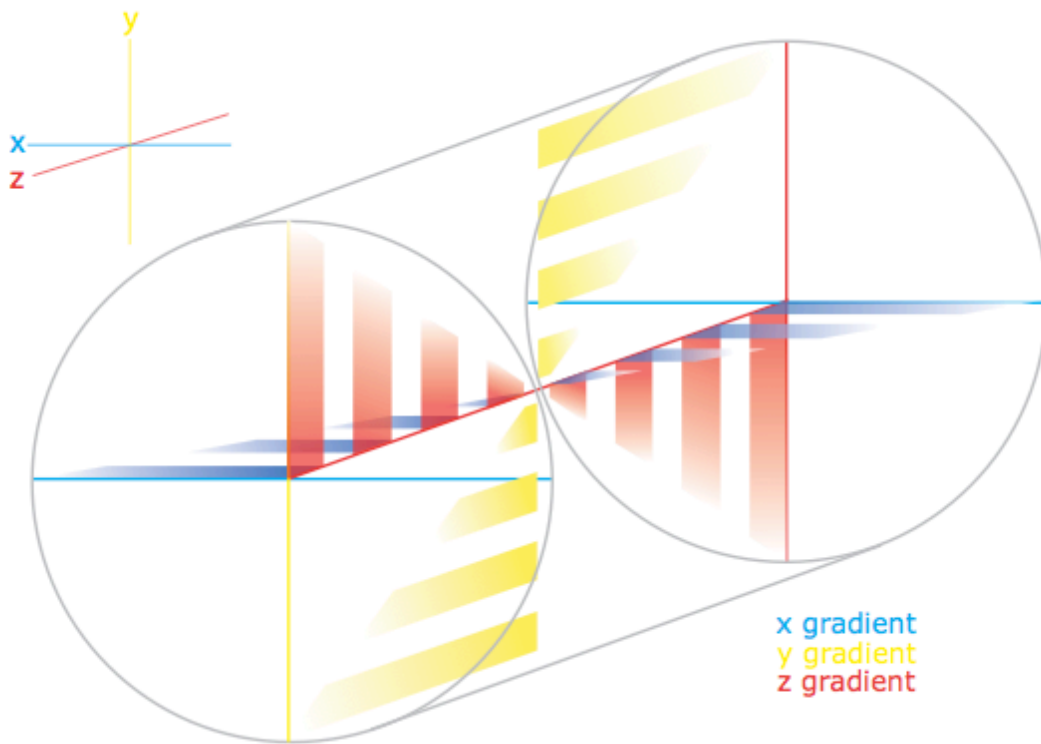


Figure 2.2 The orientation of the gradient coils in an MRI scanner. Shaded bars depict the field strength created by each gradient coil.

Gradient coils are used to localise the signal within a slice. A gradient field along the x-axis is used to vary precession frequency in a linear fashion (frequency encoding), and another field along the y-axis varies precession phase (phase encoding).

Frequency encoding works by applying a magnetic field that varies linearly over the x-axis at the time when the signal is being measured (i.e. after the RF energy has been absorbed and before it is re-emitted). As precession frequency is directly proportional to field strength, this will make protons at different x-coordinates precess at different rates and thus release radio-frequency energy at different frequencies. Fourier decomposition can then be used to calculate the signal intensity of each frequency band, and these bands are then assigned to the corresponding locations in the x-axis.

Phase encoding works by briefly turning on a gradient field immediately after cessation of the RF pulse. During the RF pulse, the spins are phase coherent,

but rapidly dephase according to $T2^*$ relaxation when the pulse is removed. If at this point a gradient field in the y-axis is briefly applied, the precession frequency of the protons in the tissue will vary linearly across the y-axis. When the gradient field is removed, the protons return to precessing at the same, uniform frequency (proportional to the B_0 field), but they retain phase differences that depend on their location along the y-axis. As Fourier analysis cannot resolve the phase composition of the signal in the way that it does for frequency-encoding, multiple phase encoding steps are acquired, each with a different phase encoding gradient that corresponds to a point in the y-axis. This means that multiple pulse sequences, equal to the number of voxels in the y-dimension, are required to acquire the whole image.

2.1.5. Echo planar imaging

Functional magnetic resonance imaging requires rapid acquisition of data from multiple slices covering the whole brain. Conventional spin-echo sequences are not fast enough for this purpose, largely because of the multiple pulses required to acquire all phase-encoded steps. In echo planar imaging (EPI), this process is speeded by acquiring multiple phase-encoding steps after each RF pulse. Each RF pulse is followed by a train of spin-echo pulses, which each encode a different phase. In addition, the spatial resolution of EPI scans for fMRI is typically lower than for structural MRI, which allows the whole volume to be acquired more rapidly, typically in around two or three seconds for a whole-brain EPI volume.

2.2. The physiological basis of functional MRI

The previous section described the methodology of MRI for acquiring structural images of the brain, where the signal intensity varies according to tissue type. Functional MRI applies the physical basis of MRI to investigate changes in neural activity related to particular cognitive tasks. The following section describes the physiological basis of the functional MRI signal.

2.2.1. Neurovascular coupling

Functional MRI (fMRI) attempts to identify the location of neural activity during a particular cognitive process. As neural activity itself cannot be measured, a surrogate marker is used, namely cerebral blood flow.

Neurons are the basic component of information processing in the brain. They are densely interconnected to form circuits or networks and communicate via synapses. A neuron conducts electrical signals (known as action potentials) through its axon, which branches into axonal terminals that synapse with the dendrites of adjacent neurons. Each individual neuron can form thousands of synaptic connections in this way. The electrical potential is created by ion channels in the neuronal membrane, which maintain a concentration gradient whereby, at rest, there is a stronger concentration of potassium ions (K^+) ions inside the cell, and a stronger concentration of sodium (Na^+), calcium (Ca^{2+}) and chlorine ions (Cl^-) ions outside the cell. When the neuron receives a synaptic input, sodium ion channels open, allowing Na^+ ions to flood into the cell. This depolarisation spreads through the cell, causing ion channels further down the axon to open. The signal is propagated in this way until it reaches the next synaptic junction.

The communication between neurons across the synaptic cleft is chemical, not electrical. The electrical depolarisation of the pre-synaptic membrane causes a release of neurotransmitters into the synaptic cleft. The increased concentration of neurotransmitters is detected by the post-synaptic neuron,

causing ion channels to open and (if enough ion channels are opened) this will trigger an action potential in the post-synaptic neuron.

The processes of maintaining the ionic concentration gradient at rest, restoring the concentration gradient after an action potential, and the re-uptake of neurotransmitters after synaptic activity all consume energy. This energy is supplied by the metabolism of oxygen and glucose from the blood. Studies in rodents have shown that 47% of the energy consumption is used to restore the pre-synaptic concentration gradient after an action potential, and 34% to the post-synaptic potentials (Attwell & Laughlin, 2001). In primates, the number of synaptic connections per neuron is considerably higher than in rodents, meaning that the post-synaptic component of energy consumption is likely to dominate. Hence it is assumed that, in humans, the rate of oxygen consumption in the brain is mostly dependent on post-synaptic activity.

After neuronal activity there will be a local deoxygenation of haemoglobin in the blood. It is now known that neurovascular coupling is not dependent on blood oxygen levels (Fox & Raichle, 1986; Mintun et al. 2001). Rather, the synaptic release of glutamate (an excitatory neurotransmitter) into the synaptic cleft leads to the release of vasodilators, such as nitrogen oxide, that cause a focal increase in blood flow. This may occur via signalling pathways in the post-synaptic neuron or in astrocytes, a type of glial cell that surrounds the synaptic cleft (Attwell et al. 2010).

2.2.2. Blood-oxygen level dependent fMRI

When a brain region is active there is an initial dip in blood oxygenation, followed by a rapid overcompensation in blood flow. Focal blood volume increases and so does the proportion of oxygenated to deoxygenated haemoglobin, as the deoxygenated blood is flushed out of the area. The blood volume and proportion of oxygenated to deoxygenated haemoglobin both increase at a rate described by the haemodynamic response function (HRF). Blood-Oxygen Level Dependent (BOLD) fMRI, devised by Seiji Ogawa

in the 1980s, uses this change to create images that indirectly represent neural activity.

Oxy-haemoglobin molecules (HbO_2) are diamagnetic, meaning that they do not have nuclear spin and therefore do not have magnetic resonance in the way that protons do. By comparison, deoxy-haemoglobin molecules (Hbr) are paramagnetic because they have unpaired electrons that create magnetic moment. In the presence of the strong B_0 field, Hbr causes local distortions in the magnetic field that increase the amount of spin dephasing due to T_2^* decay. Hence, deoxygenated blood will give a lower T_2^* signal than oxygenated blood (Thulborn et al. 1982). Echo-planar images that emphasise this BOLD contrast are used in fMRI scans.

2.2.3. Temporal and spatial specificity of the haemodynamic response

The timing of the neurovascular response and its effect on the BOLD signal is modelled by the Haemodynamic Response Function (HRF). The time course of neural activity is very rapid, but the vascular response to this activity is considerably slower. After the initial dip, blood oxygenation will gradually increase, reaching a peak approximately six to eight seconds after stimulation onset (Menon & Goodyear, 2001). Thus, the temporal sensitivity of BOLD-fMRI is both blurred and delayed relative to the underlying neural activity. This is modelled when analysing the fMRI data in order to allow changes in the BOLD contrast to be ascribed to specific cognitive process during the fMRI task.

The spatial sensitivity of the changes in blood flow must also be taken into account. Focal neural activity will cause neurovascular changes in the arterioles and capillaries over a wider area (Iadecola et al. 1997). This means that the BOLD signal will be more extensive than the neural activity itself.

2.3. The analysis of fMRI data

The EPI data collected in an fMRI scan is in the form of maps of the brain where signal intensity reflects regional blood oxygenation, which is an indirect measure of neural activity. A whole-brain EPI volume can be acquired in two or three seconds. The following section describes how the fMRI data is analysed to identify voxels where signal intensity varied with the cognitive task of interest.

2.3.1. Experimental design

There are a number of constraints on experimental design that have to be considered prior to data acquisition.

Firstly, it is critical to note that the BOLD signal is a relative measure. As the magnetic susceptibility varies across the structures of the brain, so too the $T2^*$ decay will be very different at different voxels of the image, meaning that the absolute value of the signal intensity cannot be used to reflect neuronal activity. For this reason, every experimental fMRI design needs to compare signal intensity in one task to activity during a baseline task. This design feature of fMRI experiments leads to the problem of pure insertion. Ideally, the condition of interest will differ to the baseline only in the precise cognitive process that the experimenter wishes to isolate. In practice this is very difficult, as there will inevitably be additional sensory or executive differences between task and baseline. The use of multiple baselines (for instance, a perceptually-matched baseline and an attention-matched baseline) is commonly employed to solve this problem.

The studies presented in this thesis (with the exception of Results Chapter 3.5) use either block or event related fMRI designs. Block designs offer the most robust percentage change in BOLD signal between the condition of interest and the baseline. For instance, an experiment to investigate the cortical areas involved in visual processing might interleave blocks of visual stimulation with a resting baseline task. During the stimulation blocks a visual stimulus such as a flashing checkerboard is presented to the participant for a sufficient time to allow the HRF in the visual areas to reach a

peak. Then, in the following rest block the neuronal activity will return to resting levels. Vasodilation will stop and the proportion of oxygenated to deoxygenated blood will gradually return to normal. This will be observed as a gradual reduction in signal intensity.

The timing parameters of a block design need to allow sufficient time for the BOLD response to peak during stimulation (around four to six seconds), and to return to resting levels during the between blocks (around ten seconds). At the same time, the experimenter will aim to maximise the number of block repetitions within the scanning time allowed, as having more observations will improve statistical power. In addition, fMRI data is affected by 'scanner drift' – slow, linear changes in mean signal intensity over time. If the period of change between experimental blocks is at a similar frequency to this drift, it will be impossible to determine whether the changes in signal intensity are real or spurious. Typical block durations of 10-16 seconds offer optimal efficiency (Huettel et al. 2008).

Whilst block designs are highly efficient, there are certain situations where long blocks of stimulation are impractical: for instance, where the cognitive process of interest is transient or infrequent; where the task order has to be unpredictable; or where there are significant attentional differences between the process of interest and the baseline task. In these cases, an event-related design may be more appropriate. If the experimenter wished to compare activity during a reading task with a perceptually-matched baseline task of meaningless 'false font' stimuli, he or she may be concerned that the participant would not pay attention to long blocks of passive baseline stimuli. An event related design would reduce this confounding effect by interleaving reading and false font trials in quick succession. The obvious disadvantage of event related designs is reduced efficiency: because trials are shorter, the BOLD response does not have time to reach a peak, so the difference between the mean activation level during the task of interest and the baseline will be a lot smaller.

Trial order is a critical issue in both block designs and event related designs. It is important to create the maximum variety of transitions between different experimental conditions, so that condition A does not always follow condition B, etcetera. Due to the scanner drift, it is also necessary to ensure an even spread of different condition types across the whole scanning run – if the blocks or trials of one condition are clustered at the beginning of the run they will have a different mean intensity than a condition clustered at the end of the run.

There may also be order effects associated with the acquisition of multiple scanning sessions. Participants may be more alert and engaged in initial sessions, and activation may be higher as a result. Run order can be counterbalanced across the participant group to eliminate these order effects. This can be especially important in training studies, where a comparison across time-points is used to demonstrate training effects. The experimenter must ensure that changes over time are truly due to training effects and not to a decrease in participant engagement or accommodation to the scanning environment over time.

2.3.2. Preprocessing

The fMRI data presented in this thesis (with the exception of Results Chapter 3.5) were analysed using tools from FMRIB's (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) Software Library (FSL; Smith et al. 2004; Woolrich et al. 2009). Most stages of fMRI analysis are automated in the fMRI Expert Analysis Tool (FEAT; Smith et al. 2004). There are a number of preprocessing stages that must be performed prior to the statistical analysis. These include brain extraction, temporal filtering, motion correction, spatial smoothing and registration to a standard anatomical template. In addition to the fMRI data, a T1-weighted structural image is acquired for accurate registration onto the anatomical template.

Brain Extraction

The first step in preprocessing is brain extraction. This process removes the non-brain tissue from the T1 and EPI images so that the subsequent stages of the analysis focus only on brain tissue. Brain extraction is performed using FSL's Brain Extraction Tool (Smith, 2002), which identifies the likely centre of gravity of the head, then initialises a tessellated spherical surface at the centre of gravity that gradually expands until an ideal solution is found that separates brain (with high intensity values) inside the sphere and background (with low intensity values) outside the sphere.

Temporal Filtering

Temporal filtering is performed to remove noise from the EPI data. High-pass filtering removes low frequency noise that is likely to be caused by 'scanner drift' – the slow changes in the overall signal intensity that are caused by minor instabilities in the scanning hardware (Smith et al. 1999). In a block design, the level of the high-pass filter is selected to match the period of a full cycle of functional tasks – for example, in a design with four conditions and a block length of 15 seconds, a high-pass filter with a period of at least 60 seconds should be used. The effects of scanner drift can also be reduced by manipulating the order of tasks so that each condition is evenly distributed across the run.

Motion Correction

Although measures are taken to reduce head movement during the scan, such as the use of foam padding, some movement is inevitable. Motion correction is used to ensure that the anatomical location of a single voxel within the field of view is constant throughout the data timeseries. Without motion correction, it would be unclear whether a change in signal intensity at a particular voxel was due to a genuine change in the BOLD response, or because the voxel had moved from sampling, for example, white matter to grey matter.

In FSL, motion correction is accomplished by selecting a reference volume (usually the midpoint of the timeseries) to which all other images are aligned. The amount of movement in each direction required to align each

volume is reported – if a participant shows excessive motion (i.e. more than the width of one voxel in any direction) they are excluded from the final analysis. Furthermore, these motion parameters are entered into the design matrix in order to identify and exclude any changes in signal intensity that correlate with head motion.

Whilst motion can be corrected for in the preprocessing it is critical to consider the effects of task-related motion during the design of the experiment. Adding the motion parameters to the design matrix as covariates of no interest means that any signal changes that correlate with motion will be ignored – so if head movement is regularly associated with the condition of interest, real signal in the data may be lost. This can be a problem with tasks involving large-scale eye or limb movements that cause the head to move slightly every time the participant responds. The experiments presented here use an ergonomically designed finger-press panel to collect task responses with a minimum amount of movement.

Spatial Smoothing

Spatial smoothing is performed to improve the signal-to-noise ratio of the fMRI data. It is assumed that the type of signal from biologically plausible sources will take the form of spatially smooth areas of activity, i.e. ‘blobs’ of activity that are, for example, approximately seven millimetres in diameter. Any areas of activity smaller than this are assumed to be noise. Spatial smoothing convolves the data with a Gaussian kernel with a full width at half maximum (FWHM) of the anticipated blob size (seven millimetres in this case). This has the effect of filtering out the high spatial frequency components of the data, whilst enhancing areas of contiguous activation.

Registration

Registration is performed using FMRIB’s Linear Image Registration Tool (FLIRT). The standard registration is a two-stage process: the participant’s EPI data (in ‘native space’) is spatially aligned to their T1 image (the ‘structural space’); then the T1 image is aligned a standard template image (the ‘standard space’). At each stage, a registration matrix that describes the

changes required to align one image to the other is created, and the two matrices can be concatenated to describe the full transformation from native to standard space.

FLIRT allows the user to select the number of degrees of freedom for each registration stage. Typically the native to structural space registration assumes a 'rigid body' alignment, whereby the native and structural images have the same dimensions and overall shape, but in slightly different orientations. To register these images, only six degrees of freedom are required – a translation and a rotation in each of the three dimensions, x, y and z. However, due to inconsistencies in the scanning sequences for EPI and T1 images, some of the studies presented here used higher degrees of freedom to correct for global size differences or affine warping of the EPI images. The standard to structural registration stage requires higher degrees of freedom to correct for the differences in the shape of the brain between participants. As well as the six rigid body transformations, six affine translations (shears) are used.

Recent methodological advances have resulted in a non-linear registration option, FNIRT. Non-linear registration applies a warp field that can correct for local deformations, which substantially improves the structural to standard fit (Andersson et al. 2007a; Andersson et al. 2007b). Some of the studies presented in this thesis, where data was acquired more recently, have been analysed using FNIRT rather than FLIRT.

2.3.3. Statistical analysis

The statistical analysis of fMRI data with FEAT uses a multi-level approach. The General Linear Model (GLM) is used to produce summary statistics at each level, which are then passed on to the next level. There may be one or two within-subject levels of analysis, followed by a higher between-subjects analysis.

First-Level Analysis

At the first level, each individual session of data (i.e. one run from one participant) is analysed separately. A design matrix is created that models all of the experimental conditions as 'explanatory variables' (EVs). The EVs describe the time course of each experimental condition within the run, convolved with a stereotypical HRF. The temporal derivative of each EV is also entered to enable the model to detect changes in the signal intensity that are slightly slower or faster than predicted, thus improving the model fit. Motion parameters are added to the model as covariates of no interest.

The GLM is used to find parameter estimates for each EV in the design matrix. In effect, the linear model tries to 'fit' the EVs to explain the data as fully as possible. The formula for the linear model can be expressed as:

$$Y = X \beta + \epsilon$$

where Y is a matrix of the observed data across time; X is the design matrix; β is a matrix of the parameter estimates for each EV (the weighting required for the time course of each EV to fit the data); and ϵ is the error, the residual variance that cannot be fitted to the model. When analysing the data, the time course of signal intensity at each voxel is considered, and the combination of weighted EVs is estimated that best fits the data. For example, if a visual task and an auditory task were entered as two EVs, activity in visual cortex would most closely match the time course of the visual EV, so the parameter estimate for the visual EV would be high. This process produces an image of the brain for each EV where the parameter estimate is plotted in each voxel.

When the statistical analysis is complete, FEAT computes contrasts between EVs, which subtracts the relevant parameter estimate maps to create a map representing the contrast of parameter estimates, known as a 'cope' image. These are converted into t-statistics images by dividing the parameter estimate at each voxel by the noise amplitude. Effectively, a t-test is performed at each voxel of the image, testing whether the difference between parameter estimate for condition A and parameter estimate for

condition B is significantly different to zero. Z-statistic images are created by converting the t-statistic at each voxel to a z-statistic.

Second-Level Analysis

In the studies presented here, multiple runs of data are typically acquired per participant. These runs are analysed separately at the first-level, then combined in a within-subject second-level analysis. The summary images for one contrast in each session are averaged using a fixed effects model.

Group analyses in FSL can be performed using fixed or mixed effects. A fixed effects model assumes that there are no differences between the variances of different sessions or participants, and so the results reflect the group average of the sessions or participants entered into the design. By comparison, a mixed effects model (using FLAME, FMRIB's Local Analysis of Mixed Effects; Beckmann et al. 2003; Woolrich et al. 2004; Woolrich, 2008) takes the variance of each session or participant into consideration, and the results reflect the likely group mean of the population from which the participants were drawn. The fixed effects analysis is more appropriate at the second level, as the data comes from the same subject and any differences in variance between runs are of no interest.

Third-Level Analysis

The third-level analysis typically finds the average of the whole participant group, or makes a between-subjects comparison of the control and patient groups. As there may be substantial differences between participants, a mixed-effects approach should be used.

Thresholds and the Problem of Multiple Comparisons

As the brain image is comprised of around 20,000 voxels, there is a major problem of multiple comparisons. With alpha set at 0.05 there will be around 1000 false positives across the brain. There are a number of possible ways to correct for the problem of multiple comparisons. Bonferroni correction is too conservative, as it divides the threshold alpha value by the number of comparisons – this would result in a corrected threshold of $p < .0000025$. A

more reasonable correction approach takes into account the fact that activation at each voxel is not truly independent – the signal arising from plausible biological sources is inherently smooth, and the spatial smoothing in the preprocessing stage enhances this ‘smoothness’. Instead of correcting for the number of voxels in the brain, the threshold can be corrected according to the number of possible independent observations in the smoothed data.

In FSL, Random Field Theory is used to implement cluster-based correction for multiple comparisons. The data analysis produces an image with a z-statistic at each voxel. A z-threshold (e.g. of $Z > 2.3$) is applied, so that voxels with a z-statistic lower than 2.3 are set to zero. Random field theory can be used to predict (based on the size of the field, the extent of the spatial smoothing and the z-threshold used) the average size of clusters that would be produced by chance, if a Gaussian-smoothed random field had been used instead of the real data. For instance, an average cluster size of 10 voxels might be predicted, with a standard deviation of 4 voxels. Based on this distribution, a cluster of 18 voxels would be highly surprising, and unlikely to happen by chance – using the standard assumptions of normal distributions, this can be quantified as a probability of $p = 0.05$. In practice, images are first thresholded with a z-threshold and then a p -threshold is applied to only select clusters that significantly larger than what would be expected to occur by chance.

Region of Interest Analysis

The problem of multiple comparisons can be greatly reduced if there is a clear hypothesis of where significant activity is expected. In these cases, the experimenter can define a region of interest (ROI), containing a limited selection of the total number of voxels. A single statistical test can then be computed to assess whether the average or maximum parameter estimate in that region differs between one condition and another. If multiple ROIs are tested, correction for multiple comparisons using Bonferroni may be required.

The method used to localise the ROIs is an important consideration (Poldrack, 2007). Localising ROIs according to the peaks observed in the z-statistic images in a post-hoc manner is a statistically dubious practice. For instance, consider the situation where correction for multiple comparisons means that a potentially interesting result no longer reaches significance. The experimenter might be tempted to use a ROI analysis to by-pass the problem of multiple comparisons. This logic is clearly circular, and any inferences drawn in this manner would be invalid. However, if the experimenter had made an *a priori* prediction that they would find significant activity in a particular ROI, based on results from previous studies or a functional localiser, they would be justified in only performing statistical tests within that region. They may also choose to limit the search area of the statistical analysis in FEAT to only the voxels of interest, so that the correction for multiple comparisons would be less stringent.

An alternative use for ROI analysis is to explore the differences in activation at a particular location during different conditions of interest. This can be particularly useful in complex experiments, such as those employing a factorial design, where individual contrasts do not fully convey the pattern of activation across conditions. In these instances, defining ROIs according to peak activation is an acceptable practice because the purpose of the ROI is not to enhance statistical sensitivity by limiting the number of comparisons.

2.3.4. Special considerations for analysing patient data

There are two key issues with analysing data from patients with focal brain lesions: how to register the lesioned brain and how to model the HRF.

Registering a lesioned brain to a standard brain template is problematic because the registration algorithms will try to 'regularise' the brain, stretching the intact tissue to fill the damaged area. Cost-function masking (Brett et al. 2001) is one way of avoiding this problem. A binary mask of the damaged area is created, where voxels of intact tissue have a value of one, and damaged areas have a value of zero. This mask is fed into the

registration process, informing the registration algorithms to ignore the down-weighted areas of the brain and only rely on the intact tissue. A recent paper demonstrated that cost function masking was the optimal solution for registering lesioned brains in the Statistical Parametric Mapping (SPM) software package (Andersen et al. 2010). Although an equivalent analysis has not been published for FSL, cost function masking is FMRIB's recommended solution for this problem.

When analysing fMRI data, the timecourse of each explanatory variable is convolved with a canonical HRF in order to best simulate the rate at which the BOLD response is predicted to change over time. This assumes that all participants have similar neurovascular coupling and therefore have a similar HRF and similar rates of change of the BOLD signal. However, this is not a fair assumption for elderly participants or participants with cerebrovascular disease. Normal aging is associated with reduced vascular reactivity, reduced resting cerebral blood flow and thickening of the blood vessels (Claus et al. 1998; D'Esposito et al. 2003), all of which will affect the HRF. Older participants also have a higher rate of cerebrovascular disease, which in itself is associated with a delayed time-to-peak and a weaker BOLD signal (Carusone et al. 2002; Roc et al. 2006). Furthermore, the medications prescribed to prevent or treat cerebrovascular disease are likely to affect the HRF (D'Esposito et al. 2003). Bonakdarpour and colleagues (2007) showed that there was also intra-individual variability in stroke patients, with abnormal HRFs being observed in the damaged hemisphere, and particularly long time-to-peaks in the perilesional tissue.

FSL employs temporal derivatives to minimise the impact of HRF variation across the brain and between participants. The temporal derivatives are additional EVs which model the first derivatives of each real EV can be included in the first level design matrix. The temporal derivative EV will detect changes in the BOLD signal at each voxel that are slightly slower or faster than the changes modelled in the real EV. Without the inclusion of the temporal derivative, this variation would have been included in the residuals (i.e. the ϵ , or error term of the GLM) and therefore would have reduced the

statistical strength of the subsequent contrasts. In this way, the use of temporal derivatives can ameliorate the lack of sensitivity caused by small variations in an individual's HRF.

3. Results

3.1 Investigating the reading-related networks in healthy volunteers using narrative texts

This study investigated the neural networks for reading in healthy volunteers using fMRI. There were three main aims:

- 1) to identify the reading networks that are involved in reading in healthy volunteers, in order to provide a baseline measure for the subsequent patient studies
- 2) to test the activity in response to word stimulus presentation in the left visual field in order to simulate the effects of having an RHH
- 3) to investigate the functional properties of the left vOT as predicted by the LCD model of reading (Dehaene et al. 2005): it is predicted to be preferentially activated by words over other stimulus types, irrespective of low-level stimulus properties such as location of presentation.

With regards to the first aim, the reading network was identified by comparing reading-related activity to the activity during two baseline tasks: a perceptually-matched passive 'false font' task (which subtracts visual activity that is not specific to reading) and an attention-demanding number decision task. Numbers, like letters, are two-dimensional high contrast abstract symbols encountered routinely every day. According to Dehaene's hypothesis, false font and numbers should not be processed by the vOT. In addition, the active nature of the number decision task was designed to suppress incidental semantic processing that may accompany 'passive' tasks (Binder et al. 1999), and has been used in previous studies to reveal the deeper processing of meaningful verbal stimuli perceived 'passively' without an explicit task demand (Spitsyna et al. 2006; Awad et al. 2007). The literature reviewed in the introduction suggests that the reading network should include orthographic processing areas such as the left ventral visual stream; semantic processing areas such as the bilateral anterior temporal lobes (aTL), the left inferior and middle temporal gyri (ITG and MTG) and the

left anterior-ventral portions of the inferior frontal gyrus (IFG); and phonological processing areas such as the left supramarginal gyrus, premotor cortex and posterior-dorsal portions of the IFG.

The second aim of this study was to simulate the effects of an RHH on functional activity during reading. Words were presented to the left or right visual hemifields in order to identify the visual areas that are sensitive to stimulus location, and the areas that demonstrate higher-order 'abstract' processing and are therefore insensitive to lower-order perceptual properties such as stimulus location. It was predicted that activity in the left vOT would be activated by words irrespective of stimulus location.

The left-to-right reading direction gives rise to an asymmetrical 'attentional window' that extends into the right parafoveal visual field (Leff et al. 2000). As a consequence, reading in the left visual field may be associated with increased activation of neural networks controlling visual attention. This may include the dorsal visual stream, which is known to be preferentially engaged by reading tasks with more taxing visual conditions (Mayall et al. 2001; Pammer et al. 2006; Cohen et al. 2008); or the dorsal attention network including the bilateral intraparietal sulci and superior frontal gyri (Corbetta & Shulman, 2002). Identifying the areas that are preferentially engaged during reading in the left visual field was expected to assist interpretation of the patient data by discriminating between activations related to their abnormal visual fields and their reading deficit *per se*.

The stimulus specificity of activity in the left vOT was tested by comparing activity during the reading task to the perceptually-matched false font baseline. The inclusion of a second low-level baseline (the number decision task) made it possible to examine activations in response to false font in its own right, rather than relying on direct comparisons between reading and false font. In this way, it was possible to examine the similarities between reading and false font processing, which have been frequently overlooked in the existing literature.

Experimental Procedures

Participants

Nineteen healthy, right-handed volunteers (nine female, average age 26 years) participated in this study. No participants had a history of neurological or psychiatric illness or developmental reading disorders. Written consent was obtained from all participants, and all procedures were approved by the local research ethics committee.

MRI Procedures

Functional data was acquired on a Philips Intera 3.0 tesla MRI scanner using an EPI sequence with a TR of 3 seconds, with whole-brain coverage over 48 axial slices (thickness 5mm), and an in-plane resolution of 2.5 x 2.5mm. Slices were acquired in an interleaved ascending order.

A block design was used, with two functional runs of 195 volumes each. There were 15 blocks within each run: three repetitions of five experimental conditions. Block order was counterbalanced so that there was no correlation of condition order with time, and to maximise the variety of transitions between conditions. Each block was 30 seconds long, and there was a 9 second fixation cross between each block to allow the subject to rest.

Stimuli

The five experimental conditions presented in the fMRI runs were:

- 1) Reading narratives in the left visual field ('LR')
- 2) Reading narratives in the right visual field ('RR')
- 3) Observing false font stimuli in the left visual field ('LF')
- 4) Observing false font stimuli in the right visual field ('RF')
- 5) Performing a number decision task ('ND')

Examples of the display from each condition are depicted in Figure 3.1.1.

In the LR and RR conditions participants were instructed to read narrative texts passively (silently) without moving their eyes from the central fixation point. The words were presented using a Rapid Serial Visual Presentation

(RSVP) technique, where each word of the narrative is presented serially for 500ms, thus avoiding the need for eye movements while reading. This allowed the location of presentation to be manipulated: in the LR condition, words were right justified and presented immediately to the left of fixation, and in the RR condition they were left justified and to the right of fixation. The words were presented on a white background, which extended to the vertical meridian, and the other half of the screen was rendered black.

The narratives were 60-words long, adapted from children's books to include only words between three and six letters long. Words subtended an angle of no more than 5° from fixation and could comfortably be read without moving the eyes from fixation. The LR and RR narrative stimuli were broadly matched for word length, with an average length for the LR condition of 3.7, and 3.6 for the RR condition. An independent samples t-test across confirmed that there was no significant difference in word length between the LR and RR narrative stimuli ($t_{(718)}=.70, p=.48$).

In the LF and RF conditions participants were instructed to passively view false font stimuli while maintaining central fixation. The manner of presentation was the same as in the LR and RR conditions. The stimuli were created by converting the narrative texts into Greek symbols using an arbitrary character correspondence code; hence, the false font and reading stimuli had similar visual characteristics (such as spatial frequency, contrast and shape components) and were matched for string length. The false font stimuli were effectively meaningless: none of the participants had any education in the Greek language, and the arbitrary coding of the Roman-to-Greek characters meant that the false font strings had no associated meaning. Characters that looked very similar to Roman letters (such as 'ω') were excluded. Although some participants may have been familiar with certain symbols (e.g. from mathematical notation), this level of orthographic processing would be considerably lower than the level of narrative text comprehension in the reading conditions.

The number decision baseline was chosen to provide an active, attention demanding baseline. Three-digit numbers were presented centrally on the screen for 1500ms, and participants were required to make an odd or even judgement, and signal their response with a button press. As shown in Figure 3.1.1, the left half of the screen and the area around the centrally-presented number was white and the remainder of the screen was black.

Number semantics are processed in the parietal lobe (Thioux et al. 2005; Cappelletti et al. 2010) and numbers only weakly activate the ventral visual stream (Baker et al. 2007; Reinke et al. 2008). The number decision task has been shown to be a more effective baseline than simple rest or fixation in terms of reducing activation in temporal lobe regions of interest (Stark & Squire, 2001).

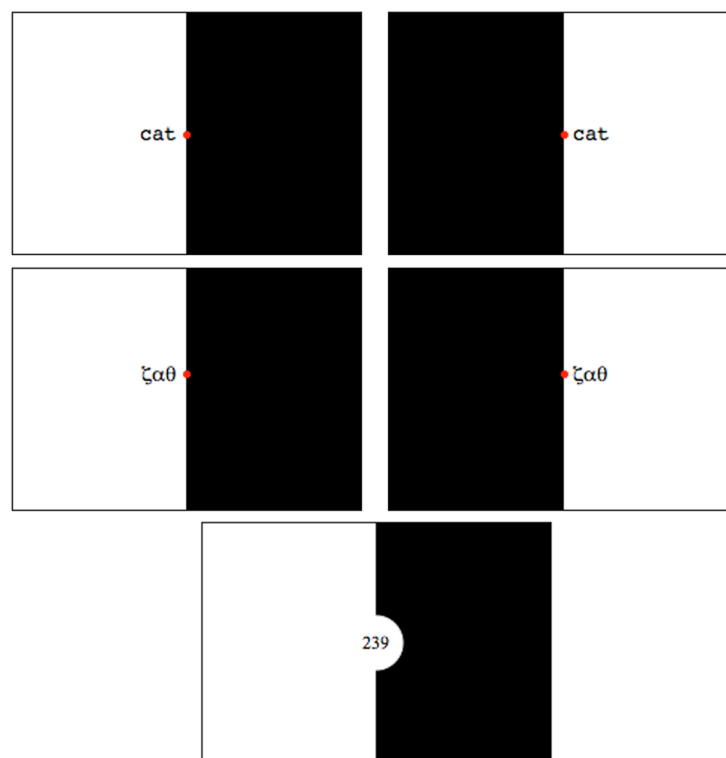


Figure 3.1.1. Sample images from (top left) left reading, (top right) right reading, (middle left) left false font, (middle right) right false font, and (bottom) number decision conditions. Font size is not to scale.

Using numbers as a low-level baseline allowed us to calculate reading versus baseline and false font versus baseline contrasts. By doing this, we were able to assess the extent to which reading-related networks are also activated by perceptually matched but meaningless false font stimuli.

Data Analysis

EPI data preprocessing was performed as described in Chapter 2. Images were smoothed at 7mm FWHM.

The first-level design matrix modelled the five experimental conditions as EVs, plus six motion parameters as regressors of no interest (a sample first-level design matrix is included in the Appendix). The resulting contrasts of parameter estimates (COPEs) were entered into a second-level, fixed-effects model that combined data from the subject's two fMRI runs. Finally, at the third-level, a mixed-effects, group analysis was performed using FLAME (Beckmann et al. 2003; Woolrich et al. 2004; Woolrich, 2008). A cluster-corrected threshold of $Z > 3.0$, $p < 0.05$ was used to present the results.

Region of interest (ROI) analysis was conducted to explore the activation in the VWFA and areas immediately adjacent to it in the ventral visual stream. The symmetrical regions in the right hemisphere were also tested. Three regions along the ventral visual stream were tested – a posterior fusiform gyrus (pFG) region, the VWFA and a mid fusiform gyrus (mFG) region. The mFG region was at the anterior extent of the ventral visual stream as it is apparent in fMRI studies; PET imaging (Spitsyna et al. 2006) suggests that it extends further into the anterior temporal lobe, but this area is subject to susceptibility artefact in fMRI (Visser et al. 2010). In addition, the response of the lateral temporal lobes was tested in order to compare the response profile of known heteromodal temporal cortex with the ventral visual stream. Symmetrical ROI in the left and right hemispheres were defined in the posterior and anterior STS (pSTS, aSTS).

Spherical ROI (diameter=7mm) were located according to published coordinates (in the case of the VWFA; Jobard et al. 2003), or using a structural atlas (Eickhoff et al. 2005) to determine anatomical location. Coordinates of the ROI locations are provided below in Table 3.1.2. For each ROI, z-statistic values from the contrasts LR, RR, LF and RF versus ND were extracted. The 90th percentile voxel value was reported rather than the

maximum in order to avoid sampling any artificially high voxels caused by noise in the data.

Eye tracking

An eye-tracking study was conducted on ten participants (7 female, mean age 35 years), with partial overlap between the fMRI and eye tracking participant groups. The eye-tracking was conducted outside the scanner to determine whether eye movements were affected by stimulus type (words or false fonts) or stimulus location (left or right visual hemifield). The LR, RR, LF and RF stimuli and protocol (the ND task was omitted for simplicity) were replicated and presented to participants using the SR Eyelink II system (SR Research Ltd., Mississauga, Canada). The stimuli were presented on a 22 inch screen with resolution of 1028 x 768 pixels, at a viewing distance of 50 cm. Stimuli were positioned with the inner extent 5mm from the central fixation point, and the outer edge up to 50mm away, a visual angle of 5.7 degrees eccentricity. Eye movements were monitored using binocular tracking at a sampling rate of 500 Hz. As in the fMRI protocol, a block design was used, with a 60-word or false font 'narrative' presented using RSVP. There were six blocks of each condition, making a total of 24 blocks split into two runs. Eye position was calibrated using a nine-point grid prior to each run, and drift correction was performed before each block.

The number of blinks and saccades during each block was recorded. Three 'interest areas' were defined within the display screen – a rectangle covering the fixation point, and two identical rectangles covering the left and right stimulus display regions. The amount of time the participant's gaze was directed towards these three areas was recorded for each trial.

Recognition memory test

An unanticipated recognition memory test was designed to establish how well the participant was able to read and remember the texts after the eye-tracking procedure. The test consisted of 44 sentences, half of which were familiar. The familiar and unfamiliar sentences were made up from separate lists of content words, but they were broadly matched for meaning: *they*

drove along the quiet windy roads (familiar); and *they walked quietly along the sandy path* (unfamiliar). Across the whole list, the familiar and unfamiliar sentences were matched for syntactic structure and length. An equal number of familiar sentences from the LR and RR blocks were used. The familiar and unfamiliar sentences were presented in random order, and the participants were required to identify them as familiar and unfamiliar as a forced two-way choice.

Results

Recognition memory test

The average score on this task, performed off-line, was a mean correct characterization (familiar versus unfamiliar) on 32 out of 44 items, range 25 to 39 (chance score 22). The average number of 'hits' (correct recognition of a familiar sentence) presented in the left visual field was 7 (with a range of 2 to 10 out of 11), and in the right visual field was 7 (range 4 to 11 out of 11). A repeated measures ANOVA showed no significant difference in recognition of sentences in the two visual fields ($F_{(1, 8)}=0.03$, $p=0.9$).

A measure of stimulus detection sensitivity was calculated for each individual (d'). This compares the likelihood of the participant correctly identifying familiar items ('hits') and incorrectly identifying unfamiliar items as familiar ('false alarms'). All participants but one had a d' score above one, indicating that they made more hits than false alarms. The average score was 1.51, standard deviation 0.65.

Between-subjects t-tests showed no difference in hit rates (left visual field: $t_{(7)}=-0.30$, $p=0.61$; right visual field: $t_{(7)}=0.32$, $p=0.40$) or d' scores ($t_{(7)}=0.02$, $p=.891$) was observed between the naïve participants and those who had previously been exposed to the stimuli in the fMRI study.

Eye tracking

Table 3.1.1 shows the percentage of time that gaze was directed at the fixation point or towards the stimulus for each condition (the eye movements towards the stimuli were a mixture of slow drifts or saccades, with saccades

back on to the fixation point). The ability to maintain central fixation was less when the stimuli were words; gaze position was analyzed using a 2 (task) X 2 (hemifield) repeated-measures ANOVA, demonstrating a main effect of task (false font > words; $F_{(1,8)}=9.1, p<0.05$), but not of visual hemifield ($F_{(1,8)}=3.3, p=0.1$). The interaction between stimulus type and location was not significant ($F_{(1,8)}=1.7, p=0.2$). Although central gaze was maintained on average for at least two-thirds of each block of 60 words, there was considerable individual variability. Including participant group (new subjects versus participants from the fMRI study) as a between-subjects factor resulted in no significant main effects or interactions.

Table 3.1.1. Table detailing the group means and standard deviations for eye tracking measures. Includes the number of blinks, number of saccades, and the percentage of time within each block where gaze was directed towards the fixation area or towards the stimulus presentation area for each condition (n=9).

Measure	LR	RR	LF	RF
No. Blinks	23.9 (30.1)	24.4 (33.0)	28.7 (35.4)	25.1 (35.6)
No. Saccades	187 (87.4)	188 (90.5)	149 (84.2)	162 (77.3)
% Gaze at fixation	73.1% (29.3)	66.3% (31.7)	84.9% (18.0)	71.8% (28.9)
% Gaze at stimulus	14.8% (27.9)	30.5% (31.1)	7.7% (9.1)	22.6% (25.8)

Whole-Brain fMRI Results

We first explored the main effect of hemifield of presentation. Contrasting the left visual field conditions (LR and LF) with the right visual field conditions (RR and RF) demonstrated activation of the contralateral visual cortex (see Figure 3.1.2).

Next, we identified reading-related activations, using a contrast of both reading conditions (LR and RR) versus both false font conditions (LF and RF), as shown in green in Figure 3.1.2. This revealed a left lateralised ventral visual response along the fusiform gyrus, which extended from the occipital lobe anterior into the ventral temporal lobe where signal was lost due to susceptibility artefact. No symmetrical activity was evident in the right hemisphere, even with a reduced threshold ($Z>2.3$, voxel-wise correction).

Extensive activity was also evident in the left and right lateral temporal lobes along the length of the STS.

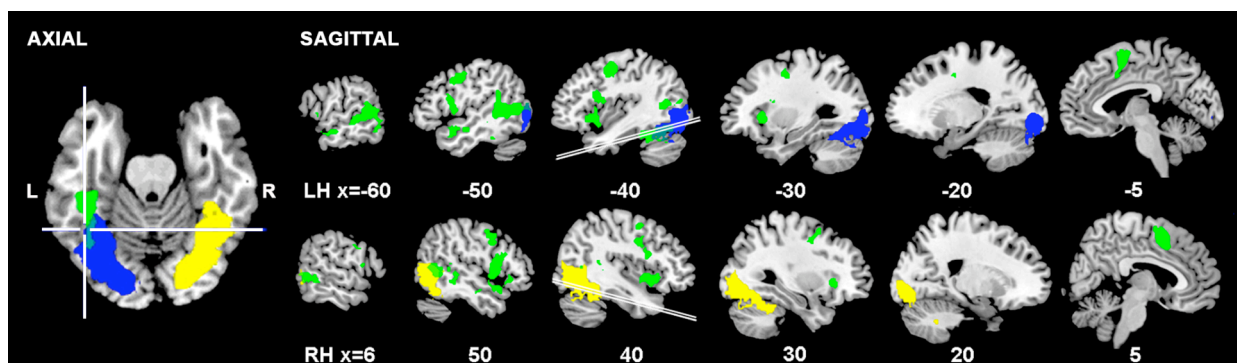


Figure 3.1.2. Color-coded overlays of increased activity in three contrasts that was significant at a cluster-corrected threshold of $Z > 3.0$, $p < 0.05$, shown on a standard T1 brain template anatomically normalized into MNI stereotactic space. The views are sagittal sections in planes either side of the midline (x co-ordinates in mm, negative to the left - LH - and positive to the right - RH). The one axial section (left panel) was oriented in the plane of the ventral temporal lobes (indicated on the sagittal planes at 40mm either side of the midline). The cross-hairs locate the center of mass of the visual word form area (Jobard et al., 2003). The yellow overlay represents activity that was stronger for stimuli presented in the left visual field ([LR and LF] versus [RR and RF]) and the blue overlay shows the reverse contrast ([RR and RF] versus [LR and LF]). The green overlay demonstrates the main effect of stimulus type; that is, regions more active during reading than during viewing false font stimuli, independent of hemifield of presentation ([RR and LR] versus [RF and LF]).

Bilateral frontal lobe activations were observed in the IFG, premotor cortex and the SMA. By examining the LR versus LF and the RR versus RF contrasts separately (shown in Figure 3.1.3), it was evident that these frontal regions were most strongly activated during the LR condition. This suggests that they may be driven by the increased executive control and attention required for reading in the left visual field, away from the natural window for attention in foveal and right parafoveal vision used for reading.

ROI Results in the Ventral Visual Stream

90th percentile z-statistic values for each ROI were calculated for each participant. ROI co-ordinates and group averages are reported in Table 3.1.2. ANOVAs were performed to assess the effects of hemifield of presentation and task in different reading-related areas.

2 x 2 x 2 repeated-measures ANOVAs with levels HEMISPHERE (left or right), HEMIFIELD (ipsilateral or contralateral) and TASK (reading or false font) was

conducted to compare the functional properties of the left and right ventral visual streams. In the earliest visual area, the pFG, there was a main effect of hemifield ($F_{(1,18)}=23.2$, $p<0.001$), but not of hemisphere or task, indicating that at this early stage, both hemispheres process word and false font similarly, and the extraction of location invariance has not occurred.

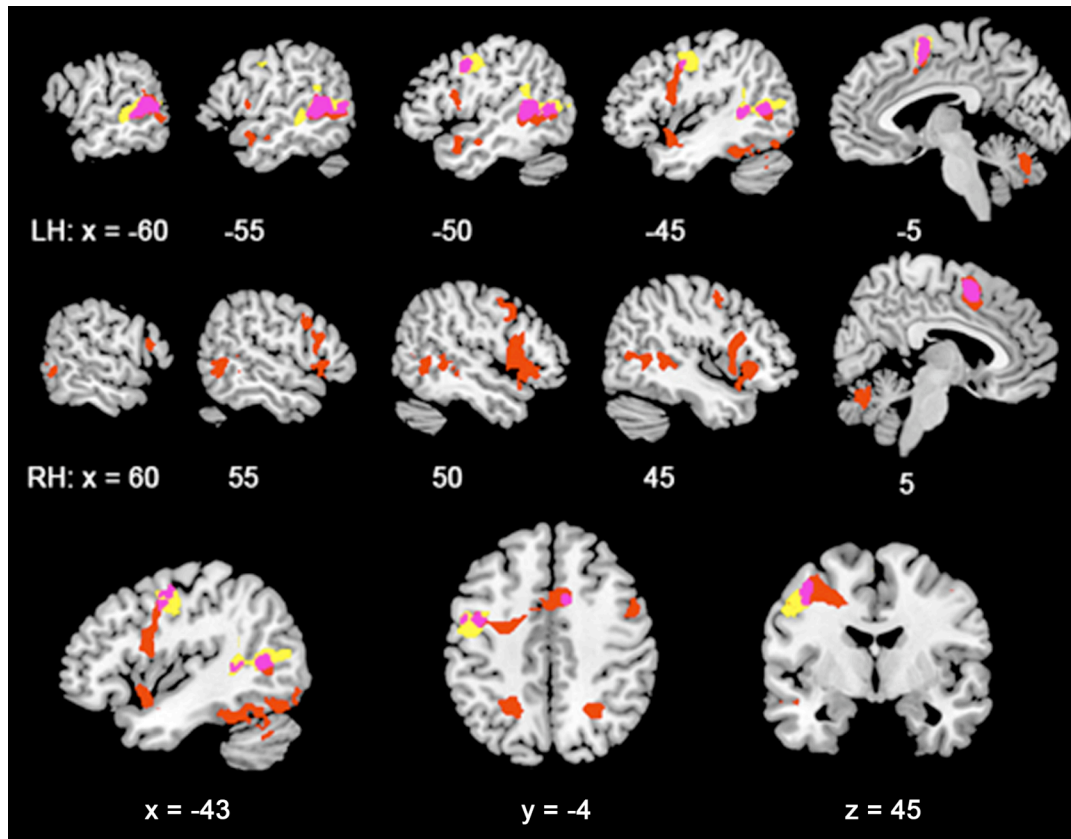


Figure 3.1.3. Color-coded overlays of activity for further contrasts, depicted as in Figure 3.1.2. On the left and right sagittal views (upper and middle rows, respectively), the red and yellow overlays demonstrate the effect of stimulus type in either hemifield: red demonstrates activity in the contrast of LR with LF, and yellow in the contrast of RR with RF. Pink demonstrates areas of overlapping activity for the two contrasts. The lower row shows these overlays on selected sagittal (left), axial (middle) and coronal (right) planes, with the x, y and z planes in mm.

Further forward in the VWFA, there was a main effect of hemifield ($F_{(1,18)}=34.1$, $p<0.001$), a hemisphere by task interaction ($F_{(1,18)}=20.5$, $p<0.001$). Post-hoc t-tests revealed that this interaction was driven by an advantage for words over false font stimuli in the left VWFA ($t_{(18)}=4.3$, $p<0.001$) but not the right VWFA ($t_{(18)}=0.5$, $p=0.6$). In the mFG, there were main effects of hemifield ($F_{(1,18)}=12.9$, $p<0.005$), task ($F_{(1,18)}=20.6$, $p<0.001$) and significant interactions of hemifield by task ($F_{(1,18)}=10.0$, $p<.01$) and hemisphere by task ($F_{(1,18)}=31.8$, $p<0.001$).

Table 3.1.2. Table detailing the location of the twelve regions of interest, their MNI coordinates, and the mean (standard deviation in brackets) change in z-statistic, 90th percentile voxel value across the ROI, for the four contrasts of interest (n=19).

Region	MNI (x y z)	Left Read	Right Read	Left False	Right False
L pFG	-26 -72 -14	4.59 (2.07)	5.02 (1.95)	4.67 (1.94)	4.84 (1.97)
L VWFA	-44 -58 -15	2.50 (1.54)	2.74 (1.62)	2.22 (1.53)	2.46 (1.60)
L mFG	-42 -40 -22	2.94 (1.30)	3.12 (1.24)	2.64 (1.17)	2.66 (1.22)
L pSTS	-58 -50 10	3.13 (1.33)	3.13 (1.37)	2.63 (1.25)	2.52 (1.17)
L aSTS	-50 0 -18	3.24 (1.49)	3.30 (1.39)	2.90 (1.11)	2.74 (1.16)
R pFG	26 -72 -14	5.01 (1.84)	4.86 (1.82)	5.06 (1.82)	4.65 (1.79)
R VWFA	44 -58 -15	2.17 (1.59)	1.83 (1.59)	2.19 (1.55)	1.88 (1.60)
R mFG	42 -40 -22	2.68 (1.27)	2.52 (1.30)	2.62 (1.35)	2.57 (1.32)
R pSTS	58 -50 10	3.53 (1.12)	3.79 (1.29)	3.52 (1.32)	3.38 (1.12)
R aSTS	50 0 -18	3.01 (1.53)	3.13 (1.48)	2.92 (1.37)	2.87 (1.30)

One obvious limitation of the design of this study was the mismatched luminance of the experimental stimuli. LR and LF stimuli had left visual field luminance; RR and RF stimuli had right visual field luminance; and the baseline, ND, had right visual field luminance. However, close inspection of the ROI results shows that the effects observed in the ventral visual areas could not have been driven by luminance alone. If results had been driven by luminance in the peripheral visual field alone, a hemisphere by hemifield effect would have been observed (as the ND baseline would have subtracted luminance effects for the LR and LF conditions but not the RR and RF conditions). This was not evident in the ANOVAs described above, suggesting that activity in the ventral visual streams were driven by the stimulus location, and not luminance alone.

3 x 2 x 2 repeated-measures ANOVAs, with the levels REGION (pFG, VWFA and mFG), HEMIFIELD (ipsilateral or contralateral) and TASK (reading or false font), were performed to investigate how the functional properties of the ventral visual streams changed along their posterior-anterior axis. In the left hemisphere, there were significant interactions between region and hemifield ($F_{(1,18)}=8.3$, $p<0.005$) and region and task ($F_{(1,18)}=10.9$, $p<0.005$), demonstrating that the effect of hemifield became weaker in more anterior

regions, whilst the effect of task became stronger. In the right hemisphere, only the region by hemifield interaction was significant ($F_{(1,18)}=6.9, p<.01$).

ROI Results in the Lateral Temporal Stream

Similar 2 x 2 x 2 repeated-measures ANOVAs (with factors HEMISPHERE, HEMIFIELD and TASK) were computed for the lateral temporal lobe regions. The pSTS region showed main effects of hemisphere ($F_{(1,18)}=6.4, p<.05$) and task ($F_{(1,18)}=26.1, p<0.001$), and a significant hemisphere by task interaction ($F_{(1,18)}=6.9, p<0.05$). The aSTS showed a main effect of task ($F_{(1,18)}=11.3, p<0.005$) and a task by hemisphere interaction ($F_{(1,18)}=9.6, p<.01$). These results demonstrate that there is no effect of hemifield of presentation in the lateral temporal streams, but there is a reliable effect of lexicality. In both regions, the hemisphere by task interaction was driven by stronger word-preferentiality in the left hemisphere than the right hemisphere.

Discussion

This study partially confirmed the predictions regarding the location of the reading networks. Reading-related activations were demonstrated in the left ventral visual stream and in the left and right lateral temporal cortices. ROI analyses demonstrated a posterior-to-anterior gradient in the left ventral visual stream of increasing preference for words and decreasing sensitivity to location. By comparison, none of the right ventral visual stream regions showed preference for words.

Although the reading-related activity was left-lateralized in the ventral temporal lobe, it was bilateral along the STS. There are a number of studies indicating that verbal semantic processing is dependent on activation of both anterior temporal lobes (Xu et al. 2005; Spitsyna et al. 2006; Awad et al. 2007; Ferstl et al. 2008; Warren et al. 2009; Visser et al. 2010), with activity greatest for narratives (Xu et al. 2005). Reading-related activity in the posterior STS has been observed less frequently – Xu and colleagues (2005) observed such a locus of activity in response to written text presented using the RSVP technique, whereas the PET study of Spitsyna and colleagues (2006), where paragraphs of text were read in the normal

manner, demonstrated that activity within the caudal right temporal lobe was no greater for text than false font. This discrepancy may relate to the manner of presentation of the narratives rather than reading per se; for example, RSVP may make greater demands on sustained visual attention (Singh-Curry & Husain, 2009). Other non-naturalistic factors were the words being presented in parafoveal vision, with the subjects instructed not to direct foveal vision towards the centre of each presented word, a response that was much easier to inhibit when false font was presented as demonstrated by the eye-tracking results.

In addition to delineating the reading-related networks in healthy volunteers, this study was designed to investigate the effects of reading in the left visual field. A bilateral frontal network was shown to be active during both LR and RR conditions, but most strongly for reading in the left visual field. This may correspond to the dorsal attention network, which is active in tasks requiring sustained, voluntary control of attention (Corbetta & Shulman, 2002). Alternatively, it may be related to the increased attentional control required to avoid the impulse to saccade towards each word, as the dorsolateral prefrontal cortex is known to be involved in response inhibition (Rubia et al. 2003; Aron & Poldrack, 2006; Li et al. 2006; Chevrier et al. 2007). This generated a prediction that studies of the patients with RHH would show increased activity in these areas due to the patients' reliance on the left parafoveal field for reading.

In relation to the final aim of this study, it is of interest that the differences between word and false-font processing were relative, not absolute. An activity profile of words > false font > numbers was observed in the 'reading-related' left ventral visual stream and the lateral temporal streams.

This observation is not easy to interpret in the context of the Local Combination Detector model (Dehaene et al. 2005). This model proposes that activity along the ventral visual stream for reading becomes increasingly selective for familiar word-like orthography. It seems plausible that false font stimuli and numbers would activate the early stages of LCD processing

hierarchy to some extent, as they share similar visual features with letters. As the stages of the LCD model are not thresholded, this low-level activity may flow forwards to subsequent stages even if the shapes do not map on to any known representation of letters, bigrams or words. Hence, the LCD model might predict weak activity along the extent of the ventral visual stream for false font and numbers; or alternatively, given that numbers, like letters, are frequently encountered, meaningful visual stimuli, it might be predicted that the same areas that encode letter identity also contain ensembles of neurons that detect familiar numbers. In this case, stronger activity would be expected for numbers than false font, not the other way around. The observed profile of false font > numbers may have been due to the fact that only single numbers were presented rather than number strings, and at a slower rate than the false font stimuli. The data presented in Results Chapter 3.2 investigates whether the same activation profile is observed in the VWFA when words, false font and numbers are presented in an identical manner.

The widespread activation of heteromodal cortex by meaningless false-font stimuli is more easily explained by a distributed interpretation of reading (e.g. Seidenberg & McClelland, 1989; Plaut et al. 1996; Patterson & Lambon Ralph, 1999). Such models propose that word recognition is not a serial, hierarchical process, but instead relies on the spreading of activation throughout a distributed network, with interactive feed-forward and feed-back activation that resolve onto a stable 'attractor' network that corresponds to a familiar word. In this model, the VWFA is not the seat of an orthographic lexicon, but a bridging point between the unimodal visual input and the heteromodal areas of the temporal lobe (Devlin et al. 2006). Although these models have not been explicitly tested on false-font stimuli, it might be predicted that they would result in widespread activation that slowly declines in the absence of the stimuli mapping on to attractors. The present study does not have the temporal resolution required to prove or disprove this hypothesis, but future studies with MEG or EEG-based connectivity methodology may shed more light on the matter.

Conclusion and future direction

This study has demonstrated reading-related activity in the left ventral visual stream and bilaterally in the lateral temporal lobes. Activity in these areas was preferential for words over perceptually-matched false font stimuli, and insensitive to the low-level visual characteristic of stimulus location. It has shown that reading in parafoveal vision, particularly in the left visual hemifield, elicits activity in a frontoparietal network that may be associated with control of attention or inhibition of eye movements. This may be pertinent to the interpretation of fMRI studies of patients with visual field defects who rely on their parafoveal vision for reading.

There were two issues with the experimental design that limit the interpretation of the results. Firstly, the number decision baseline was not closely matched to the word and false font conditions, which makes it difficult to interpret the response profile observed in the left vOT cortex. The study described in Results Chapter 3.2 investigated whether the same response profile would be observed when the number reading condition used a passive rather than active task, and when the number stimuli were matched in presentation rate and string length to the word and false font conditions.

The second issue relates to the use of narrative texts rather than unconnected words in the reading conditions. It is possible that the extensive right STS activity observed in the present study was driven by the use of narrative text stimuli, as it has been shown that increasing the contextual load of written stimuli (i.e. by presenting words in sentences or narratives) engages a more widespread, bilateral network of cortical regions (Xu et al. 2005). Results Chapter 3.2 tests this hypothesis directly by comparing blocks of narrative text with blocks of unconnected words.

3.2 Investigating the effect of sentence coherence in healthy volunteers

The previous study identified the broad network involved in reading. By varying the location of presentation it was possible to distinguish between early visual activations that were observed in the hemisphere contralateral to stimulus presentation, and higher-order 'abstract' activations, which were lateralised to the left ventral stream irrespective of stimulus location. The functional profile observed in the left vOT cortex (words > false font > numbers) cannot be explained by the LCD model of reading, which would predict equally low activation for any non-verbal stimuli (words > false font = numbers); or, if it could be assumed that numbers are encoded similarly to letters in the vOT cortex, it would predict stronger activation for numbers than unfamiliar false fonts (words =/> numbers > false font). The latter prediction cannot yet be ruled out, as it is possible that the slower rate of presentation for numbers than words or false font resulted in the reduced activation for numbers. The present study tested the activation profile for words, false font and numbers when presentation rate was matched across all conditions.

The previous study also observed reading-related activity in the anterior and posterior extents of the left and right lateral temporal lobes. The STS is an area of heteromodal cortex and has been implicated in the higher-order processing of language, irrespective of modality. Whilst activity in the left superior temporal sulcus (STS) during reading is reliably reported in the literature, the evidence for the involvement of the right STS is less consistent. Functional imaging studies of speech comprehension and speech production have shown activity in the bilateral anterior temporal lobes (aTL) and the left lateralised posterior STS (Awad et al. 2007; Warren et al. 2009), and this network has also been replicated by a metaanalysis of language tasks of any modality versus perceptual baselines (Ferstl et al. 2008). Hence, it has been proposed that the right aTL shares semantic functions with the left aTL, and possibly the left pSTS. However, Moore and Price (1999) and

Spitsyna and colleagues (2006) found largely left lateralised STS activity when comparing reading with false font conditions.

In the context of this literature, the strong right pSTS activity reported in Results Chapter 3.1 is unusual. The presence or absence of right STS activations may depend on depth of semantic processing: reading narrative texts may activate a more widespread, bilateral network than reading single words due to the increased semantic and syntactic processing involved. Xu and colleagues (2005) compared activity during word, sentence and narrative reading conditions using an RSVP protocol. In the word reading condition, activity was restricted to the left STS, but spread into the right aTL and pSTS for the other conditions with higher semantic (and indeed syntactic and contextual) load. The present study tested the prediction that activity in the right aTL and pSTS is dependent on semantic processing above the single word level by comparing the lateralisation of activations in response to narrative texts versus lists of unconnected words.

An alternative explanation for the right pSTS activity could be that the unusual mode of presentation used (parafoveal RSVP) may have made particular demands on visual attention; and visual attention, both selective and sustained, is attributed to the right temporoparietal junction and inferior parietal lobule (Singh-Curry & Hussain, 2009). This study used centrally presented words to reduce the demands on visual attention, although RSVP was still employed.

The design of this study replicated the block design of the previous chapter and used the same narrative text and false font stimuli. The narrative stimuli were shuffled at random to produce the stimuli for the unconnected word reading condition. A passive number reading task was used to allow a closer match to the word and false font conditions. In order to discriminate between domain-general effects of stimulus continuity throughout the block, and domain-specific effects of semantic coherence in the sentence reading conditions, the numbers were presented as connected or unconnected stimuli. In the connected number condition, the stimuli were manipulated to

contain sequences of increasing or decreasing numbers within the block. Hence, the nature of the 'continuity' in the reading and number conditions was very different. Thus, the conditions formed a 2 X 2 factorial design with the factors stimulus type (words or numbers) and stimulus continuity (connected or unconnected). False font and checkerboard baselines were used to evaluate the response profiles of the ventral visual and lateral temporal areas of interest.

Experimental Procedures

Participants

19 healthy, right-handed volunteers (9 female, average age 28, 10 months) participated in this study. As in Study 3.1, none of the subjects had a history of neurological, psychiatric or developmental reading disorders. Written consent was obtained from all participants and all procedures were approved by the local research ethics committee.

Procedure

As in the previous study, the MRI data was acquired on a 3-Tesla Philips Intera MRI scanner using an EPI sequence with a 3 second TR, with whole-brain coverage over 48 axial slices, thickness 5mm and no slice gap. The in-plane resolution was 2.5 by 2.5 mm. Slices were acquired in an interleaved ascending order.

A block design was used. One fMRI run of 298 volumes and one T1-weighted structural MRI scan were acquired for each participant. The fMRI run consisted of 6 repetitions of 6 experimental conditions. Of the 6 conditions, four formed a 2 X 2 factorial design with the factors stimulus type (words versus numbers) and narrative type (connected versus unconnected stimuli). The other two conditions were a false font baseline and a low-level visual checkerboard baseline. Within each block there were 37 stimuli, each presented for 470ms, making the total block duration 17.39 seconds. There was a 6 second gap between blocks, during which time the fixation cross remained on screen.

Stimuli

The stimuli for the sentences condition were the same narrative texts used in Results Chapter 3.1. The unconnected words used the same words, but shuffled into a random order. The numerical stimuli were number strings matched to the connected words stimuli for string length. In the connected numbers condition, the blocks contained sequences of increasing or decreasing numbers. These sequences were matched in length to the sentences in the connected words condition. The unconnected numbers used the same numbers, but shuffled into a random order.

The false font baseline used strings of Greek characters, following the same arbitrary Roman-to-Greek correspondence system as described in Results Chapter 3.1, meaning that the false font stimuli were unintelligible symbols, matched in string length to the number and word conditions. The checkerboard baseline presented black and white visual checkerboards where the width of the checkerboard varied from trial to trial, matching the stimulus width of the other conditions.

All tasks were passive, with no response required from the participant. The participants were instructed only to attend equally to all stimuli. They were advised that some blocks would contain sentences or connected sequences of ascending or descending numbers.

Data Analysis

EPI data preprocessing was performed as described in the Methods Chapter, except for the use of non-linear registration for the transformation of the T1 structural scan into standard space, rather than the standard linear registration approach (Andersson et al. 2007a; Andersson et al. 2007b). Data was smoothed at 7mm FWHM. The whole-brain analysis used a first level within-run analysis modelling the six experimental conditions as EVs (plus motion parameters as confounding variables), and a second level, mixed-effects group analysis (a sample first-level design matrix is included in the Appendix). Two group-level analyses were performed: one evaluating the main effects of stimulus type and stimulus continuity as a factorial design,

and one specifically comparing sentences with unconnected words. Results were presented using a cluster-corrected threshold of $Z > 2.3$, $p < 0.05$.

A region of interest (ROI) approach was used to assess lateralisation of narrative text processing in the left vOT cortex and the anterior and posterior lateral temporal lobes. The same ROI locations and analysis technique were used as described in Results Chapter 3.1. ROI spheres with a 7mm diameter were defined in the left vOT cortex (at co-ordinates matching the VWFA), and the left and right posterior STS (pSTS) and anterior temporal lobes (aTL). Featquery was used to extract the 90th percentile z-statistic value for each condition. The checkerboard condition was used as a low-level visual baseline.

Results

Effects of stimulus type and stimulus continuity

The main effect of stimulus type (depicted below in Figure 3.2.1) showed activity that was preferential for words over numbers in a similar network of reading-related cerebral activity to that described in Results Chapter 3.1. This included the left vOT cortex, the bilateral STS, IFG and premotor cortex and the SMA. A significant cluster was also observed in the right primary visual cortex.

Preferential activity for numbers over words was observed in the bilateral occipital poles, extending dorsally into posterior parietal cortex, and, in the right hemisphere only into lateral occipital cortex and the posterior extent of the fusiform gyrus. Right lateralised activity for numbers was observed along the intraparietal sulcus (IPS), extending into the post-central gyrus. Finally, activity peaks in the anterior and posterior cingulate gyrus, the precuneus and bilateral prefrontal activity were also associated with the number-reading task. This set of medial regions is commonly described as the default-mode network (Raichle et al. 2001), and may reflect the less engaging nature of the number reading tasks compared to the word reading tasks.

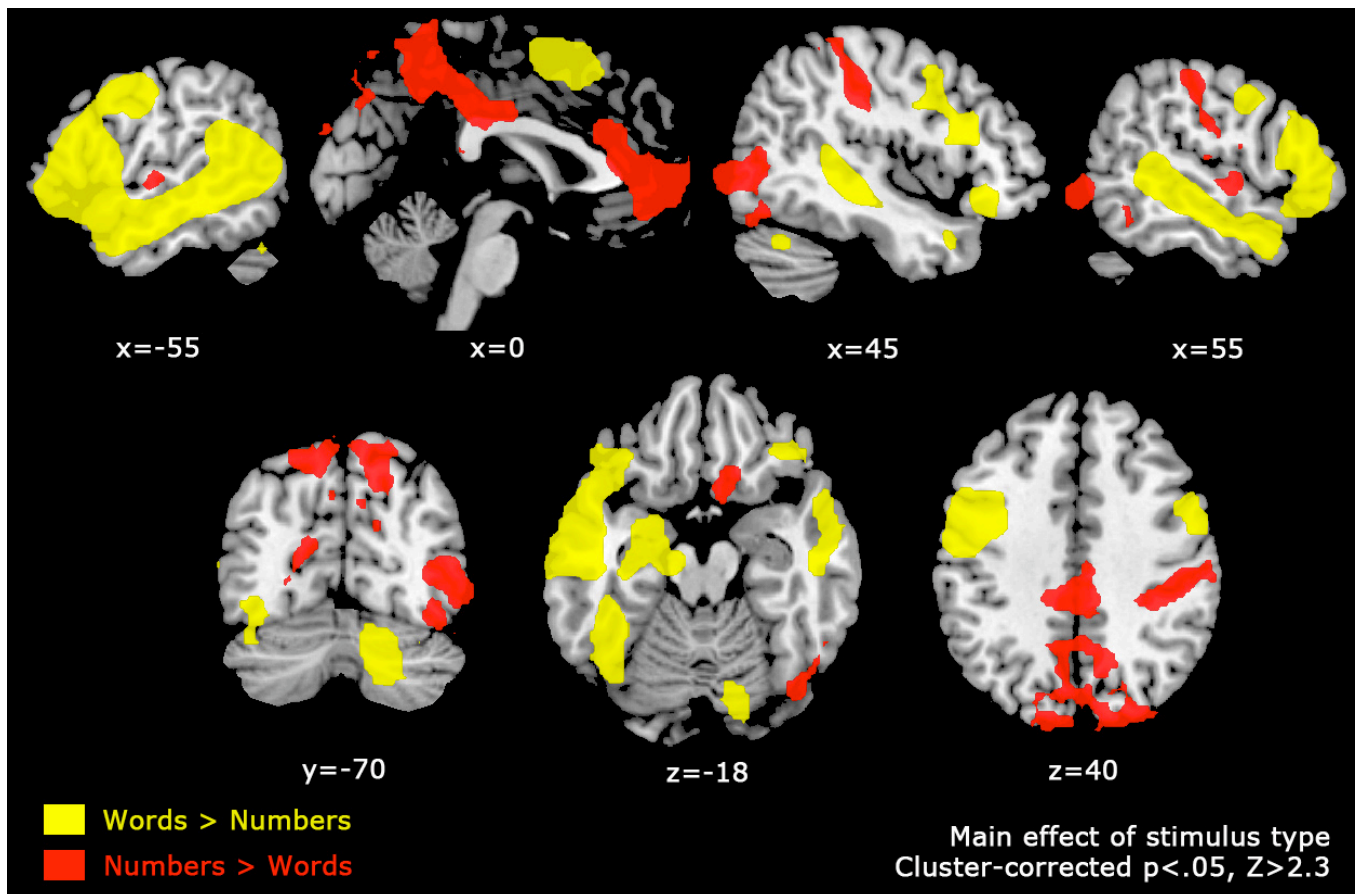


Figure 3.2.1. Statistical parametric maps of the results from the factorial analysis, showing the main effect of stimulus type. Areas shown in yellow were preferentially activated by words (sentences or unconnected words) relative to numbers (connected or unconnected numbers), including the left vOT cortex, bilateral STS, IFG and premotor cortex and the SMA. Areas shown in red were preferentially activated by numbers relative to words, including the default mode network (the posterior and anterior cingulate gyrus and the precuneus), the posterior parietal cortex, the right intraparietal cortex extending into the post-central gyrus and the right lateral occipital cortex.

The main effect of stimulus continuity did not show any activity that was preferential for connected stimuli, but showed activity that was preferential for unconnected stimuli in default mode network, including the precuneus and the anterior and posterior extents of the cingulate gyrus.

Sentences versus unconnected words

A contrast of sentences versus unconnected words was performed to directly assess the lateralisation of sentence processing in the lateral temporal lobes. This revealed one significant cluster in the left lateral temporal lobe, extending from the posterior to the anterior extents of the STS (Figure 3.2.2). The strongest peak was located at middle of the STS, at MNI coordinates -52 -20 -12, $z=3.6$. The opposite contrast of unconnected versus connected words did not reveal any significant activity.

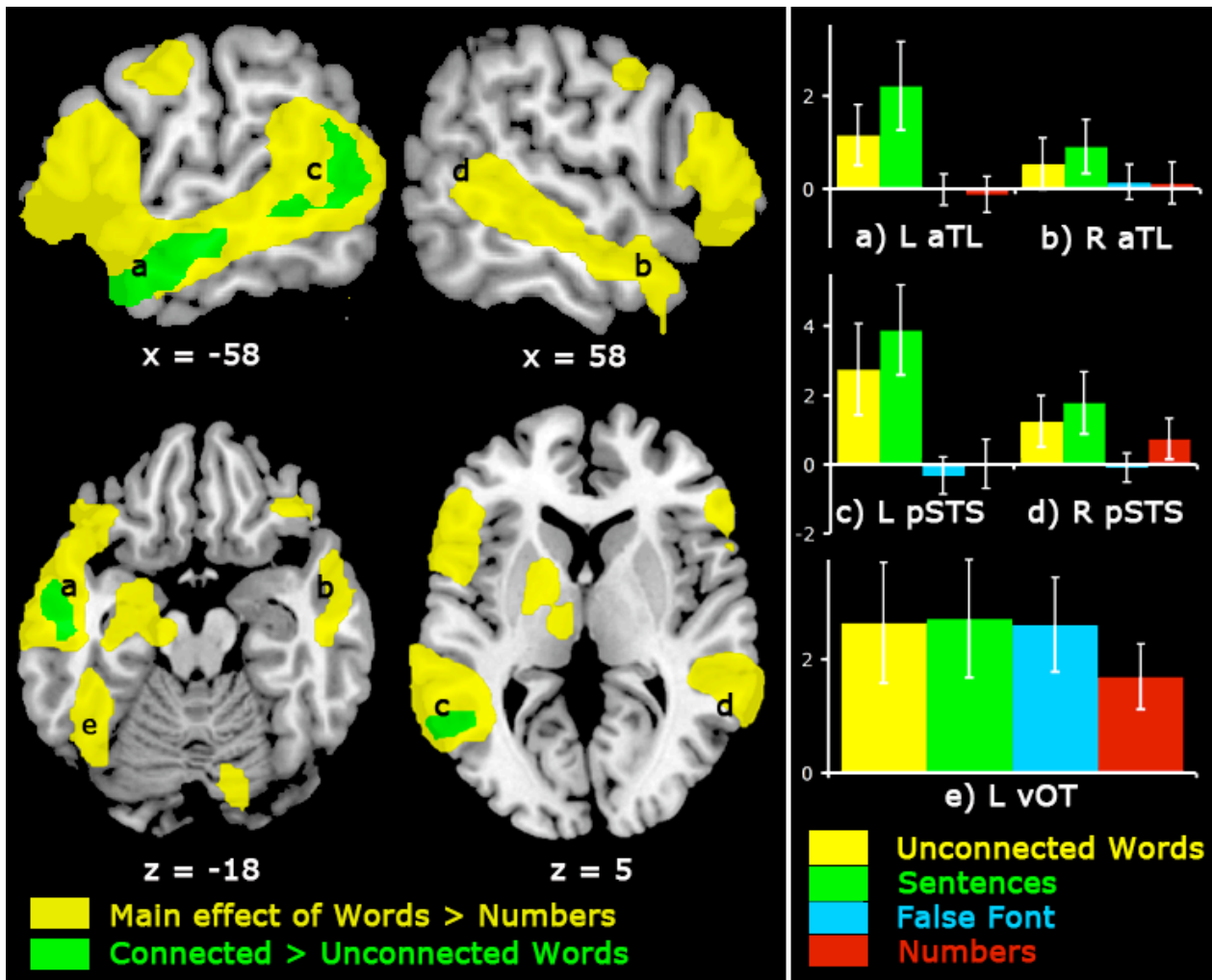


Figure 3.2.2. Left panel: statistical parametric maps showing the main effect of words versus numbers in yellow, overlaid with the contrast of sentences versus unconnected words in green. The left STS was more strongly activated by sentences than unconnected words. A cluster-corrected threshold of $p < .05$, $Z > 2.3$ was used. Right panel: bar plots showing the profile of activity in the five key ROIs: a) the left aTL, b) the right aTL, c) the left pSTS, d) the right pSTS and e) the left vOT cortex. Both the left pSTS and aTL showed significantly stronger activity for connected than unconnected words. Error bars are 95% confidence intervals.

The ROI analysis extracted the 90th percentile z-statistic value in the left vOT cortex and the posterior and anterior temporal lobes for the sentence, unconnected words, unconnected numbers and false font conditions relative to the checkerboard baseline. A repeated-measures ANOVA was conducted with the factors region (anterior or posterior temporal lobe), hemisphere (left or right) and task (connected or unconnected words). All three main effects were significant (region: $F_{(1,18)}=16.3$, $p < .005$; hemisphere: $F_{(1,18)}=20.8$, $p < .001$; and task: $F_{(1,18)}=7.0$, $p < .05$). The ROI plots presented in Figure 3.2.2 show that these main effects were due to stronger activity in the posterior regions, in the left hemisphere, and for connected than unconnected words.

The left vOT ROI showed stronger activity for words (either as sentences or unconnected words) and false font than for numbers. Paired t-tests confirmed that these differences were significant (unconnected words versus numbers, $t_{(18)}=2.6$, $p<.05$; false font versus numbers, $t_{(18)}=3.0$, $p<.005$). Surprisingly, there was no difference in the left vOT between activity for words and for false font ($t_{(18)}=.09$, $p=.9$). When a reduced threshold was used to examine the contrast of words versus false font more closely ($Z>1.9$, uncorrected), a small cluster of word preferential voxels were observed anterior to the standard VWFA coordinates, with a peak at -40 -36 -26 ($Z=2.2$).

All four temporal lobe ROI were activated by sentences and unconnected words, but were not significantly activated by numbers or false font (with an average z-statistic < 1 in each case). The left lateral temporal lobe showed a significant effect of narrative coherence, with stronger activity for sentences than unconnected words in the left pSTS ($t_{(18)}=3.0$, $p<.01$) and the left aTL ($t_{(18)}=2.6$, $p<.05$).

Discussion

The primary aim of this study was to test the effect of sentence coherence on the temporal lobe activations. The previous study demonstrated a strongly bilateral reading-related response in the lateral temporal lobes, whilst most other studies in the literature report left lateralised temporal activity. In response to this unexpected finding, it was predicted that reading narrative texts activate a more widespread, bilateral network of semantic-processing areas than single words. The results of the present study did not align with this prediction. The ROI analysis demonstrated that whilst both the left and right STS were activated during the reading conditions, only the left hemisphere regions were preferentially activated by sentences over unconnected words. Hence, the bilateral temporal activation observed in both studies could not be attributed to the use of narrative texts rather than single words.

An alternative explanation proposed in the previous chapter was that the unexpected activation in the right pSTS could have been due to the unusual visual demands of the RSVP task. The current study reduced the demands on visual attention by presenting stimuli centrally rather than parafoveally, but there was still a necessity to maintain fixation and inhibit saccades. If the pSTS activity was an effect of different attention demands, it would appear that this was selective for the reading task, as the pSTS showed very low activity for the false font condition, which was also presented using RSVP. As it stands there is not enough evidence to fully interpret the role of the right pSTS in reading, and an experiment directly comparing activity during RSVP reading and naturalistic text reading would be required to resolve this question.

Results Chapter 3.1 showed stronger activity in the temporal lobe ROI for false font over the active number decision baseline. The present study, by comparison, showed equal activations for false font, numbers and checkerboards in all of the four temporal lobe ROI, which were all only slightly higher than rest (with z-statistics around $Z=0.8$). This demonstrates that the lateral temporal ROI were preferentially activated by meaningful verbal stimuli over meaningless, perceptually-matched stimuli. The reduced temporal lobe activations for the number decision task in Results Chapter 3.1 may have been the result of the slower presentation rate, the use of small 3-digit number strings, or an effect of the active number processing task.

A second aim of this study related to the functional profile of the left vOT cortex. The previous study reported an activation profile in the left vOT cortex of words > false font > numbers, demonstrating that the specialisation of the ventral visual stream for word processing does not accord well with the LCD model of reading. However, the profile of activation could have been driven by differences in presentation style for the three conditions: the numbers were presented centrally, at a slower rate than the words and false font stimuli, and with an active rather than passive task. The present study tested whether the same activation profile would be observed when the presentation style was closely matched across conditions. The left

vOT cortex showed significant activity in all three conditions relative to the checkerboard baseline, with stronger activity for words and false font stimuli than numbers. Surprisingly, there was no difference in left vOT activation for words and false font, although a small area of activity that did not reach cluster-level significance was observed just anterior to the VWFA coordinates.

Despite the contradictory findings for the false font condition, both studies demonstrated stronger activity in the left vOT for words and false font stimuli than for numbers. The LCD model cannot explain why false font stimuli should activate the left vOT more than numbers – it would predict that either the left vOT would show a category specific preference for written words over all other stimuli, or (if it could be assumed that numbers are encoded in the ventral visual stream similarly to letters) stronger activity for numbers over false font. Neither of these possibilities was supported by the present data.

The interactive view of left vOT function raises an alternative interpretation of these results. Proponents of this view suggest that activity in the left vOT is not driven purely by hierarchical orthographic processing, but also by top-down modulation from higher order areas in a task dependent manner (Price & Devlin, 2003; Devlin et al. 2006; Starrfelt & Gerlach, 2007). When words are presented, the implicit reading task modulates activity in the left vOT cortex. However, when numbers are presented, the implicit task is not reading but number processing, which has its own distinct neural network. As number semantics are processed in the parietal lobes rather than the temporal lobes (Jefferies et al. 2005; Thioux et al. 2005; Cappelletti et al. 2010), the top-down modulation would be predicted to occur in the occipito-parietal connections of the dorsal visual stream rather than the ventral visual stream. Because the false font stimuli are ambiguous, they may elicit top-down modulation in either ventral or dorsal streams. Although this interpretation is highly speculative, it could be tested directly by presenting number words ('three') and number digits ('3'), and varying the task demands so that the stimuli are treated as words or as numbers. The distributed view would predict that the left vOT cortex would be activated for

both words and digits if the task engaged top-down control from the left temporal lobe, for instance, if a phonological decision was required. By comparison, if the task engaged top-down control from the numerical processing areas of the parietal lobe, such as in a number decision task, the left vOT activity for words or digits would be reduced. Alternatively, if the left vOT is predominantly driven by bottom-up orthographic processing, as predicted by the LCD model, it would be unaffected by task demands.

The main effect of stimulus type in the whole-brain ANOVA demonstrated number-preferential activity in the default mode network, comprising the anterior and posterior extents of the cingulate gyrus and the medial precuneus. It was inferred that was due to the more engaging nature of the implicit reading task relative to the passive number reading conditions. The main effect of numbers versus words also activated the occipito-parietal cortex, the posterior parietal cortex, the right IPS extending into the post-central gyrus.

The dorsal visual stream runs from the occipital cortex to posterior parietal cortex (PPC), and is known to be involved in vision for action (Ungerleider & Mishkin, 1982; Goodale & Milner, 1992). Whilst the posterior portion of the IPS has been implicated in processing of number semantics (Dehaene et al. 1999; Thioux et al. 2005; Cappelletti et al. 2010), this interpretation is complicated by the fact that the IPS and PPC are known to have multiple functions. The posterior eye field is located in the IPS, and is part of a frontoparietal network that controls visually-guided eye movements movements (Muri et al. 1996; Corbetta et al. 1998; Simon et al. 2002; Macaluso et al. 2003; Pierrot-Deseilligny et al. 2004). This eye movement system closely overlaps with a frontoparietal network for the control of spatial attention (Nobre et al. 1997; Gitelman et al. 1999; Simon et al. 2002; Macaluso et al. 2003; Corbetta et al. 1998), although some evidence suggests that eye movements activate a more posterior region of the IPS than tasks involving covert shifts of attention with no eye movements (Simon et al. 2002; Macaluso et al. 2003; Pierrot-Deseilligny et al. 2004). This frontoparietal network was evident in the previous study, particularly for

reading words in the left visual field where there was a strong requirement to inhibit eye movements and shift spatial attention away from fixation. As the present study used central presentation, the sustained attention required to inhibit eye movements was reduced, but it remains a possibility that participants made more attention-directed eye movements during the number conditions than the reading conditions. This could have resulted from attention being sequentially directed to only the last digit of each number, as subjects ascertained whether a numerical sequence was or was not present. The fact that only the posterior part of the frontoparietal system was observed might be taken as support for the number processing interpretation, but this is weak evidence at best. On-line eye tracking would be required to help determine whether the IPS activity in this study is related to number processing or more general visuo-spatial processes.

Finally, increased activity for numbers over words was observed in the right lateral occipital cortex and posterior fusiform gyrus. This fusiform activity was considerably more posterior than the VWFA proper (with a peak at 42 - 72 -18, $Z=3.3$), and far less extensive than the word-preferential activity observed in the left fusiform gyrus. Both the right posterior fusiform and lateral occipital peaks fell within an area known as the lateral occipital complex (LOC), which is thought to play a 'general-purpose' role in object recognition – it responds more strongly to objects than non-objects, but it is not category-preferential (Malach et al. 1995; Grill-Spector et al. 1999; Grill-Spector et al. 2001; Pourtois et al. 2009). It is not possible to say whether the right LOC activity observed in the present study finding was driven by stronger-than-normal activity for numbers or reduced activity for words – additional object processing conditions would be required to test this.

Conclusion and future directions

This study has demonstrated left lateralised activity in the STS that is sensitive to narrative coherence in reading. This may reflect the semantic, syntactic and combinatorial processing demands that are inherent to sentence reading relative to reading word lists. It has also replicated the finding that the left vOT cortex is activated by words and false font stimuli,

but only weakly by numbers. The main effect of numbers versus words suggested that number processing is more heavily dependent on the dorsal visual stream rather than the ventral visual stream, perhaps with the involvement of the lateral occipital complex for number identification.

A further study into the function of the left vOT cortex has been proposed. The activity profile of the left vOT cortex, as demonstrated in the ROI results of Chapter 3.1 and 3.2, are hard to interpret in terms of orthographic processing alone, as predicted by the LCD model of reading. It is predicted that the word-preferential activity in the left vOT cortex is driven by top-down modulation from frontotemporal language areas. This could be tested by manipulating stimulus type (e.g. number words versus number digits) independently of task demands (verbal versus numerical). This proposed study is now being carried out in collaboration with another member of the Computational, Cognitive and Clinical Neuroscience Laboratory (C3NL).

Results Chapters 3.1 and 3.2 used the same experimental stimuli for the narrative reading and false font conditions, but observed very different results in the left vOT cortex. This discrepancy may reflect the different presentation styles used in the two studies, i.e. parafoveal versus central stimulus location. This observation has direct implications for studies comparing patients with hemianopic visual fields, who necessarily use parafoveal vision for reading, with healthy volunteers who read centrally. As the results of the words versus numbers contrast were much more consistent across the two studies than reading versus false font, number decision was chosen for the baseline in the patient fMRI study reported in Chapter 3.4.

3.3 Evaluation of a novel technique for improving single word reading in patients with acquired reading disorders

The previous chapters reliably identified activity in the left vOT during reading. This chapter explores the effects of a left occipitotemporal brain injury on various reading measures in a case series of patients, and presents a pilot study testing whether whole-word rehabilitation approaches may have beneficial effects on reading speed. The aims of this study were:

1. To investigate the behavioural effects of focal damage to the left vOT cortex on reading ability
2. To investigate whether individual differences in reading ability are related to the location of structural damage
3. To test whether an intensive, whole-word recognition training protocol could improve word reading ability
4. To test whether training effects were stimulus-specific or whether they generalised to novel stimuli.

The literature reviewed in the introduction predicts that patients with HA have impaired text reading speed and accuracy but relatively spared word reading ability. Their word reading is likely to be marginally slower than normal with a small word length effect due to the effects of the callosal transfer of information from the right occipital cortex to the left language dominant hemisphere. Word reading errors might also arise where letters at the end of words fall into the hemianopic right visual field.

Conversely, patients with PA are known to be impaired at the level of whole word recognition, which causes a more severe deficit in reading speed and accuracy, and a more substantial word length effect. Although letter reading is typically reported as being relatively spared, a recent study by Starrfelt and colleagues (2009) showed that patients with PA were also impaired at single letter identification.

The behavioural profiles of a group of patients with HA or mild PA are reported here, using measures of text reading, word reading and letter reading ability. An attempt was made to relate variability between the patients on these measures to variability in their structural damage, with the prediction that damage to the left vOT cortex would cause more severe deficits in reading ability.

Patients with acquired reading disorders are rare, and are often difficult to trace as they have little or no major disability and so may have little contact with hospital stroke services. Inevitably, the patient population recruited from a single site was limited, but sufficient to test whether a larger study of reading training is warranted. Reading ability varied substantially within the patient group, allowing a further investigation of whether lesion location correlated with the behavioural measures. The patients mostly had mild to moderate reading deficits, with average reading speeds of just over one second per word, and as such were not impaired enough to warrant compensatory rehabilitation methods such as kinaesthetic training that have proven successful in patients with very slow reading speeds (Lott et al. 1994; Seki et al. 1995; Maher et al. 1998; Lott & Friedman, 1999; Sage et al. 2005). Instead, the rehabilitation aimed to improve single word reading speed using a repetitive whole-word recognition protocol, similar to the approaches described by Friedman and Lott (2000).

It has been shown that patients with PA can show significant item-specific improvements in word recognition following repeated word presentation with feedback (Friedman & Lott, 2000; Lacey et al. 2010). It was hypothesised that such rehabilitation approaches work in a similar fashion to paired associate learning – frequent exposure to the written word form, paired with the auditory feedback of the spoken word will strengthen the orthographic representation of that word, which will facilitate word recognition in future. Hence, it was predicted that training with a paired associate learning task on a corpus of words would lead to item-specific improvements in word recognition.

In order for item-specific training to be useful, a large corpus of words must be trained. As repeated presentation of each item is required, this will amount to a large total number of trials. The present study used a computer-based approach to maximise the amount of time the patient could spend on the training, and incorporated a monetary award to motivate the patients to do the training. Words were presented briefly on screen (for 500ms) to suppress the letter-by-letter reading strategy and encourage whole-word recognition instead. Words were presented simultaneously with their spoken counterparts as visual-auditory pairings. Training blocks were interleaved with testing blocks in order to keep the participant engaged. In test blocks, the participant was required to decide whether the visual and auditory stimuli matched or not.

Each patient was tested at four time points. Two baseline measures were acquired (t1 and t2), spaced by a two to four week interval, to ensure that the patient's pre-training reading ability was stable. The training then commenced for six-weeks. A further two post-training measures were acquired (t3 and t4), spaced by a two to four week interval, to test whether reading ability had changed, and whether any training effects persisted after cessation of the training. Testing materials were designed using two matched word lists (list A and list B) in order to test whether training effects generalised across stimuli.

Experimental Procedures

Participants

Informed, written consent was obtained from all participants (patients and volunteers). Participant information materials were provided in written and audio formats as required.

Thirteen patients (5 female; mean age 59 years, 6 months) with PA or HA were recruited through neurology clinics. All patients complained of slow single word reading as a result of focal brain damage. At least six months had elapsed between the onset of their symptoms and their first assessment sessions to ensure that they were stable and unlikely to show spontaneous

recovery. All participants were right handed and spoke English as their first language. Most patients had visual field defects, as confirmed by Humphrey or Goldmann perimetry. Demographic information, including lesion type and eye-field details for each patient, is given in Table 3.3.1. Exclusion criteria for participation included:

- A pre-morbid history of neurological or psychiatric illness, or a developmental reading disorder that might indicate atypical brain development
- A co-morbid deficit of speech production or comprehension that might indicate a central rather than peripheral alexia, other than mild word finding deficits, which are common in patients with PA
- Evidence of visual neglect or other visuo-spatial processing deficit (other than a visual field defect) that would prevent the patient from performing the training tasks
- Evidence of a marked verbal memory deficit that might hinder the participant's ability to comply with the experimental procedures. PCA territory infarcts may extend into the medial temporal lobe (MTL) and involve the parahippocampal gyrus or hippocampus, resulting in severe verbal memory impairment if there is extensive MTL destruction. Patients were included if they had a mild verbal memory deficit.

A control group was formed by selecting 13 participants from the larger group of 20 healthy volunteers described in the previous chapter. Each patient was paired to a healthy control participant of the same sex and of a similar age. The mean age of the control group was 58 years and 11 months. A paired-subject t-test confirmed that there was no significant difference in age between the patient and control groups ($t_{(12)}=.32, p=.76$).

Table 3.3.1. Demographic information for the patient group. [p]RHH = [partial] right homonymous hemianopia; RIQ = right inferior quadrantanopia; RSQ = right superior quadrantanopia; sparing = the extent of spared visual field expressed in degrees from the vertical meridian – if not stated, there was no sparing; HA / PA = hemianopic or pure alexia, based on a criteria of WLE < / > 100ms/letter.

Patient	Age at symptom onset (y)	Time since onset (y, m)	Sex	Visual Fields (sparing)	Cause of lesion	HA / PA
1	34	1, 10	f	RHH	Tumour	HA
2	33	8, 11	m	RHH (1°)	Haemorrhage	PA
3	64	2, 6	m	Normal	Infarct	HA
4	67	9, 6	f	RHH (1°)	Infarct	PA
5	45	8, 7	m	RHH	Head injury	PA
6	47	6, 5	m	RSQ	Infarct	HA
7	75	0, 6	f	RIQ	Infarct	PA
8	28	4, 10	f	pRHH (1°)	Haemorrhage	PA
9	67	7, 2	m	RIQ	Infarct	HA
10	69	8, 11	f	RIQ	Infarct	HA
11	61	2, 1	m	RSQ	Infarct	HA
12	61	8, 1	m	RSQ	Infarct	HA
13	53	9, 6	m	RHH (<1°)	Infarct	HA

Procedure

All procedures were approved by the local research ethics committee. A test-retest design was used, with four time points, t1 to t4. Reading was assessed at two baseline sessions, t1 and t2, separated by two to four weeks, to ensure that reading speed was stable prior to commencing the training. The training was self-administered over a six-week period, followed immediately by a post-training assessment at t3 and a follow-up assessment 2-4 weeks later at t4. The healthy volunteers participated in the t1 and t2 sessions to provide normative data for the reading tasks.

At each session, participants were tested for their letter, word and text reading speed and accuracy. In addition to the reading assessment, the patients (but not the healthy volunteers) were tested with a behavioural test battery at t1 to screen for any of the co-morbid disorders described in the exclusion criteria. A T1-weighted structural MRI scan was also acquired at t1.

Functional imaging was performed at t1-t3: this data is described in results chapter 3.4.

Behavioural Assessment

A battery of psychological tests was administered at t1 to confirm the diagnosis of a peripheral reading disorder and to rule out the presence of any confounding co-morbid impairments. The battery was comprised of:

- the Baxter Graded Spelling Test (Baxter et al. 1982) to screen for deficits in orthographic knowledge
- the Graded Naming Test (McKenna and Warrington, 1980) to screen for anomia
- the Star Cancellation subtest from the Behavioural Inattention Test (Wilson et al. 1987) to screen for visual neglect
- the Word List Recall subtest from the Kaplan Baycrest Neurocognitive Assessment (Leach et al. 2000) to screen for deficits in verbal memory.

Four patients (patients 5, 6, 8 and 11) scored in the lower quartile of the Baxter spelling test, indicating a mild deficit in orthographic knowledge. The deficits were not judged to be severe enough to warrant exclusion from the study. Two of these patients claimed to have been poor at spelling prior to their injury. Errors tended to be on the longer and less regular items of the test.

Patients 2 and 5 scored marginally below the average range on the Graded Naming Test, indicating a mild anomic deficit, which was not considered severe enough to warrant exclusion from the study.

Patient 13 missed five stars on the star cancellation task, which placed him in the 'below average' performance range, but as the missed stars were distributed across the test field and not uniformly located in one half of the field, the errors were attributed to inattention rather than neglect *per se*. Furthermore, he had been assessed with the star cancellation task and

drawing completion tests on previous occasions and had shown no deficit on either task.

Table 3.3.2. Behavioural neuropsychological assessment scores for individual patients and means (with standard deviations) for the patient and control groups. WASI, Spelling, Naming and Word List Recall figures represent scaled scores. Star cancellation figures represent the number of stars missed. * indicates a below average score.

Patient	WASI Verbal	WASI Non-Verbal	WASI IQ	Baxter Spelling	Graded Naming	Star Cancellation	Word List Recall
1	50	60	109	9	19	2	13
2	36	58	95	7	9*	1	7
3	56	65	118	9	16	0	12
4	51	50	100	19	11	3	7
5	53	31	87	8*	9*	0	5*
6	34	47	85	7*	13	2	6*
7	58	50	107	9	18	1	6*
8	64	56	118	8*	15	1	9
9	57	39	96	11	20	2	10
10	67	48	113	10	19	0	9
11	59	55	112	8*	25	1	7
12	56	65	119	14	29	0	6*
13	66	57	120	9	26	5*	6*
<i>Patients (sd)</i>	<i>54 (10)</i>	<i>52 (10)</i>	<i>106 (12)</i>				
<i>Controls (sd)</i>	<i>65 (6)</i>	<i>61 (7)</i>	<i>123 (10)</i>				

All participants (patients and controls) were assessed for verbal and non-verbal IQ using the 2-subtest scale of the Weschler Abbreviated Scale of Intelligence (Psychological Corporation, 1999). The verbal component assesses semantic knowledge and expressive ability using a word definition task. The non-verbal component assesses general visuo-spatial intelligence using a matrix reasoning task. The patients' scores on the WASI and test battery are listed in Table 3.3.2. The patients performed worse than controls on both verbal ($t_{(12)}=4.08$, $p<.005$) and non-verbal components ($t_{(12)}=2.19$, $p<.05$). However, the patient's average estimated IQ was 106, i.e. close to the population average IQ of 100, whereas the volunteers were substantially above average. It is not possible to infer whether the difference between patient and control IQs was because brain damage causes a general

impairment in intellectual ability, or because the patients had lower pre-morbid IQs prior to their brain damage. Critically, there was no evidence of a selective impairment in verbal ability: the patients' average scores on the verbal and non-verbal scales were very similar. Four individual patients scored substantially worse (based on an arbitrary difference of 10 scale points) on the verbal scale, and four scored worse on the non-verbal scale. This demonstrates that the left occipitotemporal damage that was common to all patients did not cause a general impairment in verbal ability.

Reading Training

The reading training was computer-based and self-administered. This approach allowed the patient to spend more time on the training than traditional therapist-led approaches. The training software was custom-built by Metal Beetle Ltd (www.metalbeetle.com). Patients were given a laptop computer loaded with the training software, and asked to use it for at least 20 minutes a day over the 6-week training period. The training software automatically logged time spent on the training in order to monitor usage.

The training used a cross-modal paired associative learning approach that aimed to improve whole-word reading ability. The training software cycled through training and testing modes. In the training mode, single words were presented centrally on the screen for 500ms whilst the spoken word was played simultaneously. There was no task, but patients were instructed to attend closely to the written words. The brief presentation duration was used to encourage whole-word recognition rather than a letter-by-letter reading strategy. Fifteen words were presented in the training phase, followed by fifteen trials in the testing phase. In the testing phase trials, patients were presented with a written word (that had been presented in the preceding training phase), along with a spoken word. In half of the trials, the written and spoken words matched, and in the other half they were different. The patient had to judge whether the written and spoken words were the same and respond by button press.

Task difficulty was manipulated by varying the similarity between the written and spoken words in the 'different' test trials. Each word of the training list was paired with three spoken words, ranging from easy (i.e. only having the initial letter in common), to medium (having more than one letter in common), to hard (having most letters in common). Task difficulty progressed according to the patient's performance – on the initial presentation of a particular word in a 'different' testing trial, the easy word pair was used; if they answered this correctly, the next 'different' trial for that word would use the medium word pair and so on. A monetary reward of one penny per correct answer was given in the testing trials in order to motivate the participant to maximise the time they spent training.

The training stimuli were taken from one of two word lists, each containing 500 words, matched for letter length, syllable length, written frequency and imageability (Mann-Whitney non-parametric tests confirmed no significant differences between list A and list B, with $p > 0.4$ in each case). The words were selected from the MRC Psycholinguistic Database (Coltheart, 1981) and were between three and six letters in length. Short words were used to allow reading to occur in one saccade, as eye movements may be impaired in these patients due to their limited visual fields.

Each patient was trained with one of the two word lists, with the list allocation counterbalanced across the group. The materials for the word and text reading assessments were designed to allow a comparison of reading speeds for trained and untrained words to see if any training effects generalised to novel items.

Reading Assessments

Participants were assessed for letter, word and text reading speed and accuracy at each session. It was anticipated that letter, word and text reading would be impaired in the patients with PA, but that patients with HA would only be impaired relative to controls on the text reading measures.

The letter reading test used letter and letter-triplet stimuli from the Birmingham Object Recognition Battery (Riddoch & Humphreys, 1993). The letter stimuli consisted of two testing sheets, each with 18 capital letters printed in black on a white background. The triplet stimuli consisted of two sheets with 18 capital letter-triplets (e.g. 'ODZ'), which the participant was instructed to read as individual letters. Participants were timed to read the letters on each sheet out loud as fast as possible. The comparison of letter and letter-triplet reading speeds was employed, as a selective impairment of triplet reading would be indicative of a simultagnosic perceptual deficit. Reading accuracy was assessed by scoring one point for inaccurately read letters and for errors of commission or omission, and scoring half a point for self-corrected errors or *conduite d'approches*.

The word reading test was presented using E-Prime software (Schneider et al. 2002). Words were presented centrally on a screen in black, size 36 font. Participants were instructed to read the word aloud as fast as possible. A voice-key was used to detect the latency of the response onset after presentation of the word (the reading speed). Practice items were included to allow the participant to become accustomed to speaking clearly into the microphone. Words remained on screen until a response had been detected. Trials affected by malfunction of the voice-key (for example, by erroneously detecting non-speech sounds, or by omitting to detect valid responses) were excluded. Reading accuracy was recorded manually using the same error-rating scheme as the letter reading task.

The word reading test included 128 trials, comprised of equal numbers of 3, 4, 5 and 6 letter words. Half of the stimuli were taken from word list A and half from word list B. Three different versions of the stimuli were created to ensure that no word was repeated across time-points, and the order of stimuli within each session was randomised. The stimuli in each version of the experiment were matched for written word frequency using Kucera-Francis written frequency ratings (Kucera & Francis, 1967) and word imageability. One-way ANOVAs confirmed that there were no significant

differences in word frequency or imageability between the word sets in different test versions, letter lengths or word lists ($p > .3$ in all cases).

In the word reading speed analysis, the average reading speed of 3, 4, 5 and 6 letter words was calculated, and any responses more than two standard deviations slower or faster than the mean were excluded. Word length effects were calculated by taking the average increase in reading speed per additional letter.

Text reading was assessed with two short pieces of narrative text at each time-point. While the patients were asked to read the texts as fast as possible, the volunteers were instructed to read at a natural reading pace, in order to provide 'normal' reading speeds for comparison with the patients. Accuracy was recorded using the same error-rating scheme as the letter and word reading tests.

Eight different text narratives were created, and tested in a small group of volunteers to ensure that average reading speeds for the texts did not differ significantly. The texts ranged from 87 to 94 words in length and were taken from newspaper articles, modified to remove any highly infrequent words or names. Four of the texts were modified so that a high proportion of the words came from word list A (around 30%) and a low proportion from word list B (less than 5%); the other four texts had the opposite emphasis on words from word list B and not word list A.

Lesion-symptom mapping

In order to relate behavioural scores to structural damage, the patients' T1-weighted structural MRI images were registered to standard Montreal Neurological Institute (MNI) space using FLIRT. Cost function masking was used to manually identify the damaged area of the brain and to down-weight this area in the registration process (Brett et al. 2001). The resulting transformation matrix was applied to the lesion mask images, and the registered lesion masks were overlaid to produce a lesion overlay image. A simple lesion-symptom mapping analysis was performed using an

independent samples t-test at each voxel to examine whether the patients with damage at that voxel had significantly worse word reading speed than the patients without damage. Only voxels where at least four patients had damage, and at least four patients did not have damage, were included in the analysis to ensure that there would be an adequate number of data points on either side of the comparison.

Results

Pre-training reading ability

Pre-training letter, word and text reading speed and accuracy were assessed at t1 and t2 time-points in patients and volunteers. Patient 13 dropped out of the study for personal reasons after t1, so his data (and that of his paired control) were excluded from the test-retest analysis. Paired t-tests comparing scores at t1 and t2 showed that word and text reading ability was stable over time in both patient and volunteer groups ($p > 0.2$ in every case). However, test-retest effects were observed in the letter reading test: patients were faster at reading single letters at t2 than at t1 ($t_{(11)} = 2.52$, $p < .05$), and there was a trend for the same effect in letter triplets ($t_{(11)} = 2.13$, $p = .06$). No such difference was seen in the volunteer group, nor did the patients' letter or triplet reading accuracy vary significantly over time.

Word and text reading measures were averaged over t1 and t2 for the purpose of comparing patient and volunteer performance. Data from patient 13 and his paired control were excluded from this analysis. It was inferred that the patients' letter and triplet reading speed improved as they became more accustomed to the task demands. For this reason, only the letter reading measures acquired at t2 were compared between patients and volunteers.

Independent-samples t-tests were used to compare the patients' reading speeds with their matched-volunteers' reading speeds. Table 3.3.3 shows mean performance on each task for the patient and volunteer groups. The patients performed significantly worse than volunteers on all measures

except letter reading accuracy, which was close to ceiling in both groups. Patients showed a significantly larger effect of word length on word reading speed than volunteers. Word and text reading measures were also averaged over word list A and B stimulus sets. Paired t-tests confirmed that word list had no effect on word or text reading speed or accuracy ($p > .1$ in all cases).

Table 3.3.3. Patient and control group averages (and standard deviations) on the reading assessment measures. * $< .05$, ** $< .005$, *** $< .0005$. $n=12$ in each group.

Measure	Patients mean (sd)	Volunteers mean (sd)	<i>t</i>
Letter reading speed (ms/letter)	722 (275)	370 (71)	7.5***
Letter reading accuracy (%)	99 (2.0)	100 (0.5)	1.3
Triplet reading speed (ms/letter)	768 (305)	353 (71)	8.1***
Triplet reading accuracy (%)	978 (3)	100 (0.9)	1.9*
Word reading speed (ms/word)	1158 (514)	499 (68)	4.6**
Word reading accuracy (%)	91 (9)	99 (0.6)	3.3*
Word length effect (ms/letter)	133 (126)	1.7 (8.3)	3.7**
Text reading speed (words/minute)	70 (31)	183 (25)	10.2***
Text reading accuracy (%)	96 (4)	99 (0.7)	3.4**

Figure 3.3.1 shows how each patient's word reading speed varied as a function of word length. Five of the thirteen patients had WLEs in excess of 100ms, which has previously been used as an arbitrary cut-off point for pure versus hemianopic alexia (Leff et al. 2006). However, when these five patients were excluded, the remaining seven HA patients still had significantly worse letter and triplet reading speed, and word reading speed, accuracy and WLE than controls, regardless of whether parametric t-tests or non-parametric Mann-Whitney U tests were used ($p < .05$ in all cases). Furthermore, there was no overlap between the control and patient ranges of performance on either letter reading or word reading performance.

Letter and triplet reading speed (in ms per letter) were compared to investigate whether the patients were disproportionately slow at reading triplet letters. As letter reading speed was shown not to be consistent over time, only data from t2 was assessed. Paired t-test showed that there was no significant difference in letter versus triplet reading speed for either the

patient group ($t_{(11)}=1.35$, $p=.21$) or the control group ($t_{(11)}=-2.19$, $p=.05$), although the control group showed a trend towards faster reading of triplet letters.

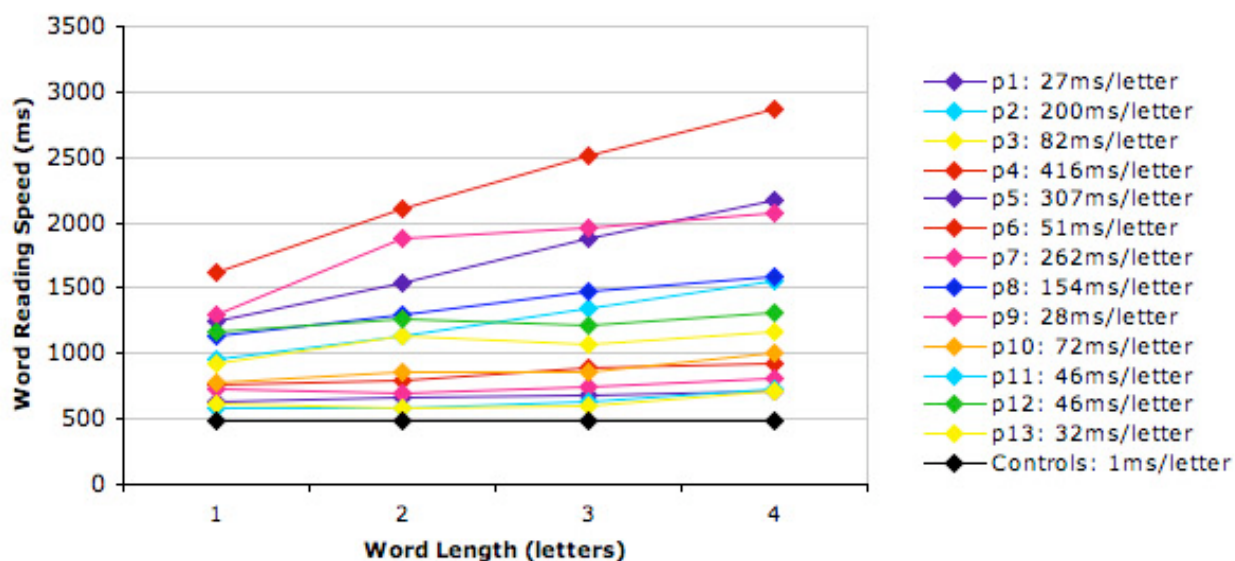


Figure 3.3.1. Word reading speed as a function of word length for each patient. The average reading speed for the control group is shown in black. Labels report the average word length effect for each patient – this is calculated by averaging the increase in reading speed per additional letter.

Lesion-symptom mapping

Figure 3.3.2(a) shows the lesion overlay map for the patient group in MNI standard space. All patients had left occipital or occipitotemporal damage. The point of maximal lesion overlap was in the white matter underlying the left occipital pole, where 10 of the 13 patients scanned had damage. The results of the lesion-symptom mapping analysis are shown in Figure 3.3.2(b). This identified voxels in the white matter underlying the occipitotemporal fusiform gyrus where damage significantly predicted single word reading speeds ($p<.05$).

The lesion-symptom mapping results were compared to the location of the inferior longitudinal fasciculus (ILF) and the forceps major (using tracts defined according to the probabilistic JHU White-Matter Tractography Atlas, Hua et al. 2008) and the occipitotemporal fusiform gyrus (defined according to the Harvard-Oxford Cortical Atlas). The voxels that predicted reading speed fell mostly within or around the left ILF. To confirm this relationship,

binary masks were created of the left ILF, the left half of the forceps major and the left occipitotemporal fusiform gyrus by thresholding the relevant anatomical regions in the probabilistic atlases at 12%. This threshold was chosen to produce masks that were as generous as possible whilst minimising the amount of overlap between the three regions. The number of voxels of each patient's lesion that fell within each of the three masks was calculated and expressed as a percentage of that region. The percentage damage in the ILF, forceps major and occipitotemporal fusiform gyrus were then plotted against word reading speed, as shown in Figure 3.3.2(c). A correlation analysis showed a significant effect of ILF damage on reading speed ($R=.60$, $p<.05$) and an insignificant trend towards an effect of forceps major damage on reading speed ($R=.49$, $p=.1$). The relationship between occipitotemporal fusiform damage and reading speed was not significant ($R=.06$, $p=.8$).

Due to the spatial proximity of these regions, the percentage damage to the ILF, forceps major and fusiform gyrus were not independent: in particular there was a close correlation between ILF damage and fusiform damage ($R=.68$, $p<.05$). To separate the effects of ILF and fusiform damage on reading speed a linear regression analysis was performed using ILF, forceps major and fusiform damage as independent variables and single word reading speed as the dependent variable. When all three variables (ILF, forceps major and fusiform damage) were entered the contribution of the ILF variable was significant ($p<.05$) but the two other variables were not (forceps major, $p=.75$; fusiform gyrus, $p=.16$).

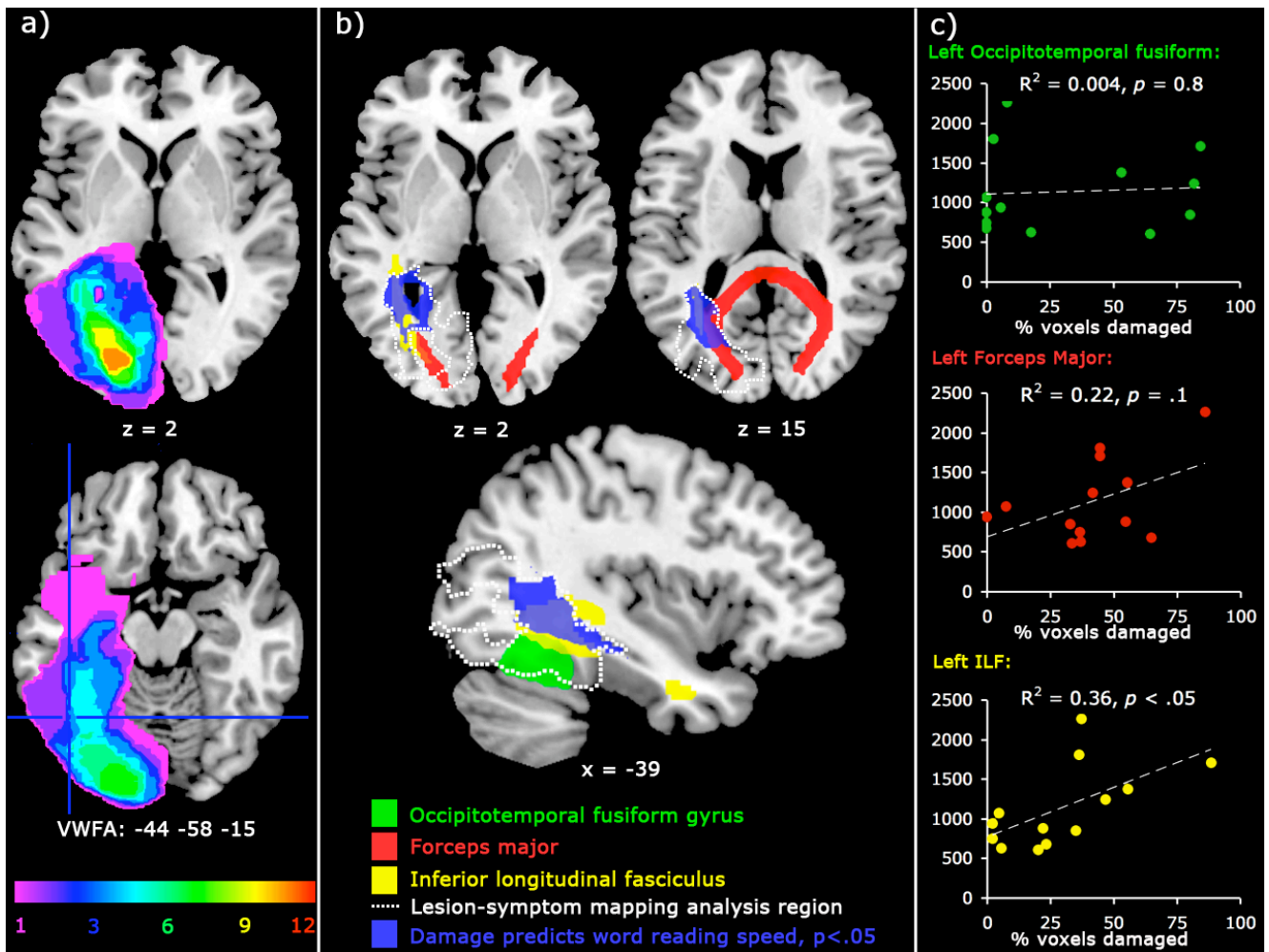


Figure 3.3.2. a) Lesion overlay map for the patient group, demonstrating the area of maximal lesion overlap in occipital white matter. b) Lesion-symptom mapping, showing the area tested in the lesion-symptom mapping analysis outlined in white. Voxels within this region where damage predicted a significant impairment in single word reading speed is shown in blue ($p < .05$). Overlays show the location of this predictive area of occipitotemporal white matter relative to the forceps major (in red), the inferior longitudinal fasciculus (in yellow) and the occipitotemporal fusiform gyrus (in green). c) Regression of regional damage (% of voxels damaged per region) against word reading speed (ms per word), showing that ILF damage significantly predicted reading speed ($R^2 = .36$, $p < .05$) but damage to the forceps major or occipitotemporal fusiform gyrus did not.

Training Effects

Patient 13 dropped out of the study after t1 and patient 8 dropped out after t2 for personal reasons. The data from the remaining eleven patients who completed the whole research protocol are presented here.

Figure 3.3.3 shows the average word reading speed for the patient group at each time-point. There was an improvement in average word reading speed between t2 and t3 of around 100ms for trained words, and 50 ms for untrained words. Repeated measures ANOVAs, with factors TIME (t1-t4) and

LIST (trained versus untrained words) were used to test the effects of time-point on word reading speed, accuracy and word length effect. There was a main effect of word list on word reading speed ($F_{(1, 10)}=9.7, p<.05$), but no other main effects or interactions reached significance. Paired t-tests demonstrated that the main effect of list on reading speed was due to faster reading speeds for trained than untrained words at t3 ($t_{(10)}=3.0, p<.05$) and at t4 ($t_{(10)}=2.9, p<.05$). Direct comparisons of word reading speed at t2 and t3 did not reach significance.

Further repeated-measures ANOVAs were performed to assess differences in text reading speed and accuracy due to time-point (t1 to t4) or text stimuli (trained versus untrained texts). No significant main effects were observed.

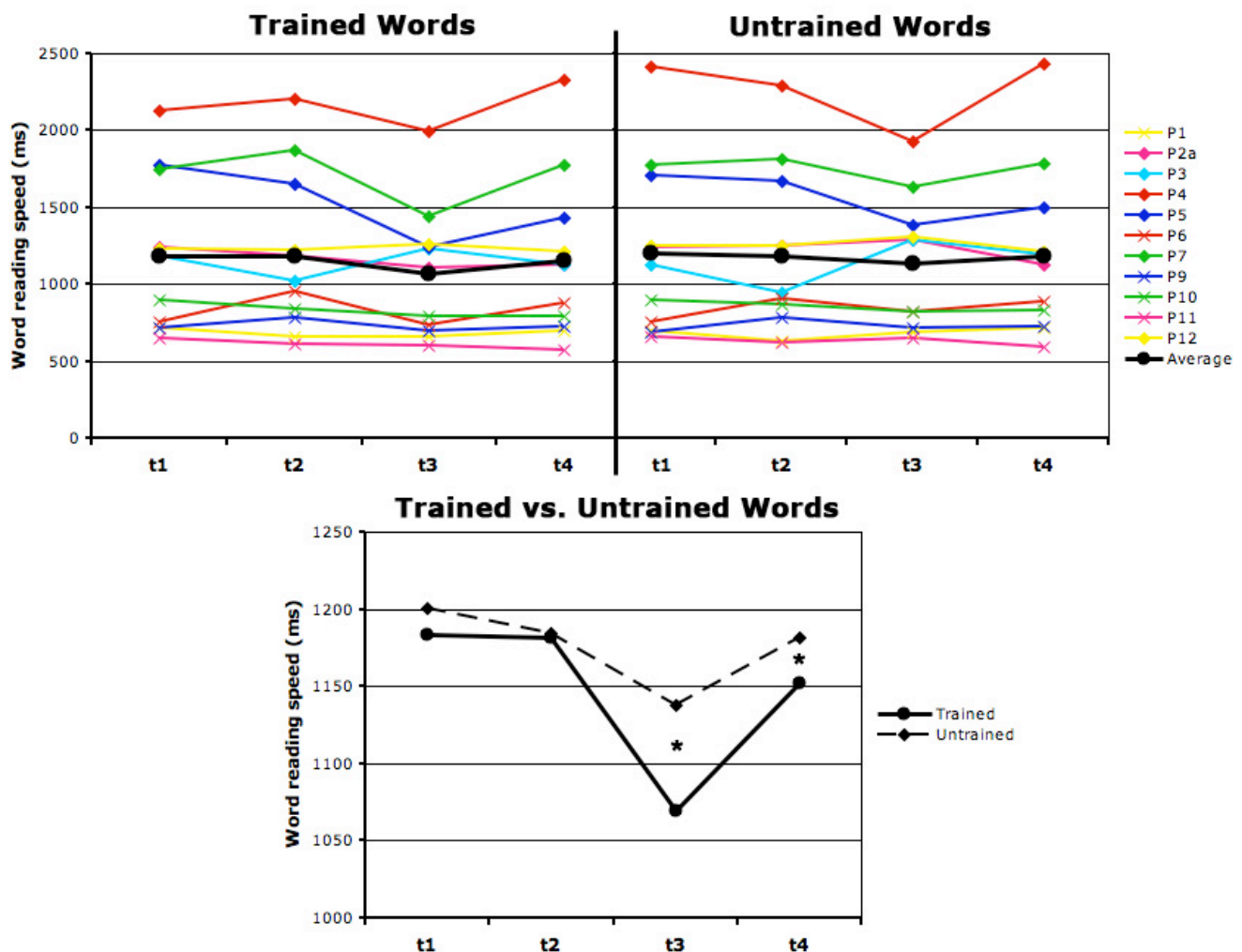


Figure 3.3.3. Top: average word reading speeds for each patient (coloured lines) and the group average (black line) at each time point, for trained words (left) and untrained words (right). Bottom: group average word reading speed for trained and untrained words at each time-point. Note that the scales of the upper and lower graphs are not the same. * indicates a significant difference between trained and untrained words at t3 and t4, $p<.05$.

Effect sizes were calculated for each patient, quantifying the efficacy of the reading training on trained and untrained word reading speeds. Mean word reading speeds for trained and untrained words were calculated for each patient before (t_1+t_2) and after (t_3+t_4) training. Effect sizes for trained and untrained stimuli were calculated by taking the difference in reading speed before and after training and dividing it by the standard deviation. Thus an effect size of > 1 would indicate that reading speed had increased by more than one standard deviation from the mean. Effect sizes for trained words varied from -0.29 to 0.89 with a mean of 0.24. Effect sizes for untrained words varied from -0.76 to 0.57 with a mean of 0.02. A paired t-test showed that effect sizes were significantly larger for trained than untrained words ($t_{(10)}=4.5, p<.005$).

The effect of pre-training reading speed on training efficacy was tested, with the hypothesis that more severely impaired patients may benefit more from the training. Pre-training reading speed did not significantly correlate with trained-word effect size ($r_{(10)}=.10, p=.78$).

Another possible factor that may have affected training efficacy was the amount of time spent on the training. Data logs from the training software showed that eleven out of the twelve patients completed an average of at least 20 minutes of training per day. Only one patient failed to comply with this requirement of the study, logging an average of 16 minutes per day. There was a lot of variation across the patient group: the mean time spent was 49 minutes per day, with a standard deviation of 25 minutes. There was no significant relationship between time on the training and trained-word effect size ($r_{(10)}=.27, p=.42$).

Discussion

This study demonstrated that damage to the left occipitotemporal cortex affects single word reading speed and accuracy. In addition to impaired word reading ability, the patients showed a significant WLE, impaired text reading speed and accuracy, and impaired letter reading speed. It is interesting to note that, in alignment with the results reported by Starrfelt and colleagues

(2009), reading ability was affected at the level of individual letters. Response times were not significantly different whether letters were presented individually or as part of letter triplets. This provides further evidence against the simultanagnostic view of PA, and also demonstrates that the impairment affects orthographic processing prior to the formation of an abstract word form. The results can be better explained by a model of PA as a domain-general perceptual deficit or a domain-specific deficit at an early stage in orthographic processing.

The patients with relatively small WLEs, who might be classified as having HA rather than PA, showed significantly worse letter and word reading ability than controls. This suggests that HA and PA are better described as extremes on a spectrum of reading performance, rather than clinically distinct patterns of impairment. However, the possibility cannot be ruled out that such a distinction between HA and PA patients would have been evident if patients with more severe forms of reading impairment had been included. A larger group size would have allowed a more sensitive analysis of group classification within the patient population.

An analysis of lesion location identified voxels in the left occipitotemporal white matter where damage predicted word reading speed. This area overlapped the left ILF and a further post-hoc analysis demonstrated that the number of damaged voxels in the left ILF significantly predicted word reading speed. The ILF runs from the occipital lobe to the anterior temporal lobe, passing lateral to the fibres of the optic radiations and forceps major (Catani et al. 2003). The lesion-symptom mapping results overlapped with the occipitotemporal portion of the ILF from $y=-70$ to $y=-32$. These results suggest that word reading deficits are caused by a disruption of information transfer along the ventral visual stream. This is supported by a case study by Epelbaum and colleagues (2008), who describe the selective degeneration of the left ILF in a patient with PA following surgical removal of cortex in the vicinity of the VWFA.

The lesion-symptom mapping results overlapped partially with the forceps major, suggesting that disconnection of the right and left occipital cortices can play a role in determining word reading speed. However, this trend did not reach significance. There was no evidence to support the view that damage to the cortex of the left vOT causes PA, but a larger group analysis including a number of patients with more severe PA might yield different results.

The main purpose of the present study was to investigate the efficacy of whole-word rehabilitation methods for patients with acquired reading disorders. Although there appeared to be some small improvement in reading speed after training (with an average training effect size of 0.24 SD) this was not shown to be a significant effect. As predicted, there was no generalisation to novel items – after training, trained words were read significantly faster than untrained words. Although there was substantial variation across the patient group in training efficacy, neither pre-training reading ability or the amount of training undertaken predicted training effect sizes.

It is possible that the simultaneous presentation of the auditory-visual word pairings used in the training protocol did not offer the optimal conditions for paired associate learning (PAL). There is evidence to suggest that the ventromedial temporal lobe is involved in the acquisition of declarative memory. For instance, research on non-human primates has shown that, after training, neurons in the anterior temporal lobe acquire response characteristics whereby they will respond to either stimulus from an associated pair of visual stimuli (Sakai & Miyashita, 1991). However, this sort of PAL typically uses a delayed match to sample paradigm, where a target stimulus is presented, then after a delay the participant has to select the paired stimulus from an array. The simultaneous presentation of auditory-visual pairs used in the present training protocol was more similar to the way that words are typically learnt in childhood, for instance, with flashcards. It remains a possibility that delaying presentation of the visual word after the presentation of the auditory word might have enhanced the efficacy of the

training programme; on the basis that prior auditory priming of vOT (Yoncheva et al. 2010), either residual tissue on the left or cortex on the right, might optimise the tuning of local neural assemblies to paired written and spoken words.

Conclusion and future directions

This study has shown that patients with acquired peripheral reading disorders (HA or PA) have impaired reading ability, affecting letter, word and text reading speed. A structural analysis of lesion location demonstrated that damage to the left occipitotemporal white matter, and more specifically the left ILF, predicted word reading speed. The patient group reported in the present study was small (n=13), and the patients had relatively mild reading disorders. The inclusion of a number of more severely impaired patients would strengthen this analysis considerably. To this end, I have recently contacted researchers from other institutions who are also studying this patient population, and I hope to share the structural and behavioural data for our mutual benefit.

The results of the training study indicate that acquired peripheral reading disorders are highly resistant to intensive, whole-word recognition training. This suggests that damage to the orthographic processing deficit caused by damage to the left vOT cortex or its white matter connections cannot easily be rehabilitated through restitutive training. However, as noted by Rothi (1995), restitutive rehabilitation (i.e. rehabilitation that aims to retrain the impaired function, rather than to teach a compensatory strategy) may be more effective in the acute post-stroke period - future studies would be required to test this hypothesis. Further investigation into the efficacy of oculomotor training to improve text reading speed or kinaesthetic training may also yield positive results.

3.4 Investigating the effects of reading training on the reading networks of patients with acquired reading disorders

The previous studies have identified the reading-related networks in healthy volunteers, and explored the behavioural consequences of damage to the left ventral visual stream. This study looks at the functional effects of this damage, with the following aims:

- 1) to investigate whether patients with relatively spared single word reading ability showed preserved activity in the left vOT cortex
- 2) to investigate whether compensatory activations (where activity is higher in the patient group than the volunteer group during reading) in the right vOT cortex or in fronto-parietal areas were present, and if so whether they correlated with reading ability
- 3) to investigate whether reading training affected the patients' functional activations, and if so whether these changes correlated with training efficacy.

Previous functional neuroimaging studies have shown that patients with HA show relatively normal activity during reading, except for a right lateralisation for visual processing. By contrast, patients with PA may show activity in the right vOT during presentation of alphabetic stimuli in the absence of the normal orthographic processing in the left vOT. Additional compensatory activity might be predicted in frontoparietal networks due to the increased demands on visual attention when reading in the right visual field. This bilateral network was observed in Results Chapter 3.1 and comprised the IFG, premotor cortex and the SMA. Other studies have attributed compensatory activation in the IFG, premotor cortex and supramarginal gyrus to the increased phonological processing required by letter-by-letter reading (Cohen et al. 2004; Henry et al. 2005; Pyun et al. 2007).

The fMRI task used in the present study was designed to be as easy as possible for the patients to perform, as it is very difficult to interpret results

from tasks that subjects cannot perform (Price and Friston, 1999). A block design similar to that reported in Results Chapter 3.2 was piloted with a small number of patients, but they reported finding it difficult to maintain attention throughout a whole block of reading trials. An event-related design was adopted to minimise the confounding affects of attention and task difficulty between the patient and control group. Due to the variability of the false font activations in the left vOT observed in Results Chapters 3.1 and 3.2, a number decision baseline was used. The same rate of presentation was used for words and numbers. Pilot testing showed that the odd-even task was too difficult in the time allowed, so a number-detection task was used instead. Rest trials were also included to provide an alternative baseline.

The data presented in this study were acquired at t1-t3 of the protocol described in Results Chapter 3.3. Time-points t1 and t2 were acquired prior to the reading training, and t3 was acquired immediately after the completion of the training. As the test-retest reliability of fMRI is not frequently investigated, a direct comparison of the fMRI effects at t1 versus t2 was also performed.

There was a concern that it would not be possible to attribute any training effects observed at t3 to improved word recognition *per se* as opposed to a simple effect of word familiarity after the repeated presentation of the words during the training period. Two approaches were taken to resolve this issue. In the fMRI protocol, each reading trial consisted of three words presented sequentially; in half of the trials the three words formed a simple coherent sentence or phrase, and in the other half they were unconnected. If the patients' word recognition had improved as a result of the training, an hypothesis was that an interaction would be observed between word type (trained versus untrained) and trial type (sentences versus unconnected words), with stronger activity in the left superior temporal lobe for trained words presented in sentences. Alternatively, if the training effect was due to improved familiarity, there would be a main effect of word type only, with no significant interaction.

The second method was to perform a linear regression analysis between the change in ROI activity for trained words, the improvement in word reading speed and the amount of time spent on the training. If the functional training effects correlated with change in reading speed this would suggest that they were driven by real improvements in word recognition. Alternatively, if the training effects correlated with the amount of training performed, this would suggest that the effect was due to word familiarity only.

Experimental Procedures

Participants

The same patient group described in chapter 3.3 participated in this study. Patients 2 and 13 had contraindications to MRI scanning and so only took part in the behavioural aspects of the study, leaving a total of 11 patients (5 female, mean age 60 years, 7 months). Patient 8 dropped out of the study for personal reasons before completing the training, so data at t3 was acquired for only 10 patients.

19 healthy, right-handed volunteers (9 female, mean age 28 years 10 months) participated in this study. From this group, 11 volunteers who were age and gender matched to the patients (mean age 60 years 3 months) were used where a direct comparison of patients and volunteers was required.

Procedure

The fMRI data were collected at time-points t1, t2 and t3. The acquisition of two pre-training scans was used to investigate whether activations were stable over time and to allow the participants to become accustomed to the scanning environment before commencing their training. Patient and control data was compared at t1 and t2 to investigate the effects of brain damage on the reading networks, and how neural activity correlated with reading ability. Comparison of patient data at t3 versus t2 demonstrated differences in the reading networks following the reading network.

At each session, two runs of functional data were acquired using an EPI sequence with a 2 second TR, with whole-brain coverage over 32 axial slices, thickness 3.25mm, slice-gap 0.75mm. The in-plane resolution was 2.5 x 2.5 x 3.2mm. Slices were acquired in an ascending order.

An event-related design was used. Each run consisted of 264 volumes, with a total of 144 trials from five experimental conditions in a pseudo-randomised order. The five experimental conditions were:

- 1) Reading three-word sentences from word list A ("A sentences")
- 2) Reading unconnected words from word list A ("A words")
- 3) Reading three-word sentences from word list B ("B sentences")
- 4) Reading unconnected words from word list B ("B words")
- 5) Number decision trials ("Numbers")

Each run consisted of 24 trials from each condition. 24 rest trials, when the fixation cross remained on the screen throughout the trial, were interspersed in a random order between the other trials. Three different versions of the paradigm were created to avoid repeated exposures of the same words across sessions. Version order was counterbalanced across the participants.

There was a five second delay at the start of the run where a fixation cross was presented. In each trial, three stimuli were presented on screen for 500ms each, with an inter-stimulus interval (ISI) of 200ms. The ISI delay was introduced following criticism that the consecutive stimulus presentation in the pilot study led to a perceived flicker on the screen. It had the added benefit of slowing presentation rate down to a speed that would be better tolerated by patients. A 1500ms fixation cross was presented between each trial. In number trials, three single digit numbers were presented centrally in place of the fixation cross. Participants were required to detect a target number ('9') and respond by button press at the end of the whole trial if the target was present.

Stimuli

In the reading trials participants were instructed to read the stimuli passively. Words were presented centrally on the screen in place of the fixation cross. To reduce screen glare, the words were presented in black font on a grey background. The words were three to six letters in length and were selected from word lists A and B as described in the previous chapter. In each of the three alternate versions of the protocol, the A and B stimuli were matched for word length, Kucera-Francis written frequency and imageability ($p > .4$ in each case).

In sentence reading trials, the three consecutive words formed a meaningful phrase or sentence, such as “mother left early”. In the word reading trials, the stimuli from the sentence trials were shuffled at random and carefully checked to ensure that no meaningful combination of words remained. The validity of the sentence constructions was judged by presenting all sentence and word trials to five volunteers who did not participate in the fMRI study, using the same presentation method as the fMRI protocol. Participants judged by button press whether the trial formed a coherent sentence (according to their own subjective definition of a sentence) or not. Any trial that was mis-categorised by two or more participants was excluded from the final set of stimuli.

The stimuli for the number study were single digits presented centrally in black font. The number of repetitions of each number from 0-8 was roughly equal across each run. There were no repetitions of the same number within a trial. The target number 9 appeared on half of all number trials. There were equal numbers of trials where the target number was presented first, second or third within the trial.

Data Analysis

EPI data preprocessing was performed as described in Chapter 2. The data was smoothed at 7mm FWHM. Motion parameters were included in the first level model as covariates of no interest.

Four different whole-brain group analyses were conducted:

- 1) a comparison of t1 and t2 scans to evaluate test-retest reliability
- 2) an examination of the reading network and the effect of sentence coherence in the healthy volunteers
- 3) a comparison of patients and volunteers where data was combined across the pre-training sessions, t1 and t2
- 4) a comparison of the patient data at t3 versus t2 to investigate training effects.

For the test-retest reliability analysis, the contrast of reading (words or sentences, from list A or list B) versus rest was evaluated at the first level (a sample first-level design matrix is shown in the Appendix). The second level analyses used a fixed-effects model combining the two runs of a particular session for each participant (i.e. not collapsing the data across t1 and t2). At the third level, mixed-effects analyses were performed for the patient and volunteer groups separately, modelling a paired t-test comparing activity at the t1 and t2 sessions (the design matrix for this group analysis is shown in the Appendix).

For the volunteer group analysis, contrasts of reading (words or sentences, from list A or list B) versus rest, reading versus number decision and sentences versus unconnected words were evaluated at the first level. The second level analyses used a fixed-effects model combining all four runs per participant (runs A and B from t1 and t2 sessions). The third level, mixed-effects analysis combined data from the group of 19 volunteers.

For the patient versus volunteer comparison, the contrast of reading versus rest was performed at the first level for the patients and 11 matched volunteers. The results were passed on to the second level analyses, which used a fixed-effects model combining all four runs per participant (runs A and B from t1 and t2 sessions). The third level, group mixed-effects analysis modelled an independent samples t-test comparing the patient and control groups (again, the design matrix for this analysis is shown in the Appendix).

Finally, for the training effects analysis, the first level contrasts were structured to test for trained versus untrained words rather than A words versus B words (as training list allocation was counterbalanced between patients). The second level, fixed-effects analyses were performed to combine the two runs from a particular session for each patient (i.e. not collapsing across t2 and t3 sessions). The third level, group mixed-effects analysis modelled a paired t-test to comparing activity at the t2 and t3 sessions. The results of all whole-brain analyses were presented using a cluster-corrected threshold of $Z > 2.3$, $p < 0.05$.

Because of the small group size ($n=11$ at t1 and t2, $n=10$ at t3), there was a concern that the whole-brain analyses would lack statistical power, and that the cluster-based correction for multiple comparisons may be too conservative. For this reason, a region of interest analysis was performed in addition to the whole-brain analysis. As described in previous chapters, the ROI analysis was conducted in Featquery by taking the 90th percentile voxel value within the ROI for each run of each participant.

The ROI analysis tested whether activity in the left and right vOT cortex (using the same ROIs as in Chapters 3.1 and 3.2) differed between patients and healthy controls, and whether the patients' reading abilities correlated with preserved activity in the left vOT or compensatory activity in the right vOT. Paired t-tests were used to compare regional activity levels in the Patient and Volunteer groups and to compare between pre-training and post-training activity in the Patient group. A regression analysis was used to investigate whether activity in either ROI correlated significantly with reading ability or time spent on training.

An additional ROI analysis was performed to test the hypothesis that the left pSTS and aTL would be preferentially activated by sentences rather than unconnected words. The left pSTS and aTL used the same ROI locations described in Results Chapter 3.1.

Results

Test-retest reliability

The functional data acquired at t1 and t2 were compared in order to test the stability of the reading networks over time. The analysis was performed separately for the patient and volunteer groups. Interestingly, both groups showed significant test-retest differences, and in different places, as depicted below in Figure 3.4.1.

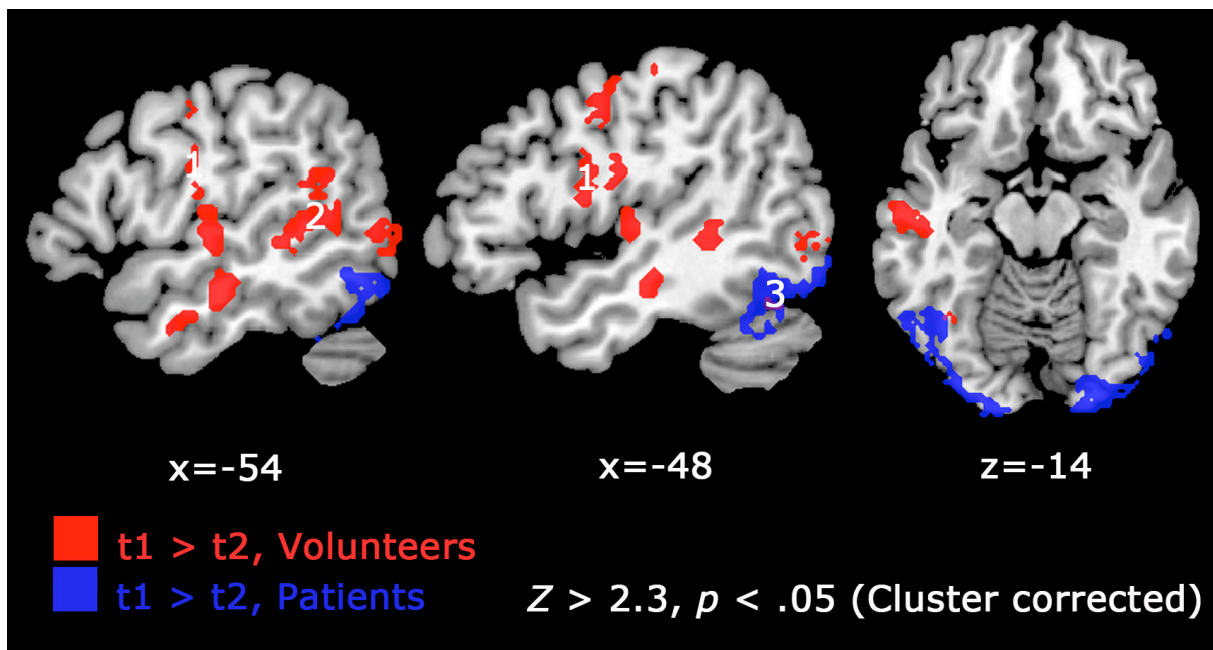


Figure 3.4.1. Statistical parametric maps comparing activity for the Reading condition at t1 versus activity at t2 for healthy volunteers (in red) and patients (in blue). Significant areas of activation differences in the volunteer group included: 1) the left precentral gyrus, and 2) the left STS. In the patient group, significant differences were observed in area (3), the left occipital cortex extending into the ventral visual stream. A cluster-corrected threshold of $Z > 2.3, p < .05$ was used; $n=11$ in both groups.

The volunteer group showed significant decreases in activation over time, with stronger activity at t1 than t2 in the left STS (peak -60 -52 12, $Z=3.69$) and the left precentral gyrus bordering dorsolateral prefrontal cortex (-48 -2 42, $Z=3.35$).

The patient group showed significant decreases in activation over time in the right occipital cortex (20 -100 -10, $Z=3.83$) and the left occipital cortex (-20 -105 -16, $Z=4.04$) extending into the left ventral visual stream (-48 -58 -22, $Z=2.96$). The left hemisphere occipital activations were observed along the

edge of the damaged cortex, and may have been caused by minor registration differences between the t1 and t2 scans.

No significant increases in activation over time were observed in either group. It was inferred that physiological decreases in activation observed over time were due to accommodation to the task.

Volunteer group analysis

The reading-related networks (words or sentences relative to the resting baseline) are presented in Figure 3.4.2 using a cluster-corrected threshold of $Z > 3.0$. This contrast revealed a widespread, bilateral network of regions that were activated during the reading tasks (sentences or words combined). This included bilateral visual cortex, bilateral ventral visual and dorsal visual streams, bilateral lateral temporal streams and extensive inferior frontal and premotor activations. The contrast of reading versus the number decision task showed similar, but even more extensive results than reading versus baseline (not illustrated).

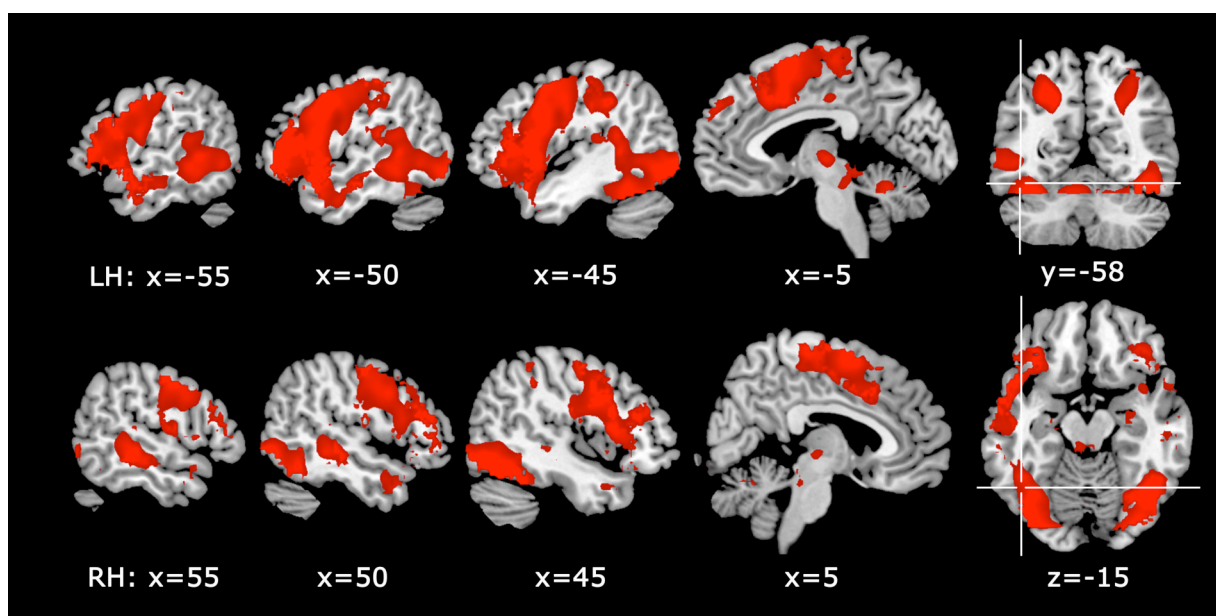


Figure 3.4.2. Statistical parametric map of activation that was significantly greater in the Reading condition relative to baseline. A cluster-corrected threshold of $Z > 3.0$, $p < .05$ was used. Crosshairs indicate the location of the VWFA in the left ventral visual stream, using coordinates defined by Jobard et al. (2003).

The contrast of sentence trials versus word trials showed no significant activation at the standard cluster-corrected threshold of $Z > 2.3$, $p < 0.05$.

Sub-threshold activity was observed in bilateral inferior occipitotemporal cortex, the left STS and the SMA, as shown in green in Figure 3.4.3. False Discovery Rate correction for multiple comparisons (Genovese et al. 2002) was used as an alternative and more liberal thresholding method, which identified the peaks of the left posterior STS and SMA activations as being significant (shown in blue in Figure 3.4.3).

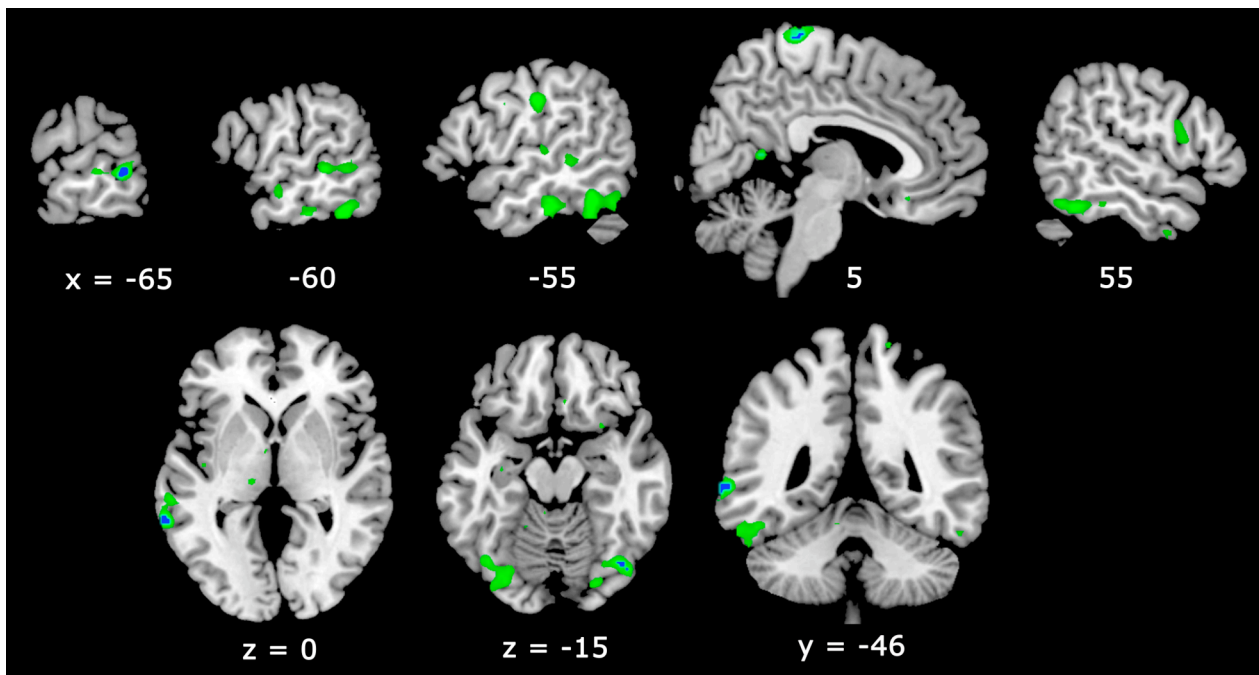


Figure 3.4.3. Statistical parametric map of activation that was significantly stronger in the Sentence Reading condition than the Word Reading condition. Activations in green are thresholded at $Z > 2.3$, uncorrected for multiple comparisons. Overlaid in blue are areas that survived False Discovery Rate correction for multiple comparisons.

An ROI analysis was performed to test whether the left pSTS and aTL showed a preferential response for sentences over unconnected word trials, as predicted. The 90th percentile z-statistic in the left pSTS and aTL ROI were extracted from contrasts of sentences versus rest and unconnected words versus rest at the first level. Paired t-tests revealed no significant difference in activation for sentences and unconnected words in either region (L pSTS: $t_{(19)} = .50$, $p = .6$; L aTL: $t_{(19)} = .49$, $p = .7$).

It was inferred that the three word sentences were not sufficient to elicit a differential response in the left temporal lobe areas that were shown in Chapter 3.2 to be involved in sentence processing. For this reason, the

comparison of sentences versus unconnected words was not performed in the subsequent patient analysis.

Patients versus volunteers

A direct comparison between Volunteers and Patients before training (t1 and t2 combined) was performed in order to investigate the effects of the patients' brain damage on their functional networks for reading. The results are depicted below in Figure 3.4.4.

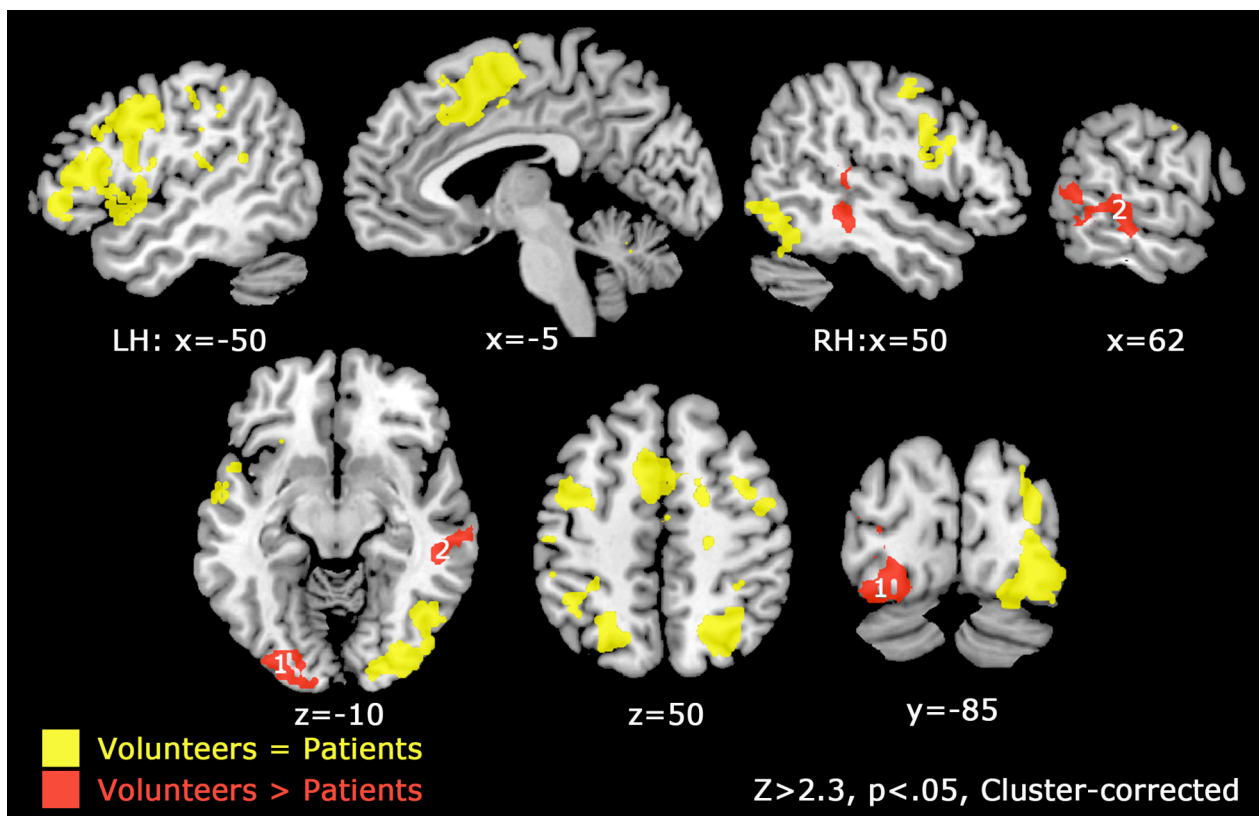


Figure 3.4.4. Statistical parametric maps showing areas of activity for the Reading condition that were commonly activated in the patient and volunteer groups (yellow) and that differed significantly between the volunteer and patient groups (red). Significant differences were observed in: 1) the left occipital cortex extending into the ventral visual stream and 2) the right posterior half of the STS. A cluster-corrected threshold of $Z>2.3$, $p<.05$ was used; $n=11$ in both groups.

This analysis demonstrated two clusters of significant between-group differences in brain activation during the reading task (relative to the resting baseline). Volunteers showed stronger activation in the left occipital cortex, extending into the ventral visual stream (peak -32 -92 -12, $Z=3.58$) – this result is unsurprising as it is within the damaged area of cortex in most

patients. A second area significant cluster was observed along the posterior half of the right STS and MTG (peak 70 -22 -8, $Z=4.33$).

There were no areas where patients showed significantly stronger activations than volunteers. However, as the statistical power of the analysis was compromised by the very low number of participants ($n=11$ in each group), it was considered that real results could have been obscured by the correction for multiple comparisons that is necessary in the whole brain analysis. A region of interest analysis was performed on the *a priori*-defined ROI: the left and right vOT cortex ($\pm 44 -58 -15$). In light of the whole-brain results, additional 'post-hoc' ROIs in the left and right posterior STS ($\pm 56 -40 2$) were also investigated. These ROIs were included in order to test whether the apparent difference between patients and controls was truly right lateralised, or whether this was an artefact of the conservative threshold approach used. It should be noted that no correction for multiple comparisons were applied to these tests.

Paired t-tests confirmed that the Volunteer group showed significantly higher activations than the Patient group in the left vOT ROI ($t_{(10)}=2.3$, $p<.05$), but there was no difference in the right vOT ROI ($t_{(10)}=.53$, $p=.61$), with both patient and control groups showing low activity in this region (patient average $z=1.0$; volunteer average $z=1.3$). Within the patient group, there was no significant correlation between single word reading speed and activity in the left vOT ($R^2=.09$, $p=.37$) or the right vOT ($R^2=.02$, $p=.68$). Two of the eleven patients had damage that affected the entire left vOT ROI, and a further three patients had partial damage to this area. As the ROI analysis used the 90th percentile voxel value rather than the mean of all voxels with in the ROI, it was still possible to test for left vOT activity in patients with partial damage in this area. When the two patients with total left vOT damage were excluded, the difference between patient and volunteer activity was no longer significant ($t_{(8)}=1.7$, $p=.13$), even if a non-parametric Mann-Whitney U test was used ($U=20.0$, $p=.08$). Taken together, these results demonstrate that the difference in reading related activity at the left vOT

between patients and volunteers was due to the structural damage in this area, and not due to real differences in functional activity *per se*.

In the temporal lobe ROI, the Volunteer group showed significantly higher activity in both the left and right posterior STS regions (left: $t_{(10)}=2.4$, $p<.05$; right: $t_{(10)}=2.5$, $p<.05$). Within the patient group, there was a significant negative correlation between activity in the left posterior STS and word reading speed ($R^2=.50$, $p<.02$). There was an insignificant trend for the same effect in the right hemisphere ($R^2=.30$, $p=.08$).

Training effects

As described previously, significant test-retest effects were observed between the patient's fMRI data at t1 and t2, with decreased activation over time in bilateral visual and visual association areas. In order to make a conservative comparison of pre- and post-training effects, the patients' fMRI data at t3 was compared to t2 rather than t1.

The whole-brain comparison of the patients' pre-training (t2) versus post-training (t3) activity did not reveal any significant differences. A ROI analysis was used to test whether training caused a significant change in activity in the left or right vOT. Paired t-tests showed no significant difference in activity at t2 versus t3 in the left or right vOT (left vOT: $t_{(9)}=.25$, $p=.81$; right vOT: $t_{(9)}=.65$, $p=.54$). To separate the effects of training efficacy and training duration on the functional results, a linear regression analysis was performed to see whether changes in left or right vOT activity correlated with the behavioural training effect size for trained words, or the amount of time spent on the training. In the left vOT, neither of the behavioural measures predicted reading-related activity (effect size: $p=.49$; training duration: $p=.86$). In the right vOT, activity correlated significantly with training duration ($p<.05$) but not effect size ($p=.31$).

Discussion

This study aimed to identify differences in the reading-related functional networks of patients and age and gender matched volunteers. The whole-

brain analysis demonstrated that the patients had reduced reading-related activity in the left vOT cortex and the right lateral temporal lobe. An ROI analysis confirmed the patients also had reduced activity in the left posterior STS, and this activity correlated negatively with word reading speed. In Results Chapter 3.2, the posterior STS was shown to be involved in higher-order processes related to sentence reading. Hence, it seems likely that this correlation reflects the fact that the brief presentation durations (500ms per word) were not sufficient for the patients with slow reading speeds to access the higher-order properties of the words.

Although the whole-brain and ROI analyses showed that the volunteer group had higher activity in the left vOT cortex than the patients, when the patients with damage affecting this area were excluded from the analysis this difference was no longer significant. It was predicted that preserved activity in this region would correlate with better reading speed, but this was not the case, nor did the results support the hypothesis that patients with acquired reading disorders show compensatory activity in the right ventral visual stream or in more general executive control networks.

The failure to identify compensatory activation in the patients may reflect the relatively mild level of the patients' disorders, or it may be because compensatory strategies are so heterogeneous that they are lost in a group analysis. Alternatively, it is possible that the study design was not sufficiently sensitive to detect differences between patients and volunteers. The contrast of reading versus rest, as shown in Figure 3.4.2, activated a widespread reading network in the healthy volunteer group. When this network was compared to the patient data, it may have served to mask compensatory activations in the patient group. Although the use of a false font baseline was ruled out because of the variable findings observed in chapters 3.1 and 3.2, the inclusion of a perceptually-matched baseline such as checkerboards or consonant strings may have resulted in a less extensive reading-related network, allowing a more effective comparison between patients and controls.

A second aim of the study was to investigate whether the reading training led to changes in functional activity. No significant changes were observed in the patients' reading-related activity before and after the training period. It appears that even with intensive whole word reading training, the effects of damage to the left ventral visual stream are highly persistent. Activity in the right vOT ROI for the contrast of trained versus untrained words at t3 was shown to correlate significantly with the amount of training performed, but did not correlate with improvement in reading speed. This suggests that the change in right vOT activity was driven by word familiarity rather than an improvement in word recognition.

The region of interest approach was used in order to maximise the sensitivity of the analysis due to the small number of participants. However, it is still possible that real effects were missed due to the low statistical power of the analysis, or the heterogeneity of the patient group. It is also possible that test-retest effects may have obscured real changes before and after training. Test-retest effects between t1 and t2 were observed as a decrease in activity in areas of the reading network, in the left lateral temporal lobe and IFG in controls and in the bilateral visual cortex of the patients. If this effect had also occurred between t2 and t3, it may have had the effect of cancelling out real training-related increases in activity.

It is not clear why this study failed to identify significant differences in reading-related activations between the patient group and their matched controls, while other case-studies have identified such differences. There are three possible explanations for this. First, the approach of selecting single case-studies for publication may mean that idiosyncratic findings at the single subject level are falsely inferred to be representative of the wider patient population. However, this would not explain why findings such as the observation of compensatory fronto-parietal activations during reading, which have been commonly reported in the case-study literature, were not also observed here. There may be a selection bias that means that only case studies yielding results that are in line with the existing literature are reported.

The second possibility is that the patients in the present study did not have severe enough reading disorders to elicit compensatory activations; however, if there was a linear relationship between reading ability and compensatory activity this would have been identified in the ROI correlation analysis. Similarly, the amount of time that had elapsed between the patients' brain injury and their participation in the study may have been too long to detect compensatory effects – it is possible that patients in the chronic phase of their disorder, years after their injury, no longer show the compensatory strategies that are evident in patients in the acute phase. This hypothesis is supported by the repeated studies of patient CZ (Cohen et al. 2004; Henry et al. 2005): at the initial session (6 months post-stroke), CZ showed compensatory right vOT activity, but by the second session (14 months post-stroke) this had decreased to normal levels. Further testing of a larger and more varied group of patients would be required to investigate this hypothesis.

The third possibility is that the present study used a short presentation duration to encourage whole-word reading, whereas previous case studies have used longer durations to allow serial letter-by-letter (LBL) reading. The compensatory networks observed in these case-studies may therefore be specific to the additional processing requirements of LBL reading, including eye-movements, phonological processing and executive control. If this assumption is correct, the results of the present study would imply that compensatory reorganisation of the orthographic input system for whole-word recognition does not, or cannot, occur.

Conclusion and future directions

This study showed that patients with acquired peripheral reading disorders show largely similar brain activations to healthy volunteers during single word reading. Activity in the left pSTS was shown to be stronger in the volunteers than the patients, and also to correlate with reading speed. Additional differences between patients and volunteers may have emerged if the experimental protocol had allowed the use of a LBL strategy, or if a more

tightly matched baseline condition had been employed. No changes in functional activity were shown following the 6-week period of reading training. The results suggest that the orthographic processing underlying rapid whole-word recognition cannot be replaced by functional reorganisation.

This study showed significant test-retest effects between t1 and t2. These appeared as a general reduction in activation over time in both the volunteer and patient group, and were attributed to accommodation to the scanning environment and task demands. It is important to be aware of the test-retest effect when designing training studies, in order to avoid the mistake of falsely attributing such changes to real training effects.

The present study may have lacked the sensitivity to detect perilesional activation, due to differences in HRF in these areas. Bonakdarpour and colleagues (2007) showed that stroke patients have delayed HRFs in their damaged hemisphere, particularly in perilesional cortex. Although the use of temporal derivatives will have made the analysis more sensitive to variations in HRF, it remains a possibility that positive results may have been missed. Future studies are required to see whether improved sensitivity in perilesional tissue can be achieved by modelling the HRF on a regional basis for each participant.

This can be done by acquiring an additional fMRI run with a long-trial, single-event related design, and then plotting the timecourse of the HRF in regions of interest (Bonakdarpour et al. 2007); or by creating custom basis-sets in FMRIB's Linear Optimal Basis Sets (FLOBS) tool (Woolrich et al. 2004). The latter technique is an extension of the temporal derivative approach, and involves setting a range of parameters using prior knowledge about the likely shape of the HRF, then creating a large set of possible HRFs within these parameters. Principle Component Analysis is then used to determine the optimal basis set of two or three basis functions that describe a high proportion of variance in the set of possible HRFs, and these optimal basis functions are used to create additional EVs in the design matrix, in the same

way that the temporal derivative is modelled. Future studies could investigate whether either of these methods can improve signal detection in the perilesional cortex.

3.5 Investigating whether perceptual features could cause lateralisation in the ventral visual stream

The behavioural data shown in Results Chapter 3.3 showed that patients with left occipitotemporal damage are impaired at letter, word and text reading. The fact that letter reading is affected suggests that the locus of the deficit is either domain-specific at an early stage in orthographic processing, or domain-general. The literature reviewed in the Introduction highlighted the evidence in favour of the domain-general, perceptual view: patients with PA are detrimentally affected by stimulus complexity (Mycroft et al. 2009), and by letter confusability (Arguin et al. 2002; Arguin & Bub, 2005). Mycroft and colleagues (2009) suggested that a low-level deficit in spatial frequency perception could explain these findings. The present study explores the possibility that the left vOT cortex is preferentially recruited for processing high spatial frequency stimuli.

It has been frequently reported that the ventral visual processing for word recognition is left lateralised, whilst face processing is right lateralised or bilateral. Cai and colleagues (2008) demonstrated that the lateralisation of visual word recognition is strongly related to the lateralisation of speech production. Speech, which is innate, precedes reading, which is acquired, and the inference is that top-down signal from anterior speech production regions influences the lateralisation of the VWFA, thereby minimizing the need for callosal transfer of information within the reading network. By contrast, the Fusiform Face Area (FFA, Kanwisher et al. 1997) in the right posterior fusiform gyrus, roughly symmetrical to the VWFA, is reliably activated by face processing tasks and is frequently observed as a lesion site in patients with acquired prosopagnosia (Meadows, 1974; Damasio et al. 1982; Benton, 1990; Barton, 2008b). The case for lateralisation of face processing is less clear cut than for words – face processing tasks commonly show bilateral activation, but with a tendency towards stronger activation in the right hemisphere (McCarthy et al. 1997; Kanwisher et al. 1997). Similarly, lesions causing prosopagnosia may be bilateral or right lateralised (Meadows, 1974; Damasio et al. 1982; Benton, 1990; Barton, 2008b), but

rarely left lateralised (Mattson et al. 2000; Barton, 2008a). Willems and colleagues (2010) recently showed that lateralisation of the FFA depended on handedness: in right-handed participants the FFA was right lateralised, whereas left-handed participants showed no reliable lateralisation. Given that right-handedness also predicts left-hemisphere language dominance, it is unclear whether lateralisation of word and face processing operate independently or are mutually dependent on a more general, heritable trait.

A number of studies have questioned whether basic perceptual features such as eccentricity may influence the organisation of the ventral occipitotemporal cortex. Malach and colleagues (Levy et al. 2001; Hasson et al. 2002) showed that retinotopic eccentricity mapping in the visual cortex extends into ventral occipitotemporal cortex, with central vision represented laterally and peripheral vision represented medially. This mapping may explain why words and faces (which are typically viewed in foveal vision) activate regions in the lateral bank of the fusiform gyrus, whereas the parahippocampal place area (PPA, Epstein & Kanwisher, 1998) is located more medially, reflecting the greater reliance on peripheral vision for viewing buildings and landscapes. Although this factor may influence intra-hemispheric organization of visual association cortex, it may also have an influence on inter-hemispheric organization.

Although words and faces are similar in their reliance on high acuity foveal vision, they differ in terms of spatial frequency content, another basic perceptual feature. Spatial frequency (SF) is defined as the change in luminance across space, and can be quantified as the number of cycles per degree of visual angle (cpd). As written words are composed of high-contrast edges, high spatial frequencies predominate; whereas as faces have a combination of sharp edges and smooth contrast gradients they comprise a broader range of frequencies, with more low SF power than words. The object of this study was to explore whether SF differences between words and faces correlated with the hemispheric dominance for the VWFA and the FFA.

The idea that there might be a dissociation between visual processing in the left and right hemispheres, rather than a within-hemisphere dissociation between medial and lateral cortex, was first explored in the late 1970s in behavioural studies using split-field presentation. These studies indicated a LVF/RH advantage for large stimuli or stimuli presented to the periphery of the visual field, and an RVF/LH advantage for small stimuli or stimuli presented foveally (Polich, 1978; Marzi et al. 1979; Sergent, 1982; Sergent, 1983). Recent behavioural studies have found similar effects using highpass or lowpass filtering to remove low or high spatial frequency information from images respectively. Using this technique, Peyrin and colleagues (2006) demonstrated a RVF/LH advantage for perceptual decisions about highpass filtered images of natural scenes and a LVF/RH advantage for lowpass filtered images. Functional imaging studies have shown that spatial filtering can modulate lateralisation of activations. Iidaka and colleagues (2004) showed that highpass filtered images of houses and faces preferentially activated an area of the left occipitotemporal cortex compared to low-pass filtered images. In a study using electroencephalography, Mercure and colleagues (2008) showed that the N170 response for normal and highpass filtered words was left-lateralised, but it was bilateral when the high frequency information was removed using lowpass filtering. By comparison, the N170 for unfiltered images of faces was bilateral, and filtering had no effect on lateralisation.

These studies consistently indicate a bias towards high spatial frequency processing in the left hemisphere, but this interpretation is limited due to the use of filtered images, so that it remains unclear whether the results are driven by stimulus legibility rather than the manipulation of frequency content *per se*. If the effects are truly related to SF, then lateralisation should be apparent for simple stimuli that vary only in SF.

The design of the present study, which aimed to assess the influence of SF on the lateralization of ventral occipitotemporal activations in the absence of any intelligibility effects, employed simple sine-wave gratings rather than filtered images. It was predicted that left vOT cortex would be preferentially

activated by high spatial frequencies, and right ventral occipitotemporal cortex by low spatial frequencies. Word or face processing areas in vOT cortex were identified using appropriate functional localizers, and the preferred spatial frequency within these regions of interest was directly compared.

The data were acquired on a 1.5 Tesla MRI scanner, as lower field strengths reduce the effects of susceptibility artefact in the ventral occipital cortex (Devlin et al. 2000; Visser et al. 2010). As the areas of interest were clearly defined, a partial field of view EPI acquisition was used to allow smaller voxel sizes and a fast acquisition time whilst sacrificing whole-brain coverage. Furthermore, the data were analysed on the inflated cortical surface in order to improve inter-subject registration and to map sensitivity to spatial frequency using phase encoded mapping. Analysing fMRI data on the flattened surface of the cortex can yield more accurate localisation of results, as it takes the curvature of the cortex into account, rather than smoothing across sulci and gyri. This can improve co-registration between subjects, which increases the chance of finding overlapping activations, and therefore can increase statistical power.

Experimental Procedures

Participants

Twelve healthy, right-handed volunteers (six female, mean age 31.5 years) participated in this study.

MRI Procedures

Data were acquired on a Siemens Avanto 1.5 Tesla MRI scanner. Functional data were acquired using a partial field-of-view EPI sequence with a TR of 2 seconds. 24 slices of 3.2mm thickness were acquired in an interleaved order, covering a field of view of 205mm. This sequence allowed a fast repetition time, small voxel size and no slice gap to maximise the chance of detecting signal in the ventral occipitotemporal cortex.

Each functional run had 256 volumes, and three runs were acquired per participant: one functional localiser, and two SF mapping runs. Head position and scanning geometry were kept the same throughout the whole protocol to allow accurate co-registration between runs.

The functional localiser run used a block design, and consisted of six blocks of four experimental conditions: words, faces, scrambled words and scrambled faces. Block order was counterbalanced so that there was no correlation of condition order with time, and to maximise the variety of transitions between conditions. Each block was 12.6 seconds long, with a 6 second fixation cross after each block. Each block contained 14 trials, during which a stimulus was presented centrally on screen for 300ms, followed by presentation of a fixation cross for 600ms.

The SF mapping runs used a different protocol, where the stimuli varied in SF continually over a 64 second period, which was repeated eight times per run. One run used a low-to-high spatial frequency cycle, and the other was high-to-low: run order was counterbalanced between participants to avoid order effects.

Stimuli

The four experimental conditions presented in the functional localiser were:

- 1) Reading single words ('words')
- 2) Viewing faces ('faces')
- 3) Viewing fourier-scrambled versions of the word stimuli ('scrambled words')
- 4) Viewing fourier-scrambled versions of the face stimuli ('scrambled faces')

Examples of the stimuli from each condition are depicted in Figure 3.5.1. In all conditions, a dot-detection task was used to maintain attention throughout the run. Participants were required to respond by button press whenever a red dot appeared on screen, which happened once or twice per block. The dots were superimposed on the stimulus less than 5cm from

central fixation. The quadrant that the dot appeared in was varied at random, and balanced between conditions. The stimuli were presented using a custom-written script in the Psychophysics Toolbox (Brainard, 1997) for Matlab (Mathworks).

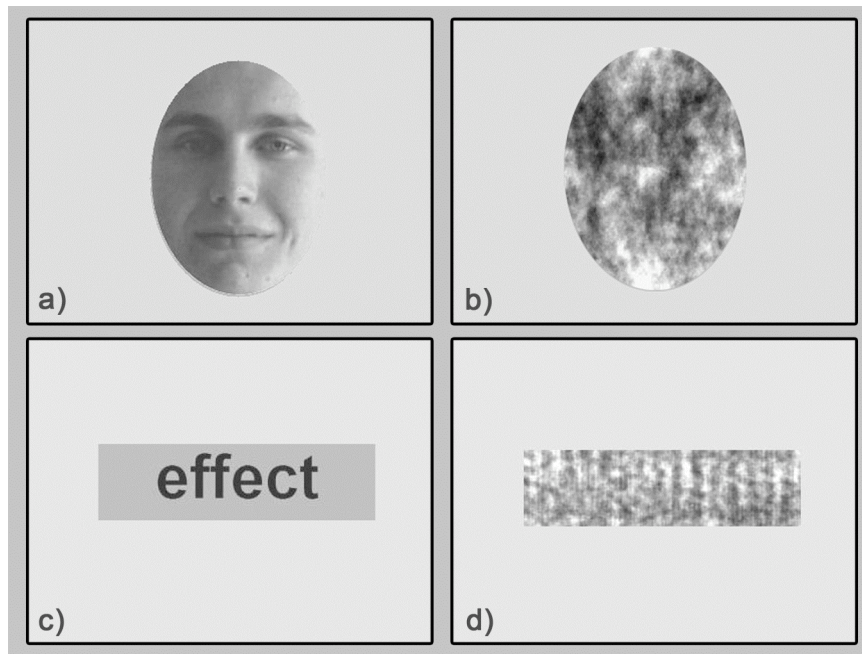


Figure 3.5.1. Examples of stimuli used in the functional localizer scan, from the conditions (a) Faces, (b) Scrambled faces, (c) Words and (d) Scrambled words.

Stimuli for the words condition were selected from the MRC Psycholinguistic Database (Coltheart, 1981). The words were chosen for their high written frequency rating (KF written frequency >200) and high imageability (imageability rating >250), and were all three to seven letters long. Words were presented centrally on the screen in black, Arial font on a grey rectangular background.

Face stimuli were greyscale photos of neutral-expression faces in a frontal position. The faces were taken from the CRL Faces Database (Solina et al. 2003), then cropped using an oval mask of fixed dimensions to exclude hair, clothing or background details. A custom Matlab script was written to match the face and word stimuli for luminance.

The scrambled word and face images were made using a Fourier-scrambling procedure previously described by Eger et al. (2005). This involves taking

the Fourier transform of the original word or face image, permuting the phase information, and inverting the fourier transform to revert the phase and magnitude information into an image. This procedure has the advantage of removing any recognisable structure from the image whilst retaining the luminance and SF power distribution of the image. Hence, the scrambled versions of the word and face stimulus sets were matched to the originals in terms of SF.

The SF stimuli were greyscale sine-wave gratings, ranging from 0.05 to 7 cycles per degree that filled the entire screen. Grating orientation varied throughout the run, with angle changing by random increments approximately every 800ms. An oddball detection task was used to maintain the participant's attention throughout the run. They were required to detect brief events within the smoothly changing SF cycle where the SF suddenly doubled or halved. This occurred approximately 24 times per run.

Data Analysis

The functional localiser data were analysed using FSL as described in previous chapters, with a 7mm FWHM smoothing Gaussian kernel. The first level GLM modelled blocks of the word, face, scrambled word and scrambled face conditions. Motion parameters were entered as regressors of no interest. Contrasts of words versus scrambled words and faces versus scrambled faces were evaluated and passed to the second level, mixed-effects group analysis. A pre-threshold mask of the fusiform gyri, extending from occipital to anterior temporal lobes (as defined by the Harvard-Oxford Cortical Structural Atlas) was used to define the area of interest for the statistical analysis. Within this area, voxels from either contrast (words versus scrambled words or faces versus scrambled faces) that reached a cluster-corrected threshold of $Z > 2.3$, $p < 0.05$ were considered to be word- or face-preferential, and were used to define regions of interest for the subsequent analysis.

The SF data were analysed in two different ways – a conventional analysis in FSL (Smith et al. 2004), and a cortical surface-based mapping approach (Sereno et al. 1995) using Freesurfer (Dale et al. 1999; Fischl et al. 1999).

The analysis in FSL followed the conventional approach, with a 7mm smoothing kernel. At the first level, the GLM modelled high or low spatial frequencies using a simple median split of each 64-second cycle. Contrasts of high versus low SF and low versus high SF were evaluated and passed on to the second level, a within-subjects fixed-effects analysis. The group level analysis used mixed-effects, and applied a pre-threshold mask of the word- or face-preferential fusiform voxels defined in the functional localiser analysis. Results were displayed using a cluster-corrected threshold of $Z > 2.3$ and $p < 0.05$. The appendix shows sample first-level design matrices for the functional localiser analysis and the spatial frequency analysis in FEAT.

The surface-based analysis used a phase-encoded mapping approach (Sereno et al. 1995). The functional localiser data was analysed in FSL, using the same approach as that described above, but with no spatial smoothing. Each subject's results for the words versus scrambled words and faces versus scrambled faces contrasts were transformed into the surface-space and then smoothed (using a 5mm FWHM Gaussian kernel). Cortical reconstruction of the inflated surface was performed with the Freesurfer image analysis suite (Dale et al. 1999; Fischl et al. 1999). Each subject's functional data was then co-registered to a standard cortical surface template, smoothed to 5mm FWHM and averaged across the group to produce surface-based group maps of word and face preferentiality. The two masks were combined to form a surface functional localiser mask of word or face preferential areas in the fusiform gyri.

Phase-encoded mapping calculates the SF that maximally activates each voxel, thereby building a map of SF preferentiality on the cortical surface. The timeseries for each voxel was motion corrected using the 3dvolreg tool from AFNI (Cox & Jesmanowicz, 1999), detrended and analyzed with a Fourier transform. The phase angle at the stimulus frequency of eight cycles

per scan corresponds to the preferred SF for that voxel and was used in surface-analyses and subsequent region of interest analyses. In the region of interest analysis, the mean phase angle across all voxels was calculated within the functional localiser mask for each hemisphere of each individual to create an average SF response for the left and right hemisphere word- or face- preferential areas. These were then compared across subjects with a paired t-test to see if there was a lateralisation bias in preferred SF.

Results

Functional Localiser

The results of the functional localiser analysis are shown in Figure 3.5.2. The contrast of words versus scrambled words revealed word-preferential activity in the left occipitotemporal fusiform gyrus and (predominantly left) temporal and frontotemporal cortex.

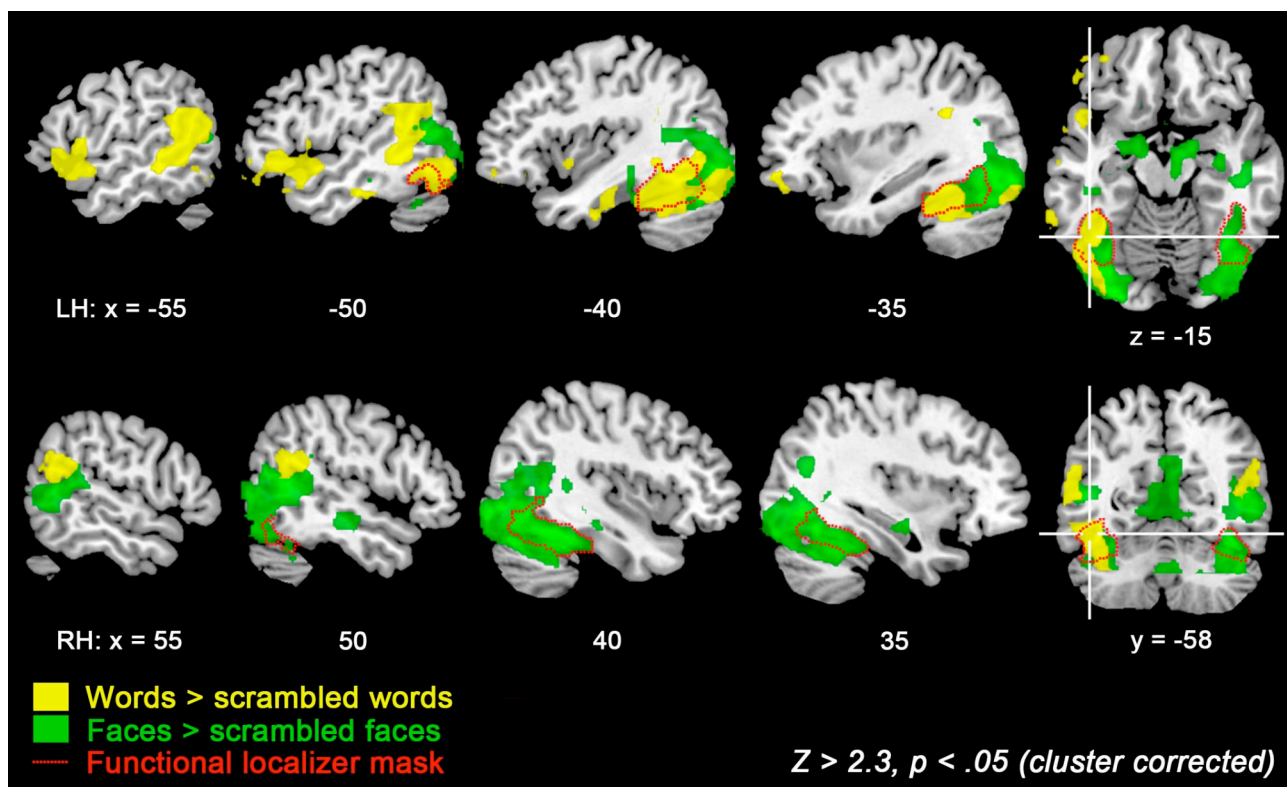


Figure 3.5.2. Statistical maps of the functional localizer results, using a cluster corrected threshold of $Z > 2.3$, $p < .05$. Areas shown in yellow were significantly more active during presentation of words than scrambled words, including the left fusiform gyrus and (predominantly left) temporal and frontotemporal cortex. Areas shown in green were significantly more active for faces than scrambled faces, including bilateral fusiform gyrus, extending into more anterior temporal cortex. The red outline depicts areas within the fusiform gyrus (as defined by the Harvard-Oxford Cortical Structural Atlas) that were significantly active in either contrast – this combined area across both hemispheres was used as the ‘functional localizer mask’ in subsequent analyses. Crosshairs indicate the location of the ‘Visual Word Form Area’ in the left fusiform gyrus (coordinates from Jobard et al. 2003).

The equivalent contrast for faces revealed bilateral face-preferential activity in the left and right posterior fusiform gyri, and more anterior bilateral temporal areas. *Post-hoc* repeated-measure t-tests on ROI data revealed that face-preferential activity was significantly stronger activation in the right occipitotemporal fusiform gyrus than the left ($t_{(11)}=3.2$, $p<0.01$).

Spatial Frequency Analysis

The analysis in FSL compared activation for low and high SF within word- and face-preferential fusiform areas. This analysis (depicted in Figure 3.5.3) revealed greater activation for low than high SF in the right fusiform gyrus, where two significant clusters were observed: the first had a peak at 44 -32 -30 ($Z=4.0$) and the second had a peak at 40 -54 -18 ($Z=3.9$). The opposite contrast of high versus low SF revealed one cluster of activation in the left fusiform gyrus, with peak coordinate -38 -54 -10 ($Z=4.0$). All three clusters were located on the lateral side of the fusiform gyrus, roughly as far anterior as the occipitotemporal junction.

This result indicates that the lateralisation of SF processing was as predicted: low SF preferentially activated the right fusiform gyrus, and high SF preferentially activated the left fusiform gyrus. A further analysis was performed using subject-specific functional localiser masks in order to investigate how reliable these effects were across individuals. Individual localiser masks were created for each participant, and split into their left and right halves. The individual-level results of the low versus high SF contrast were masked with the subject's functional localiser masks. Ten out of twelve subjects showed higher average z-statistics for the contrast of low versus high SF in the right hemisphere localiser region of interest than in the left hemisphere. This was confirmed by a paired subjects t-test, which showed significantly higher average z-statistics for the low versus high SF contrast in the right ROI than in the left ROI ($t_{(11)}=2.73$, $p<.02$).

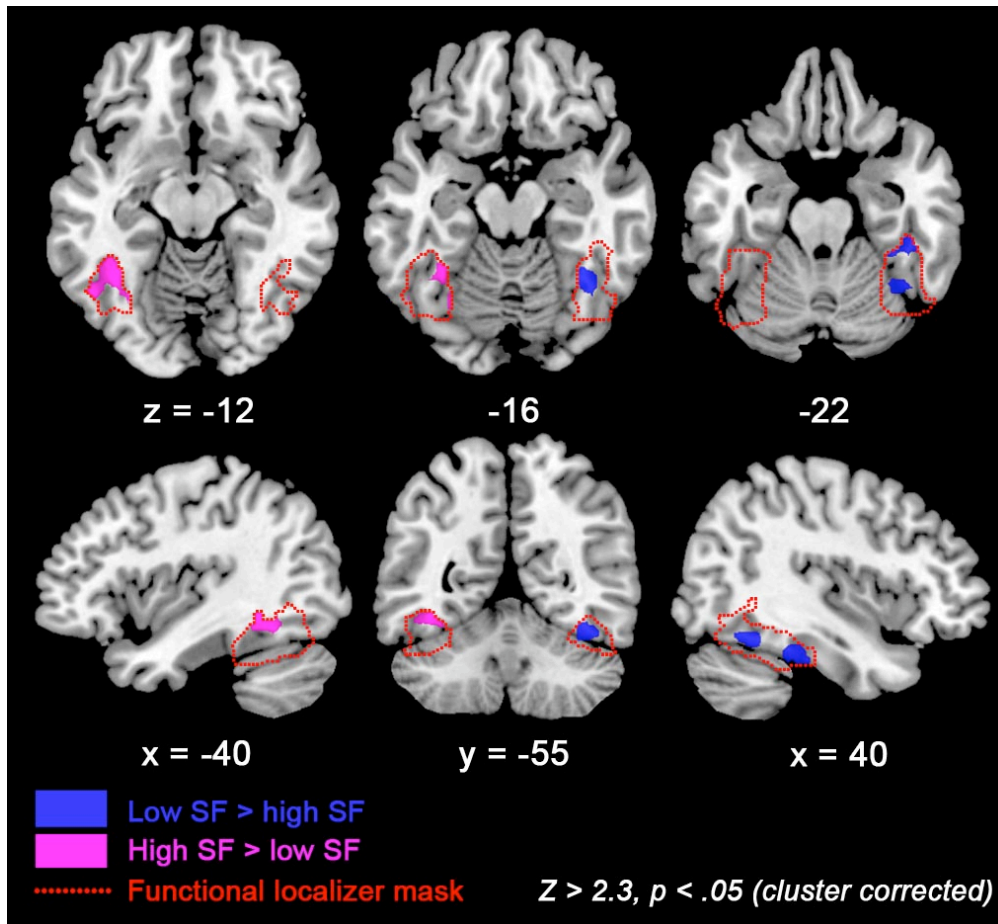


Figure 3.5.3. Statistical maps of the Spatial Frequency analysis results, using a cluster corrected threshold of $Z > 2.3$, $p < .05$. The functional localizer mask (outlined in red) was used to constrain the area of interest. The contrast of low versus high SF (in blue) revealed two significant clusters, both in the right occipitotemporal fusiform gyrus. The opposite contrast of high versus low spatial frequency (in purple) revealed one significant cluster in the left occipitotemporal fusiform gyrus.

This result was replicated in the surface-based analysis. Figure 3.5.4 demonstrates the surface maps for a representative subject to demonstrate the broad pattern of SF sensitivity across the cortex. SF sensitivity was observed extending from primary visual cortex into more anterior ventral occipitotemporal and dorsal occipitoparietal areas. There was a gradient of high to low SF preference moving from the occipital pole outwards. Qualitatively similar results were observed in all subjects. These findings are in agreement with the broad pattern found in previous mapping studies of SF (Sasaki et al. 2001; Henriksson et al. 2008).

The preferred SF of the left and right word- or face-preferential areas were calculated and statistically compared using a within-subjects t-test. This

revealed lower preferred SF in the right hemisphere than the left hemisphere regions of interest ($t_{(11)}=2.7$; $p<0.05$).

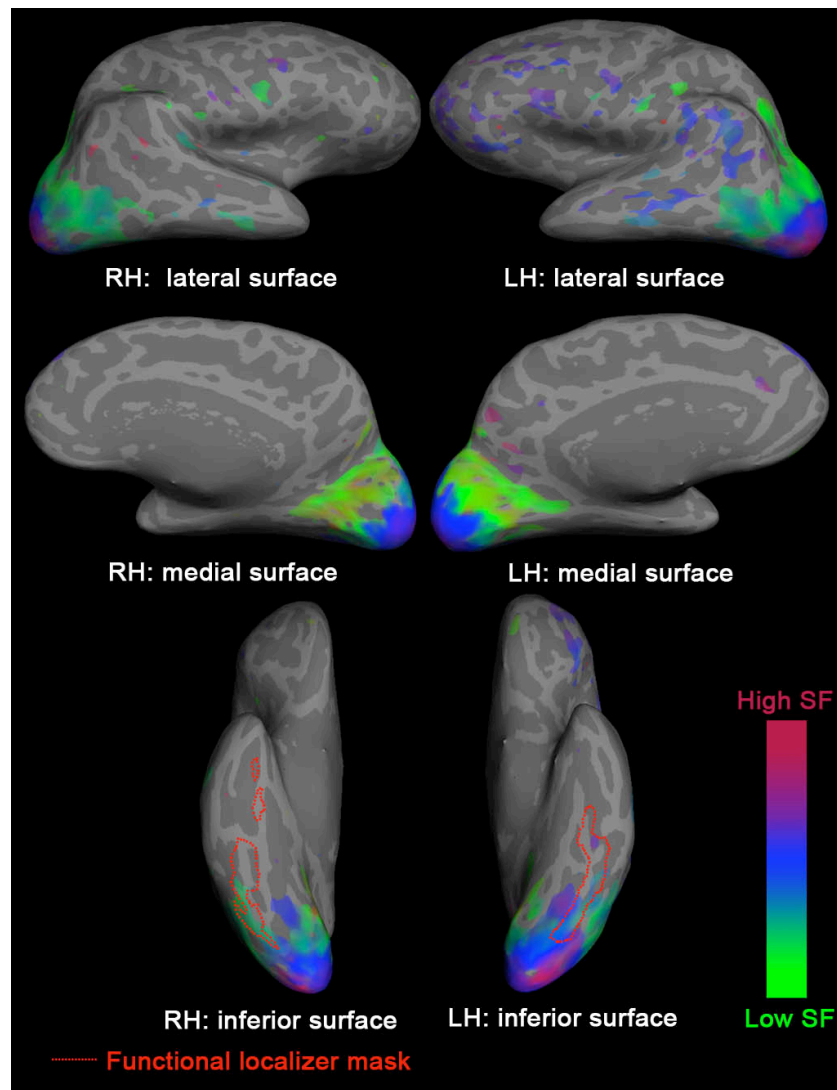


Figure 3.5.4. Surface maps of preferred spatial frequency for a representative subject. A liberal threshold was used for demonstrative purposes.

Discussion

Using simple sine-wave gratings this study showed differences in spatial frequency sensitivity in vOT cortex: object-processing areas in the left vOT cortex were more strongly activated by high than low spatial frequencies, and areas in the right vOT cortex were more strongly activated by low than high spatial frequencies. This finding demonstrates that SF, a low-level visual property, modulates activity in high-order ventral visual association cortex. Furthermore, the hemispheric asymmetry of high SF and low SF processing is concordant with the known lateralisation of word and face processing. This dissociation is compatible with the hypothesis that a predisposition for high

or low SF sensitivity in the left and right hemispheres respectively may influence the development of lateralisation for word and face processing. Hence, damage to the left vOT cortex may cause a general perceptual impairment that predominantly affects high SF stimuli, such as written letters and words. Further investigation into the SF sensitivity of patients with left or right vOT damage is needed to test this hypothesis further.

The relationship between SF sensitivity and reading has also been explored in the context of developmental reading disorders. Compared to children with normal reading development, children with dyslexia may have impaired contrast sensitivity for SFs of around 2 to 8 cpd (Cornelissen, 1993; Skottun, 2000); furthermore, it has been demonstrated that contrast sensitivity around 2 to 4 cpd in preliterate children is a significant predictor of subsequent reading ability two years later (Lovegrove et al. 1986). These findings suggest that there is an association between the development of SF sensitivity and the acquisition of reading expertise. Further studies are needed to address the causal nature of this association, and whether it can be used to develop more effective rehabilitation techniques for patients with acquired reading disorders.

This response of the fusiform gyrus to a low-level visual feature is in addition to the many known high-order effects, such as sensitivity to stimulus category, lexicality and expertise; it is clear from the results presented in Results Chapter 3.1 and 3.2 that these regions are not primarily involved in SF processing. Instead, it is speculated that SF may bias functional lateralisation in the fusiform gyrus. This could occur early in development, allowing hemispheric asymmetry of high-level, abstract processes to develop subsequently, or on the other hand, it may emerge as a component of the specialization for words and faces that becomes established through experience. Whether innate or acquired, it is predicted that sensitivity to SF may effectively channel the processing of particular classes of objects along visual pathways that are best adapted for their efficient processing: this might be tested by predicting the lateralisation of occipitotemporal

activations following training with novel object categories with high or low SF characteristics.

Our results are in agreement with a recent study by Andrews and colleagues (2010), which demonstrated preferential activation of the FFA and PPA to images of faces and places respectively and revealed that the FFA was more strongly activated by Fourier-scrambled faces than scrambled places, and vice versa for the PPA. This suggests that the FFA and PPA are sensitive to low-level visual features (such as SF) that remain intact after Fourier-scrambling has removed all meaningful structure from the image.

It is unclear to what extent our results could be explained by retinal eccentricity rather than SF *per se*. Visual stimuli with high SF are normally viewed in high acuity foveal vision in order to perceive the fine-grained information of the image; by contrast, stimuli with low SF tend to be larger and extend further into peripheral vision. As a result, retinotopic maps of eccentricity and SF in early visual cortex are very similar (Sasaki et al. 2001). Our results may be equally well described by differences in eccentricity preferentiality between word and face processing areas, and as such may extend the organizational framework described by Levy, Hasson and colleagues (Levy et al. 2001; Hasson et al. 2002).

Conclusion and future directions

This study has demonstrated preferential activity for high spatial frequency processing in the left vOT cortex and for low spatial frequency processing in the right vOT cortex. This implies that the lateralisation of spatial frequency processing and the lateralisation of category-preferential object recognition in the vOT cortex are related, but the causal nature of this relationship is not known.

Further work is required to confirm the result presented here, and to investigate the direction of causality between spatial frequency lateralisation and the lateralisation of word and face processing. It is predicted that damage to the left vOT cortex causes impaired sensitivity in the high spatial

frequency range, and vice versa for the right vOT cortex. This could be tested by comparing the visual contrast sensitivity functions of patients with left or right occipitotemporal damage. If the hypothesis was confirmed it could lead to future avenues for rehabilitation of conditions like pure alexia or prosopagnosia. The question of whether a spatial frequency bias causes the lateralisation of word and face processing, or vice versa, could only be answered by conducting a developmental neuroimaging study of pre-literate children.

4. Discussion

4.1 Summary of key results

The three broad aims of this thesis, as laid out in the Introduction, were:

- 1) to address questions about the normal reading system that are key to understanding the nature of acquired reading disorders
- 2) to identify what reading disorders can tell us about the intact reading system
- 3) to test the efficacy of a reading training programme for patients with acquired reading disorders.

With regards to the first aim, the work presented in this thesis investigated the nature of the visual input system for reading (Chapter 3.1), the case for word-preferential processing in the left vOT cortex (Chapters 3.1, 3.2 and 3.5) and whether lateralisation of activity in the vOT cortex is sensitive to the spatial frequency content of visual stimuli (Chapter 3.5).

Chapter 3.1 demonstrated that the initial visual activation during word reading is contralateral to visual presentation, but that word-preferential activity in the vOT cortex is strictly left lateralised. For patients with an RHH, this means that activity in the right visual cortex has to be transferred via the splenium of the corpus callosum to the left vOT. Activity in the left vOT was demonstrated to be preferential for words over perceptually-matched stimuli, irrespective of the location of presentation.

Chapters 3.1 and 3.2 characterised the response profile of the left vOT cortex. The first study (using parafoveal stimulus presentation) showed a profile of words > false font > numbers. The second study aimed to replicate this finding using a central presentation location and a number reading task that was more closely matched to the other conditions. The profile observed was words = false font > numbers. Hence, it is unclear whether the left vOT cortex is preferential for words over false font stimuli, but it is evident that it is preferential for words or word-like stimuli over numbers. It is hard to

reconcile this finding with the LCD model of reading, which would predict that the left vOT cortex is specialised for word recognition, and should not show a differential response to different categories of non-word written stimuli such as false font and numbers. Instead, the results may reflect the impact of task-dependent modulation on the left vOT. According to this view, the reading task elicits top-down modulation from the left frontotemporal language network onto the left vOT cortex. Number reading does not engage the same task-dependent state, as the ultimate aims of digit recognition are numerical rather than verbal. Further work is currently in progress to discriminate between the effects of orthography type (words versus digits) and task (verbal versus numerical) on activity in the left vOT. If this work demonstrates that task-demands significantly affect activity in the left vOT, it would suggest that damage to the backward temporal-to-occipital connections could play a role in the word recognition deficits in patients with PA, as well as the forward occipital-to-temporal connections.

Finally, Chapter 3.5 showed evidence suggesting that the lateralisation of word processing to the left vOT may be related to the spatial frequency content of written words. This work predicts that patients with left occipitotemporal damage may have a general impairment in sensitivity to high spatial frequencies, which would fit in with the perceptual view of pure alexia.

To address the second aim, Chapters 3.3 and 3.4 presented behavioural and functional imaging data from a group of patients with acquired peripheral reading disorders. Chapter 3.3 showed that patients with damage to the left occipitotemporal cortex have impaired word, text and letter reading ability. A deficit at the level of single letters argues against the simultanagnostic view of PA. A domain-general perceptual deficit, or a domain-specific deficit at the level of single letters is more likely. Further work into the perceptual abilities of patients with left occipitotemporal damage is required to distinguish between these two possibilities. If the perceptual view of PA was proven to be correct, this would also imply that the role of the left vOT cortex in

healthy volunteers is domain-general rather than being specialised for written words.

The structural lesion-symptom mapping reported in Chapter 3.3 indicated that damage to the left occipitotemporal white matter, in the vicinity of the ILF, is associated with slow word reading. The existing literature on the structural pathology of PA (Damasio & Damasio, 1983; Binder & Mohr, 1992; Leff et al. 2006) has relied on structural overlay mapping to demonstrate the areas most commonly damaged in patients with PA. The lesion-symptom mapping approach used here is an improvement on this methodology, as it takes into account the severity of the reading impairment, rather than using a binary classification. The dataset reported in Chapter 3.3 would benefit from the inclusion of more patients, and particularly patients with more severe reading disorders, before firm conclusions can be drawn about the critical lesion site for PA.

The final aim of this thesis was addressed by Chapters 3.3 and 3.4, which reported the behavioural and functional imaging results of a training study. The first study tested the efficacy of an intensive, computer-based, whole-word recognition training protocol. As reported in Chapter 3.3, this training resulted in an average reduction in reading speed of roughly 110ms per word. However, this improvement was not statistically significant, and it did not persist until the follow-up reading assessment a few weeks after cessation of the training period. The failure of the reading training was reflected in the lack of positive training effects in the functional imaging data (Chapter 3.4). These findings suggest that the impairment caused by left occipitotemporal damage cannot be ameliorated by functional reorganisation and is insensitive to training – at least of the kind used in this study. Regardless of whether the role of the vOT is reading-specific or domain-general, the data presented here demonstrates that it is critical for rapid whole-word recognition and cannot easily be replaced by compensatory activity elsewhere in the brain.

4.2 Future direction

The work presented here has raised a number of predictions for investigation in future studies. Firstly, the response profile of the left vOT cortex, as observed in Chapters 3.1 and 3.2, led to the prediction that activity in this area is modulated by task-dependent feedback from the frontotemporal language networks. A study is currently under way at the C3NL to investigate the influence of task-dependent modulation on activity in the left vOT cortex. It will compare left vOT activity during presentation of number words ("three") and number digits ("3"), and will test whether activity is affected by the explicit task employed. It is predicted that strong activity will be observed in the left vOT for either stimulus type when a phonological decision is required (which engages the frontotemporal networks), but activity will be low when the task is numerical.

Secondly, the results presented in Chapter 3.5 suggests that PA could be related to impaired visual sensitivity to high spatial frequency (SF) stimuli. This could be tested directly by measuring contrast sensitivity across a range of SFs in patients with left or right occipitotemporal damage. If this work confirmed that patients with left occipitotemporal damage have impaired high SF vision, this would strengthen the argument for a perceptual basis of PA, and could lead to new approaches for rehabilitation.

Finally, the lesion-symptom mapping described in Chapter 3.3 warrants further investigation. A larger patient population is required to validate the finding that damage to the left ILF causes impaired single word reading ability. If this is confirmed, it might be beneficial to acquire tractography data in order to relate white-matter integrity in the ILF to word reading ability.

Two methodological recommendations can be drawn from the patient work presented in this thesis. Stroke patients have been shown to have abnormal HRF in their damaged hemisphere, and especially in perilesional cortex

(Bonakdarpour et al. 2007). This is likely to cause reduced sensitivity for detecting perilesional activations, and may therefore lead to an underestimation of the restitutive role of neuronal recovery around the lesion site. Future studies should investigate whether using custom basis sets (e.g. in FMRIB's Linear Optimal Basis Sets tool, FLOBS; Woolrich et al. 2004) or plotting the HRF on a region of interest basis in each individual (Bonakdarpour et al. 2007) can recover perilesional signal, and whether there is evidence of perilesional activity playing a functional role in stroke recovery.

The second methodological issue relates to patient recruitment. In Chapter 3.3, the inclusion criteria for patient recruitment were the presence of a left occipitotemporal focal lesion and impaired reading ability. There may, however, be a number of patients with similar lesions that do not experience reading problems. Hillis and colleagues (2005) tested language abilities in a group of 80 right handed patients with acute left hemisphere ischemic stroke. Of the 53 patients with VWFA damage (in the cortical location of the VWFA defined by Cohen et al. 2000), only 31 demonstrated word recognition deficits; and of the remaining 27 patients who did not have VWFA damage, 11 had word reading deficits. This failure to relate left vOT damage to reading impairments may have been because the area tested was cortical, whereas Chapter 3.3 showed that damage to the occipitotemporal white-matter was more closely linked to reading ability; but regardless, it demonstrates that future studies should take a broad approach to patient recruitment. It might be beneficial to define the inclusion criteria according to either the presence of an acquired reading disorder, or damage to the left vOT cortex, but not both.

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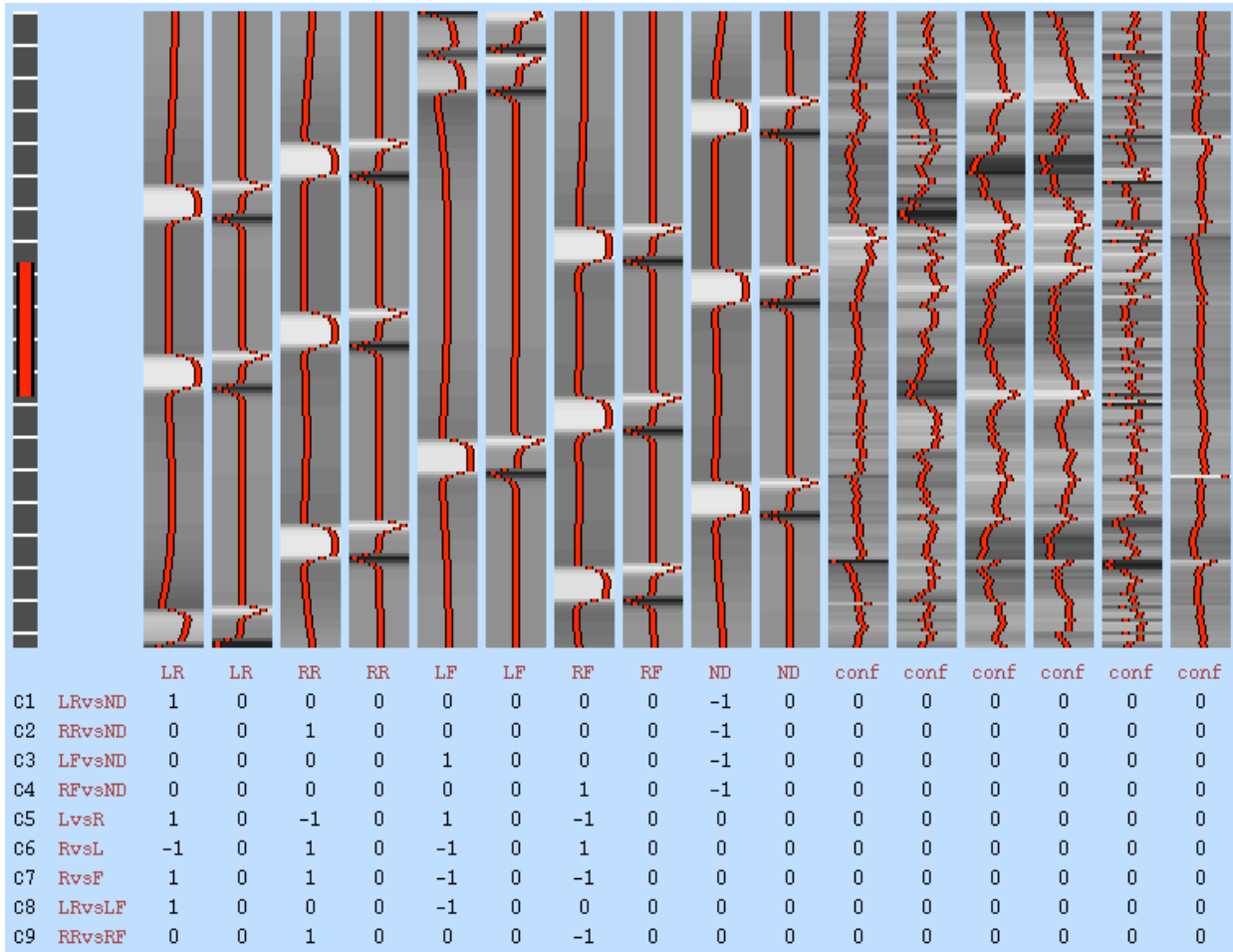
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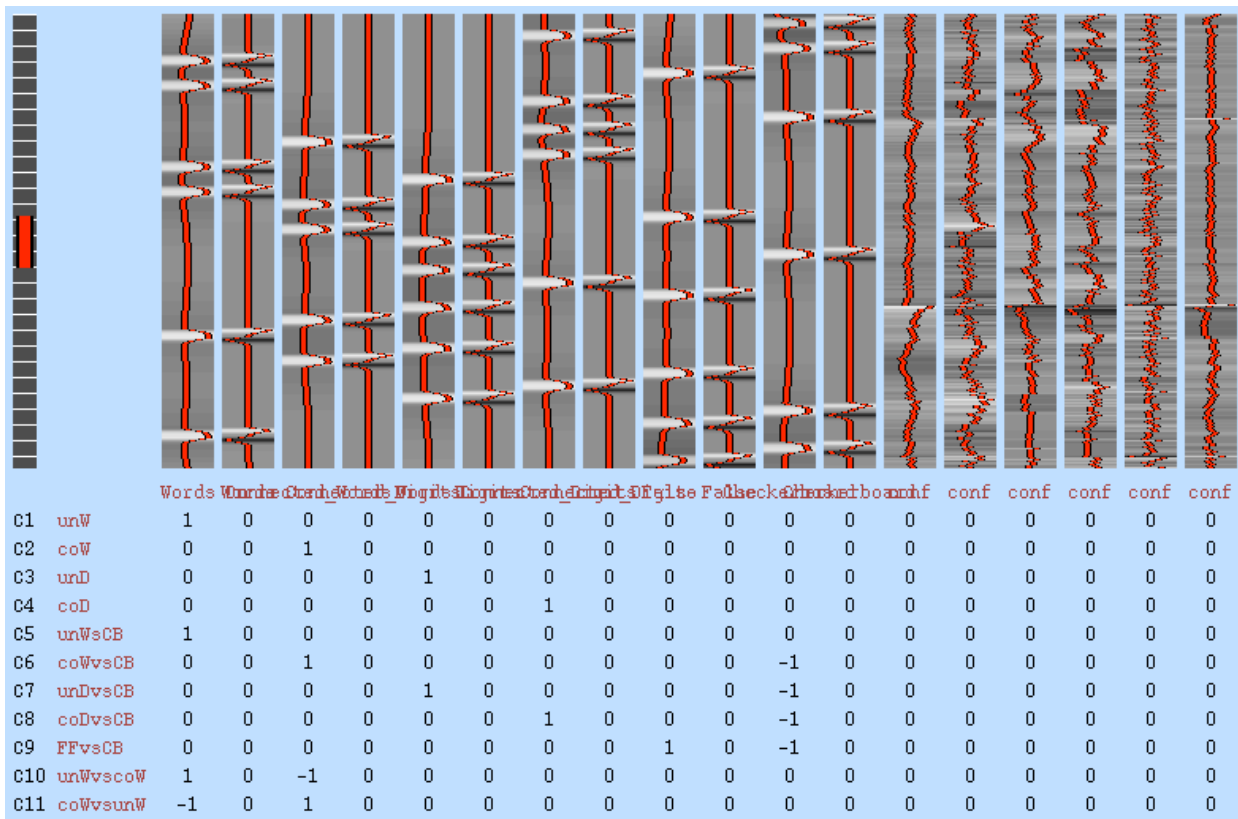
Appendix – FEAT design matrices

Chapter 3.1



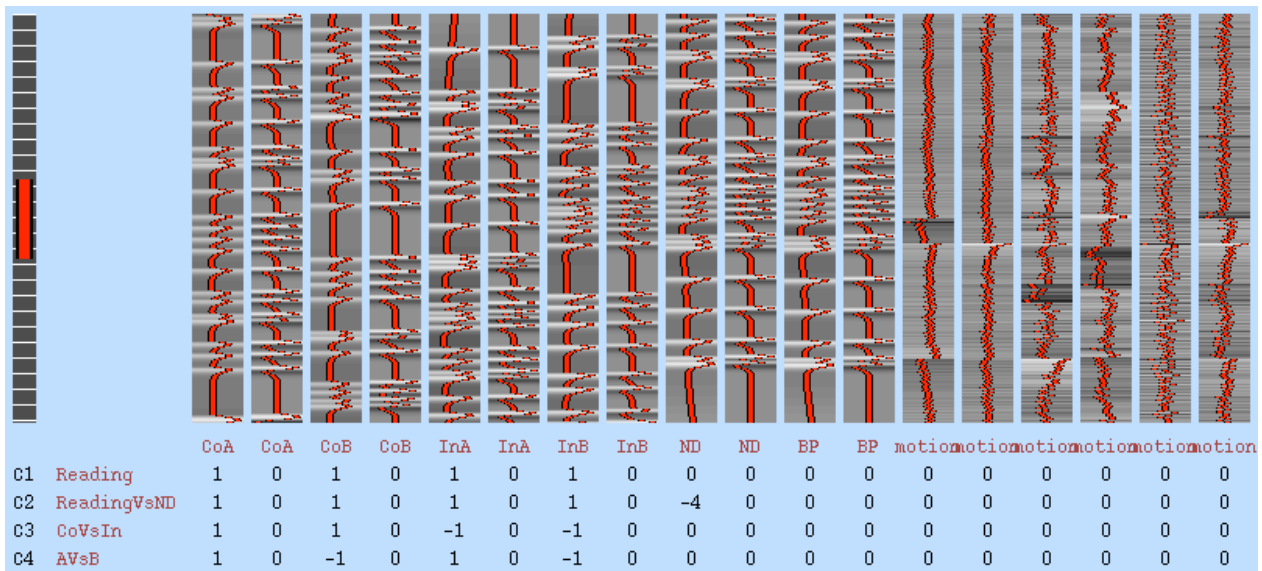
First level design matrix: Showing the EVs for the left reading (LR), right reading (RR), left false font (LF), right false font (RF) and number decision (ND) conditions, their temporal derivatives and the motion parameters.

Chapter 3.2

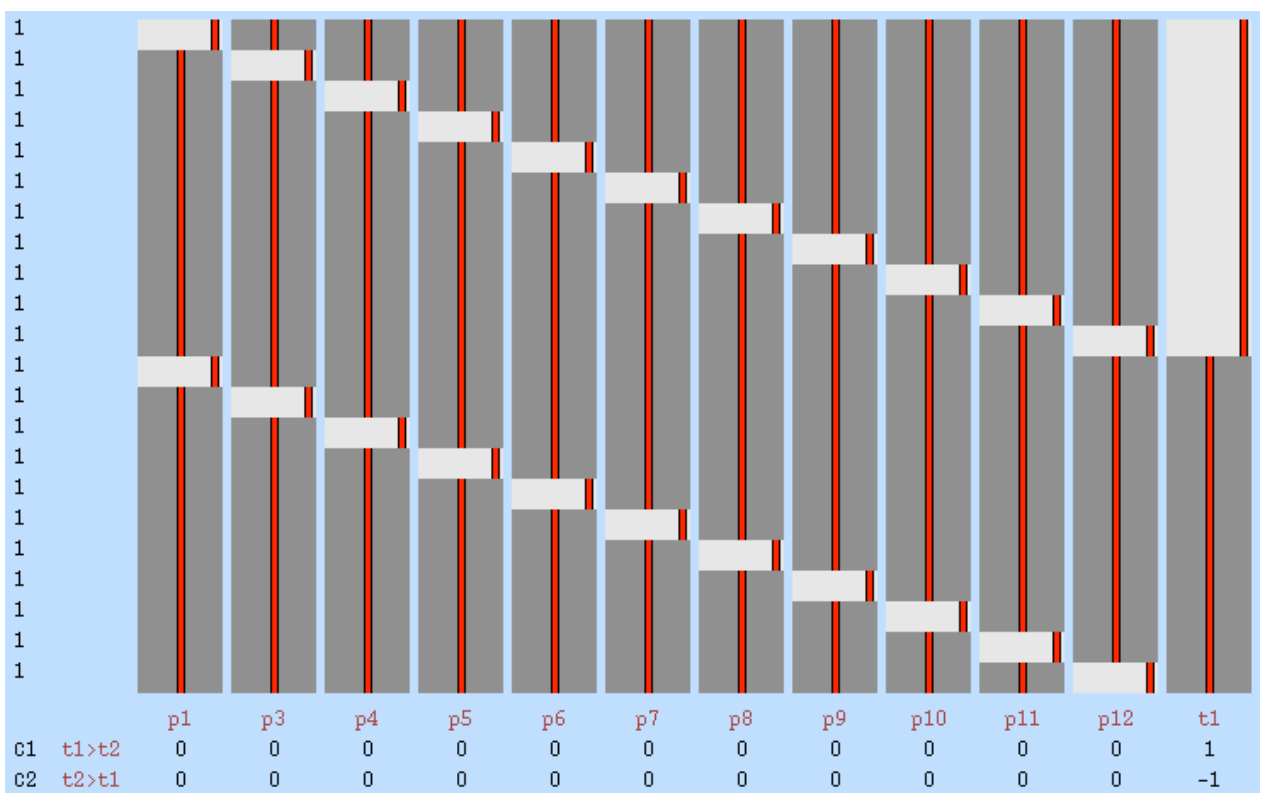


First level design matrix: Showing the EVs for the unconnected words, connected words, unconnected digits, connected digits, false font and checkerboard conditions, plus the temporal derivatives and motion parameters.

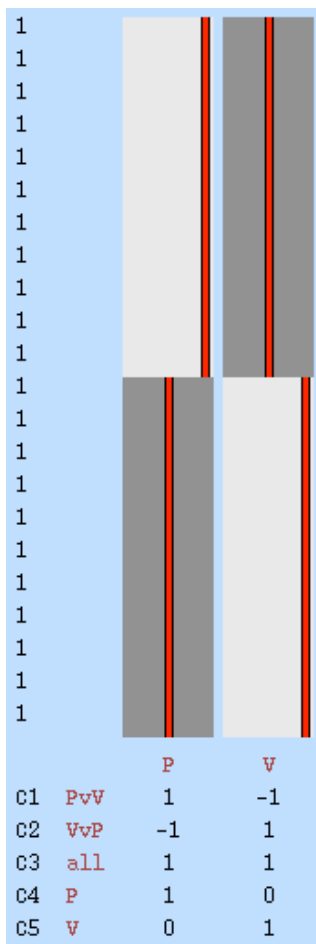
Chapter 3.4



First level design matrix: Showing EVs for the connected words from word list A (CoA), connected words from word list B (CoB), unconnected words from word list A (InA), unconnected words from word list B (InB) and number decision (ND) conditions, plus the button press response (BP), the temporal derivative of each EV and the motion parameters.

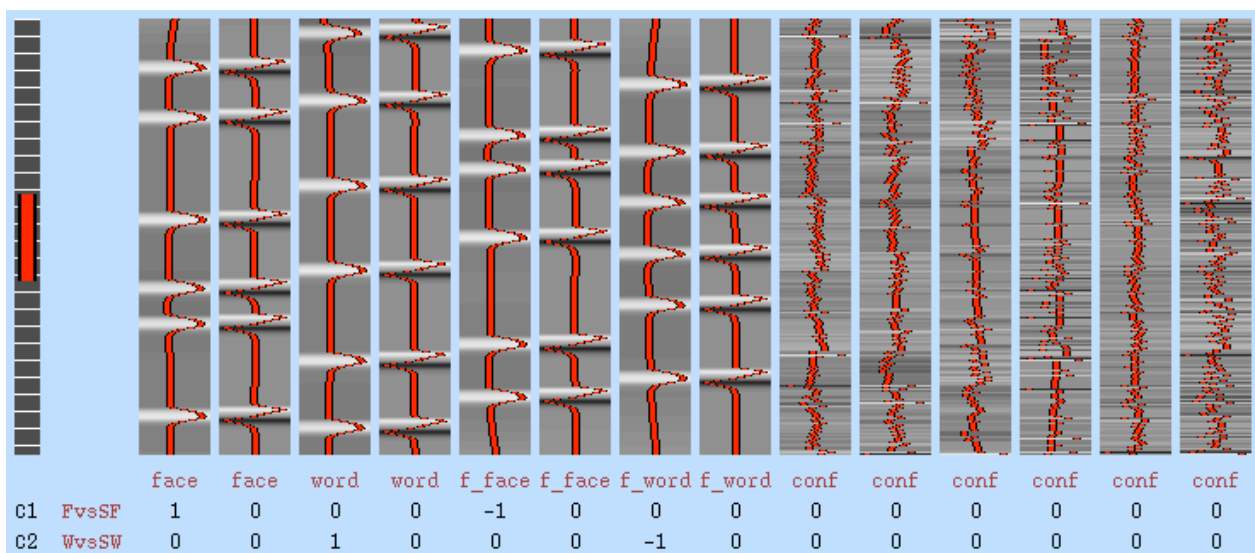


Higher level test-retest design matrix: A paired t-test group-level design. The design matrix includes an EV for each patient of the group, and a final EV modelling the difference between t1 and t2 sessions.

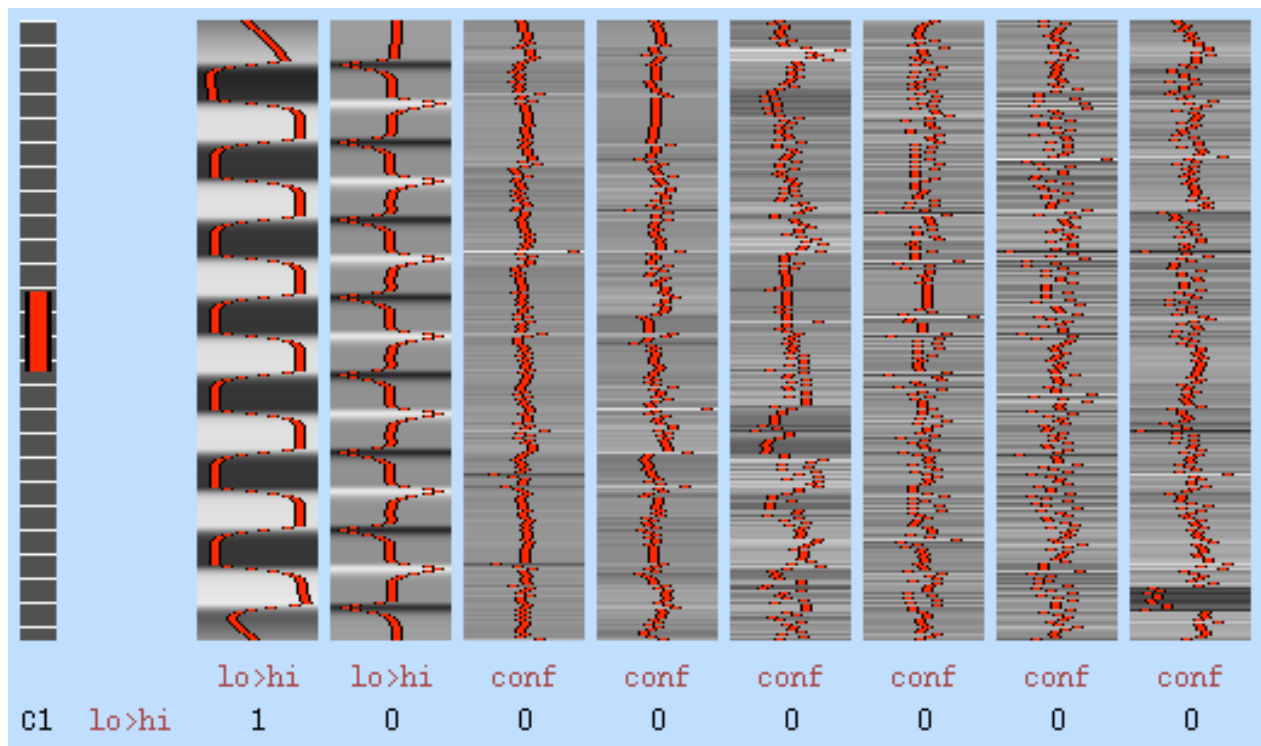


Higher level group comparison design matrix: An independent t-test design. There are two EVs – one modelling the patient scans, and one modelling the volunteer scans. The contrasts evaluate the differences between patients and volunteers.

Chapter 3.5



First level functional localiser design matrix: The EVs model the face, word, scrambled face (f_face) and scrambled word (f_words) conditions, plus the temporal derivative of each EV and the motion parameters.



First level spatial frequency design matrix: One EV modelling the low spatial frequency half of the spatial frequency cycle, plus the temporal derivative and the motion parameters.