USING DIFFUSION WEIGHTED IMAGING TO MAP CHANGES IN WHITE MATTER CONNECTIVITY IN CHRONIC STROKE APHASIA

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Using Diffusion Weighted Imaging to Map Changes in White Matter Connectivity in Chronic Stroke Aphasia

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Abstract

The role of white matter pathways in language networks has received much attention in recent years. This is largely due to advances in diffusion imaging techniques, which have enabled exploration of white matter properties *in vivo*. The emergent model from such work proposes that language processing is underpinned by a dorsal and a ventral pathway connecting anterior and posterior regions involved in language. This thesis aimed to explore whether consideration of white matter measures could aid understanding of performance profiles in chronic stroke aphasia. To this end, a group of participants with chronic stroke aphasia were recruited and their performance on a large battery of language assessments was related to their neuroimaging data. The neuroimaging data comprised high resolution T1-weighted structural scans, fractional anisotropy (FA) maps, and data generated using a tractography-based technique called Anatomical Connectivity Mapping (ACM) which provides an index of long-range connectivity that has not yet been applied to chronic stroke aphasia.

Chapter 3 established, in a small series of case examples, that connectivity information from ACM can help explain variations in performance in chronic stroke aphasia. **Chapter 4** extended this work to a larger group of participants. Differences between aphasic participants and controls, and between groups with different aphasic subtypes and controls, were calculated and compared across imaging methods. ACM offered insights into connectivity differences that were complementary to information from T1-weighted and FA data. In addition to revealing areas where connectivity was reduced relative to controls, ACM revealed an increase in connectivity in the right hemisphere dorsal route homologue of aphasic participants.

Chapter 5 aimed to improve our ability to capture aphasic performance and to relate it to neuroimaging data. Principal components analysis (PCA) was used to derive factors underlying performance on the language battery. Phonological, semantic, and cognitive factors emerged from the PCA and participants' factor scores were used as continuous regressors in a voxel-level analysis of their T1-weighted images. Regions that emerged as significantly related to language abilities aligned with those found using other methodologies. **Chapter 6** brought together work from the previous chapters by relating PCA-derived factor scores to FA maps and ACM, in order to assess the relationship between behavioural performance and the status of key white matter pathways. In line with recent characterisations of the dual route system, phonological performance related to dorsal route measures and semantic performance related to ventral route measures. Better cognitive performance was found to relate to increased connectivity relative to controls in the right frontal lobe. Overall these results suggest that consideration of white matter abnormalities, both reductions and increases, can help explain patterns of performance in chronic stroke aphasia and that ACM can be a useful source of such information given its sensitivity to connectivity remote from the lesion. These findings both provide hypotheses for future research and could be used to inform therapeutic interventions.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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The Author

I graduated from the University of Manchester in 2005 with a BSc (Hons) in Psychology. After graduating I worked as the Assistant Manager of the Clinical Information team at Manchester Heart Centre, before moving to the Healthcare Commission, where I worked as a Case Manager. In 2008 I undertook a Masters of Research in Psychological Research Methods, again at the University of Manchester. My masters research project was supervised by Dr Anna Woollams and investigated the effects of semantics on past-tense verb inflection. Following completion of my masters in 2009, I began my four-year PhD. I have very much enjoyed having the opportunity to conduct detailed research into neuroimaging of chronic stroke aphasia. I have thoroughly enjoyed expanding my knowledge of aphasiology and neuroanatomy, and gaining skills and experience in neuropsychological assessment and acquisition and analysis of structural neuroimaging data. I am particularly grateful to have had the experience of working with such an inspiring and interesting group of participants.

CHAPTER 1

INTRODUCTION

Thesis Overview

This thesis is presented in alternative format, meaning that Chapters 3 - 6 are written in the style of journal articles. As such, each of these self-contained chapters provides details of the motivation for the work contained within it, a review of relevant background literature, and an interim discussion of the results obtained. Chapter 1 provides a broader review of the background literature relevant to the thesis as a whole and identifies the key research questions the thesis aims to address. Chapter 2 describes key methodological issues which have needed to be considered in the process of conducting this research. The final chapter, Chapter 7, constitutes a general discussion of the research findings, their implications, as well as future directions.

This introductory chapter will begin by describing classification systems that have been developed to attempt to capture behavioural performance of individuals with stroke aphasia, along with some of the issues associated with such systems. Ways in which previous work has attempted to relate aphasic performance to underlying brain bases will then be explored, alongside key findings obtained using such methods. The notion that considering the impact of stroke upon white matter connectivity may aid understanding of patterns of performance in aphasia will then be introduced. Previous work examining the role of white matter pathways in language and the abnormalities in such pathways underlying aphasic performance will then be described. Finally, the aims of the current thesis in the context of this prior work will be outlined.

Stroke Aphasia: Classification of Behavioural Performance

According to World Health Organisation criteria, a stroke, or cerebrovascular accident (CVA), is defined as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin” (Aho et al., 1980, pp.114). Broadly

speaking, stroke arises from either the occlusion of blood vessels supplying the brain, or haemorrhage of such vessels, which results in neuronal death and dysfunction (Lo, Dalkara, & Moskowitz, 2003). Deficits following stroke can impact upon motor, sensory, affective, cognitive, and linguistic systems (Adamson, Beswick, & Ebrahim, 2004; LeBrasseur, Sayers, Ouellette, & Fielding, 2006). One of the most frequently occurring and debilitating sequelae of stroke is aphasia, a condition which undermines the ability to communicate verbally. Aphasia is a central linguistic impairment, independent of articulation ability, which can affect speech comprehension as well as production. That said, some individuals with aphasia have comorbid deficits in the motor production of speech, such as dysarthria or apraxia of speech, both of which can affect articulation (Wade, Hewer, David, & Enderby, 1986).

Although the majority of individuals who present with aphasia will demonstrate some improvement in language function in the acute phase following stroke, and even into the chronic phase (Brust, Shafer, Richter, & Bruun, 1976; Heiss, Thiel, Kessler, & Herholz, 2003), a significant proportion of individuals will remain aphasic chronically (Gresham et al., 1979; Matsumoto, Whisnant, Kurland, & Okazaki, 1973; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Wade et al., 1986). The magnitude and course of improvement in language function post-stroke is highly variable between individuals and there has been considerable research interest in the mechanisms underlying recovery from aphasia (e.g., Blank, Bird, Turkheimer, & Wise, 2003; Crinion & Leff, 2007; Crinion & Price, 2005; Crosson et al., 2007; Hillis & Heidler, 2002; Price & Crinion, 2005; Saur et al., 2006; Warburton, Price, Swinburn, & Wise, 1999) and factors affecting the rate and extent of such recovery (e.g., Brust et al., 1976; Crosson et al., 2007; Kertesz & McCabe, 1977; Kertesz, 1984; Pedersen et al., 1995; Sarno, Silverman, & Sands, 1970; Vignolo, 1964).

Individuals with aphasia vary, not only in terms of the severity of their language deficits, but also in terms of the character of such deficits. Stroke aphasics constitute a heterogeneous group, with language dysfunction varying along several dimensions. Classification systems which have attempted to capture this variation and allow clinicians to assign individuals to an aphasic subtype include the widely used Boston Diagnostic Aphasia Examination (BDAE) (Goodglass, Kaplan, & Barresi, 2000; Goodglass & Kaplan, 1983) and Western Aphasia Battery (WAB) (Kertesz, 1982). Equivalent systems in other languages include the Aachen Aphasia Test (Huber, Poeck, & Willmes, 1984), designed for German speakers. Figure 1.1 shows the different aphasia classifications that the BDAE allocates individuals to and the dimensions which these classifications are based upon.

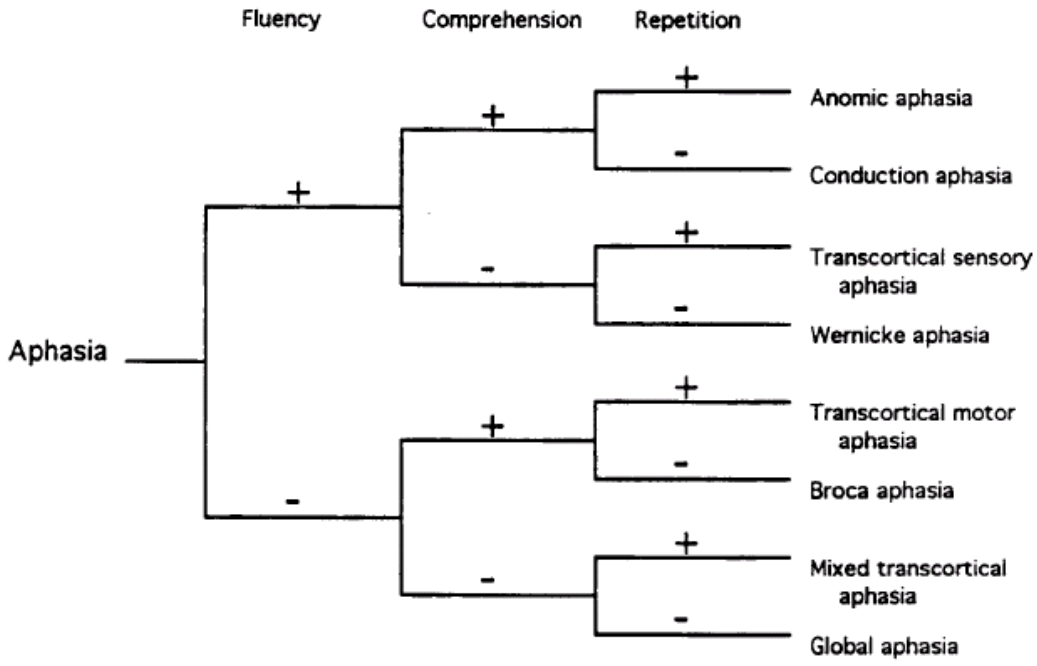

Figure 1.1. Illustration of the dimensions along which different aphasic subtypes are classified in systems such as the Boston Diagnostic Aphasia Examination (Goodglass et al., 2000; Goodglass & Kaplan, 1983). Taken from Saver (2002) (p.32).

Classifications on the BDAE range from anomic aphasia, in which the primary deficit shown is word-finding difficulty, in the context of fluent speech, and preserved comprehension and repetition, through to global aphasia, which is characterised by deficits in all aspects of language, with minimal (if any) verbal output and severe deficits in comprehension of words and sentences (Alexander, 1997; Hillis, 2007). Between these classifications lie aphasia types where certain aspects of language are impaired whilst others are spared, such as Wernicke's aphasia in which output is fluent but relatively devoid of meaning, and both repetition and comprehension are impaired. Whilst classifications such as those derived from the BDAE provide convenient labels for clinicians and researchers, aphasic individuals often do not fit neatly into diagnostic categories (e.g., Albert, Goodglass, Helm, Rubens, & Alexander, 1981; Ardila, 2010; Basso, Lecours, Moraschini, & Vanier, 1985; Brust et al., 1976; Prins, Snow, & Wagenaar, 1978). Dissociations between intact and impaired performance on different language tasks are usually relative rather than absolute. Individuals often do not fully meet the criteria for one aphasia type, and broad variations in performance exist within the same aphasia subtype (e.g., Brust et al., 1976). As a result, assigning an individual an aphasia type derived from such a classification may not be the most precise or informative way of describing their language performance. **Chapter 5** demonstrates an alternative way of defining aphasic individuals' performance, using Principal Components Analysis (PCA) to capture performance on a large battery of language assessments. An additional benefit of these PCA-derived measures is that they constitute ideal regressors when attempting to relate variations in language ability to underlying brain measures (as demonstrated in **Chapters 5** and **6**).

Stroke Aphasia: Identifying Underlying Brain Bases

Whilst this thesis addresses structural abnormalities in the brain underlying aphasic behaviour, changes at the functional level may mediate the structure-behaviour relationship. Functional imaging studies have investigated issues such as the evolution of aphasia from the acute to the chronic phase (e.g., Saur et al., 2006), predicting language outcome after stroke (e.g., Saur et al., 2010), mechanisms underpinning different aspects of aphasic performance such as comprehension (e.g., Crinion & Price, 2005) and production (e.g., Fridriksson, Richardson, Fillmore, & Cai, 2012), and functional reorganisation supporting recovery from stroke, including that associated with treatment (e.g., Crinion & Leff, 2007; Crosson et al., 2007; Heiss et al., 1997; Meinzer et al., 2008; Warburton et al., 1999). There are a number of challenges associated with functional imaging of individuals with stroke aphasia, from disruptions to the BOLD response soon after the stroke to more general issues concerning use of a paradigm that can be accurately performed by the participants in order to avoid imaging activations associated with erroneous responses (Price & Friston, 1999; see also Crosson et al., 2007; Lee, Kannan, & Hillis, 2006; Price, Crinion, & Friston, 2006; Price & Friston, 2002). Changes in brain function in stroke aphasia are likely to reflect underlying structural brain abnormalities resulting from stroke lesions. Such structural abnormalities are the focus of this thesis and are investigated by attempting to relate structural imaging to the accuracy of participants' performance on different language tasks.

According to the lesion-symptom approach, if we look at individuals with a certain behavioural deficit, they should have similar regions of brain damage, and if we look at individuals with lesions to a particular brain region, they should demonstrate equivalent performance on relevant behavioural measures. The lesion-symptom approach has an intuitive appeal, and has contributed greatly to our understanding of language, and other cognitive capacities of the human brain (Bates et al., 2003; Rorden & Karnath,

2004). Seminal findings using this approach include the observation made by Carl Wernicke that damage to the left posterior superior temporal cortex was associated with deficits in language comprehension (Eggert, 1977; see also Blunk, De Bleser, Willmes, & Zeumer, 1981; Hillis, 2007; Naeser & Hayward, 1978) and Paul Broca's work which revealed a relationship between damage to the posterior left inferior frontal gyrus (Broca, 1861; see also Hillis, 2007) and deficits in language production. Lesion-symptom methodology has continued to be widely used in neuropsychology and has led to the advancement of knowledge regarding brain-language relationships (Rorden & Karnath, 2004).

However, the consistency of mappings between specific aphasia types and underlying lesion locations has been challenged by exceptions to expected lesion-symptom mappings. For example, authors have noted that lesions to Broca's area do not always produce the symptom profile associated with Broca's aphasia and, conversely, that Broca's aphasia can occur without concomitant lesions involving Broca's area itself (Basso et al., 1985; Hillis, 2007; Mohr et al., 1978). Willmes and Poeck (1993) found that only 17 of 48 individuals with anterior damage could be classified as Broca's aphasics, and 23 of 48 individuals with posterior lesions met the criteria for Wernicke's aphasia. Conversely, only 17 of the 29 Broca's aphasics had anterior lesions, and 23 of the 26 Wernicke's aphasics studied had posterior damage. The authors concluded that there was no evidence for an unequivocal association between aphasia type and lesion location in their study (Willmes & Poeck, 1993 ; see also Basso et al., 1985; Vignolo, Boccardi, & Caverni, 1986).

Given these inconsistencies in lesion-symptom mapping based on traditional aphasiological classifications, in more recent years lesion studies have tended to focus on neural substrates of performance on specific language tasks. One method for relating behavioural performance to imaging data is voxel-based morphometry (VBM), which

involves conducting parametric statistical analyses on a voxel-by-voxel basis throughout the entire brain, to identify group differences in tissue concentrations (Ashburner & Friston, 2000; Rorden & Karnath, 2004). The output obtained from VBM is a statistical parametric map, which illustrates regions of significantly differing tissue concentrations between groups (Ashburner & Friston, 2000). Because VBM is a whole-brain approach there is no need for *a priori* specification of relevant structures, meaning any relevant regions should emerge from analyses irrespective of the expectations of investigators (Ashburner & Friston, 2000; Draganski & May, 2008; Timmann et al., 2009). However, results of VBM analyses have been shown to be influenced by choices made during processing of data (Jones, Symms, Cercignani, & Howard, 2005).

In traditional VBM the investigator is required to make a binary distinction between normal and abnormal behavioural performance, meaning that potentially informative gradations in language performance are lost (Borovsky, Saygin, Bates, & Dronkers, 2007; Tyler, Marslen-Wilson, & Stamatakis, 2005). A variant of VBM that utilises continuous behavioural data is voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003). Unlike traditional VBM, which requires participants to be divided into distinct groups, for example, based on normal versus impaired scores on a behavioural test, with VLSM, participants' scores on a continuous measure are compared at a voxel level. As with VBM, the output is a statistical parametric map showing which brain voxels are significantly related to performance on the given behavioural measure (Baldo & Dronkers, 2007; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Bates et al., 2003; Saygin, Wilson, Dronkers, & Bates, 2004).

A study of 64 chronic aphasic individuals which employed VLSM found that comprehension performance was associated with several left hemisphere regions, including posterior middle temporal gyrus (and underling white matter), anterior superior temporal gyrus and sulcus, angular gyrus, mid frontal cortex, and pars orbitalis in the

inferior frontal gyrus (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). A VLSM study of speech production conducted by Borovsky et al. (2007) found that deficits in production were associated with anterior insula damage in a sample of 50 aphasic individuals. VLSM has also been used in conjunction with functional neuroimaging to look at brain areas involved in language comprehension (Dick et al., 2007). Using continuous measures of language performance to correlate with lesion data has clearly been a useful development in the study of aphasia (see also Baldo & Dronkers, 2007; Baldo, Katseff, & Dronkers, 2011; Baldo et al., 2006; Piras & Marangolo, 2007; Saygin et al., 2004; Schwartz et al., 2011; Schwartz, Faseyitan, Kim, & Coslett, 2012; Turken & Dronkers, 2011; Wilson & Saygin, 2004).

Whilst VLSM employs continuous behavioural measures, a binary distinction is made at the brain level between intact and damaged tissue. Some studies have combined the benefits of continuous behavioural measures, as used in VLSM, with continuous brain measures, as used in VBM (Geva, Baron, Jones, Price, & Warburton, 2012; Leff et al., 2009; Tyler et al., 2005a). Tyler et al. (2005a) refer to this approach as 'voxel-based correlational methodology' (VBCM). Throughout this thesis the term 'VBM' will be used to refer to voxel-wise lesion analyses using discrete behavioural measures (with continuous brain measures). Voxel-wise analyses using VBM techniques that incorporate continuous behavioural data will be referred to as 'VBCM', as per Tyler et al. (2005a). Differences between these lesion-symptom mapping techniques are discussed further in **Chapter 2**.

It should be borne in mind that certain brain regions may emerge more frequently in lesion-symptom analyses, whichever method is employed, due to regional differences in vasculature. Brain regions that are only supplied by a particular cerebral artery, such as the left mid cerebral artery (MCA) (Phan, Donnan, Wright, & Reutens, 2005), are more vulnerable to ischaemia (Hillis et al., 2004) than regions such as the left anterior temporal

cortex, which have a dual blood supply in many individuals (Borden, 2006; Conn, 2003). Consequently, power to detect relationships with behaviour will be differentially distributed throughout the brain when studying lesions induced by a particular type of stroke.

Chapter 4 of the current thesis reports results obtained using a VBM approach, whilst **Chapters 5** and **6** employ the VBCM method. **Chapter 5** describes a further development of the use of continuous behavioural measures in lesion-symptom mapping, using PCA-derived measures of behaviour to correlate with imaging data. In addition to improving the 'symptom' side of the lesion-symptom mapping relationship through improved behavioural measures, improvements on the 'lesion' side of the relationship, in the form of more advanced consideration of brain-based factors, may help to further explicate the brain bases of aphasic performance. Basso et al. (1985) argued that "exceptions" in lesion-symptom mapping demonstrate the need to consider factors affecting brain-language relationships other than cortical integrity (Basso et al., 1985). The focus of this thesis is on a key factor potentially affecting brain-language relationships in aphasia, that of white matter connectivity.

White Matter Pathways and Language

Although cortical damage clearly has an important role to play in explaining behavioural impairments seen in aphasia, variations in aphasic performance after stroke may also reflect abnormalities in connectivity between brain regions. Consideration of abnormalities in long range white matter connections may lead to improved success in relating stroke lesions to aphasic symptoms. White matter tracts in the human brain are classified into three groups: association fibres, which connect cortical regions within the ipsilateral hemisphere; commissural fibres, which link cortical regions in contralateral hemispheres; and projection fibres, which connect cortical regions to subcortical

structures, such as the thalamus (Catani & ffytche, 2005; Schmahmann & Pandya, 2008; Schmahmann, Smith, Eichler, & Filley, 2008). Association fibres can be divided into local association fibres (or U-shaped fibres), which connect adjacent gyri; neighbourhood association fibres, which connect nearby cortical regions; and long-range association fibres, which connect distant cortical regions (Schmahmann & Pandya, 2008; Schmahmann et al., 2007). Higher order cognitive functions are the result of co-ordinated activity over large-scale neural networks, rather than the operation of isolated cortical modules (Catani & ffytche, 2005; Catani & Mesulam, 2008a; Mesulam, 1990; Schmahmann et al., 2008; Thiebaut de Schotten et al., 2008). Long-range association fibres are therefore likely to be critical to language functioning.

As stroke damage usually affects both grey and white matter, taking into account the effects of lesions that disrupt communication between different brain regions, i.e., those affecting long-range association fibres, as well as damage to cortical regions, may improve lesion-symptom mapping in stroke aphasia, and other neurological disorders. Doricchi, Thiebaut de Schotten, Tomaiuolo, and Bartolomeo (2008) argue that disruption of long-range white matter pathways could result in more substantial behavioural deficits than cortical damage alone. This claim was based upon the reasoning that damage to long association fibres could result in quantitatively more disruption than damage to equivalently sized cortical regions, because of the potential impact on larger cortical areas (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007). Furthermore, the authors argued, alternative cortical regions may be able to compensate functionally for cortical damage, whilst disruption to entire functional networks arising from white matter damage may be more difficult to compensate for (Catani & Mesulam, 2008a; Doricchi et al., 2008).

Developments in neuroimaging in recent years have enabled the imaging of white matter pathways in the human brain *in vivo*. This is especially useful in the study of

aphasia, as it means investigators can relate participants' white matter status to their performance. Diffusion-weighted imaging (DWI) is a non-invasive magnetic resonance imaging (MRI)-based technique, which utilises diffusion of water molecules to characterise different brain tissues (Catani, Howard, Pajevic, & Jones, 2002; Clayden, Storkey, & Bastin, 2007; Jones, 2008; Le Bihan, 2003; Parker, Wheeler-Kingshott, & Barker, 2002). Several different measures can be derived from DWI. The most commonly used of these is fractional anisotropy (FA), a measure reflecting the magnitude of anisotropy of the diffusion tensor, at a voxel level (Basser, Mattiello, & LeBihan, 1994; Basser & Pierpaoli, 2011; Catani et al., 2002; Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008; Jones, 2008; Pierpaoli & Basser, 1996). Other DWI-derived measures include mean diffusivity, the net movement of water molecules, independent of tissue directionality; radial diffusivity, diffusivity across the tract; and parallel diffusivity, diffusivity along the tract (Ciccarelli et al., 2008). Such measures provide indirect information regarding the organisation of brain tissue and the orientation of diffusion tensors (Basser et al., 1994; Basser & Pierpaoli, 1996; Catani et al., 2002; Ciccarelli et al., 2003; Le Bihan, 1995; Pierpaoli & Basser, 1996), which can reveal white matter damage that may not be visible on standard structural images (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008).

Information regarding how white matter tracts are connected between adjacent voxels can be obtained using tractography (Catani & Mesulam, 2008; Ciccarelli et al., 2003; Clayden et al., 2007; Jones, 2008; Parker et al., 2002). Tractography is a diffusion-based method which yields information regarding the trajectories of white matter tracts, which is then used to algorithmically reconstruct continuous three-dimensional (3D) tracts (Catani & Mesulam, 2008a; Clayden et al., 2007; Jones, 2008). Tractography allows investigators to quantify and visualise white matter tracts *in vivo*, enabling examination of the character and integrity of long-range association tracts in healthy and

diseased brains (McDonald et al., 2008). The impact of neurological disorders, such as stroke, on white matter connectivity can be evaluated in this way (Clayden et al., 2007). Whilst diffusion MRI tractography-derived connectivity is taken as reflecting 'true' anatomical connectivity, it is important to remember that the two are not equivalent. Tractography results can be affected by issues such as false positives, false negatives, and distance effects (Johansen-Berg & Behrens, 2006; Jones, 2008; Morris, Embleton, & Parker, 2008). Thus, in this thesis 'connectivity' will be used as a shorthand for information obtained using probabilistic tractography, which is a proxy for true anatomical connectivity.

An exciting recent extension of tractography techniques is anatomical connectivity mapping (ACM) (Embleton, Morris, Haroon, Lambon Ralph, & Parker, 2007; Parker & Alexander, 2005). ACM is conducted by launching multiple tractography streamlines from every brain voxel. The resultant maps provide information regarding the relative anatomical connectivity of each grey and white matter voxel in the entire brain (see **Chapter 2** for more details). The current research has utilised these whole-brain connectivity maps, in concert with FA data, to aid understanding of the brain abnormalities underlying stroke aphasia. **Chapter 3** presents case studies where ACM is used to assess whether changes in connectivity can explain variation in lesion-symptom mapping. In **Chapter 4** ACM is employed in order to investigate abnormalities in brain-wide connectivity in stroke aphasics compared to controls at a group level. Finally, in **Chapter 6** ACM is used to help identify relationships between abnormalities in connectivity and performance on different language abilities across a case-series.

Advances in neuroimaging, including diffusion imaging, have been key in the development of contemporary models of language, which propose the existence of dual processing streams supporting language in the human brain (e.g., Hickok & Poeppel, 2004, 2007; Parker et al., 2005; Saur et al., 2008). This dual route system is characterised

as including a dorsal and a ventral route connecting anterior and posterior cortical regions. The specific fasciculi that have been identified as constituting the dorsal and ventral routes will be described below, as well as the roles that have been attributed to the two routes.

A dorsal pathway connecting anterior and posterior language regions has long been argued for, and the specific association fibre bundle traditionally attributed the role of conveying information between Broca's and Wernicke's regions is the arcuate fasciculus (AF) (Anderson et al., 1999; Catani & ffytche, 2005; Catani & Mesulam, 2008; Dejerine, 1895). This white matter pathway connects temporal and inferior frontal cortices (Ciccarelli et al., 2008; Glasser & Rilling, 2008). Originating in the caudal portion of the superior temporal gyrus, the AF arches around the insula, and connects to the posterior part of the ventrolateral frontal lobe (Breier et al., 2008; Catani, Jones, & ffytche, 2005; Frey, Campbell, Pike, & Petrides, 2008; Nieuwenhuys, Voogd, & van Huijzen, 1988; Petrides & Pandya, 1988). As shown in Figure 1.2, tractography work suggests that the AF actually consists of two independent paths, one connecting Broca's and Wernicke's regions directly, which corresponds to the classical description of the AF, and a second indirect path, which runs parallel and lateral to the AF and comprises an anterior segment, connecting Broca's area to the inferior parietal lobe, and a posterior segment, between the inferior parietal lobe and Wernicke's area (Catani et al., 2005).

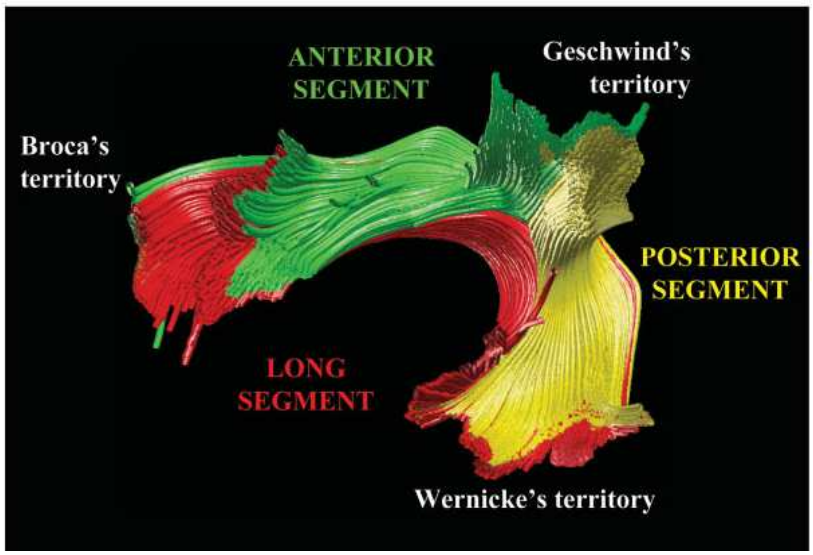

Figure 1.2. A tractography-based reconstruction of the arcuate fasciculus. Taken from Catani et al. (2005) (p.11).

The AF is often considered to be a subdivision of a larger dorsal white matter tract, the superior longitudinal fasciculus (SLF), shown in Figure 1.3. The fibres of the SLF can be traced in a posterior direction from the prefrontal and premotor gyri in the lateral frontal cortex to parietal, occipital, and temporal regions, including Wernicke's area (Catani et al., 2002; Dejerine, 1895; Nieuwenhuys et al., 1988; Parker, 2004; Petrides & Pandya, 1988). Although some studies have treated the AF and the SLF as synonymous (e.g., Bates et al., 2003; Catani et al., 2002; Powell et al., 2006), others cite evidence suggesting that the two represent independent tracts (Makris et al., 2005). Whether the AF and SLF are independent or not does not affect the interpretation of the work presented in this thesis, wherein both tracts are treated as constituents of the dorsal language route.

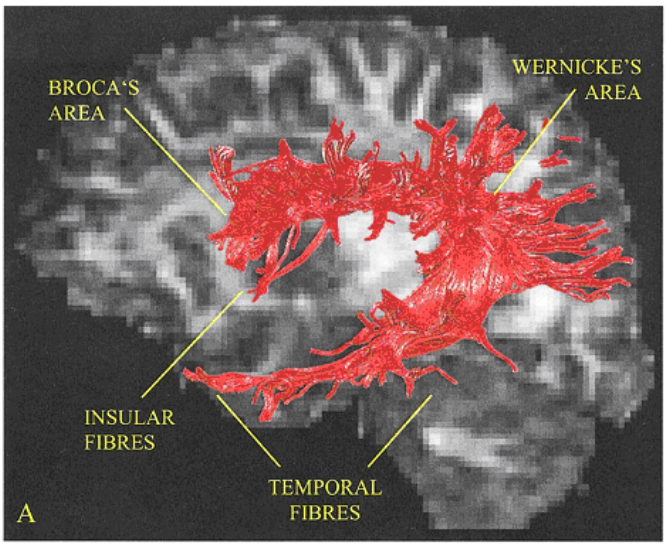

Figure 1.3. The superior longitudinal fasciculus, as depicted by Catani et al. (2002) (p.83).

Traditionally, the AF has been associated with repetition of spoken language, with the repetition deficits seen in conduction aphasia classically being attributed to lesions involving the AF and conduction aphasia being cited as a paradigmatic example of a 'disconnection syndrome' (Catani & ffytche, 2005; Catani & Mesulam, 2008a; Geschwind, 1965a, 1965b), although this view has not gone unchallenged (Anderson et al., 1999; Selnes, van Zijl, Barker, Hillis, & Mori, 2002). Breier et al. (2008) sought to identify relationships between FA levels in regions of interest placed within specific white matter pathways and performance on different components of the WAB (Kertesz, 1982) in individuals with stroke aphasia. They found that increased damage to the AF and SLF, as indexed by decreased FA, related to poorer repetition performance, independent of cortical damage (Breier et al., 2008). VLSM studies have shown that lesions likely to include dorsal language pathways are also associated with reduced fluency (Bates et al., 2003; Borovsky et al., 2007) and with phonological errors in

naming performance (Schwartz et al., 2012)[1]. Intra-operative electrical stimulation of the AF has been shown to result in production of phonological paraphasias in individuals undergoing surgery for glioma removal (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009). Decreased FA and increased mean diffusivity in the AF of both hemispheres has also been associated with poorer naming performance on the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), in a study of 17 individuals with temporal lobe epilepsy and 17 matched controls (McDonald et al., 2008).

Work such as that described above has contributed to the characterisation of the dorsal route as playing a key role in phonological processes, such as those involved in production of spoken language (Hickok & Poeppel, 2004, 2007; Saur et al., 2008; Schwartz et al., 2012). According to Saur et al. (2008), the primary function of the dorsal pathway is the sensory-motor conversion of acoustic to motor representations (see also Weiller, Bormann, Saur, Musso, & Rijntjes, 2011). This notion is supported by the findings of a recent tractography study by Bernal and Altman (2010), which suggested that the AF (and SLF) terminates in premotor/motor regions in the majority of healthy controls. Whilst Duffau (2008) treats the AF as part of the SLF, he argues that the two play different roles within the dorsal language route, with the AF being responsible for phonological processing, and the SLF being involved in speech perception and articulation. The dorsal route has also been implicated in syntactic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Friederici, 2009, 2012; Wilson et al., 2012).

[1] It is worth noting, however, that these VLSM findings are not based on diffusion data, but were obtained using standard structural imaging from stroke aphasic participants, with the likely involvement of white matter pathways inferred from the position of pathways in healthy individuals.

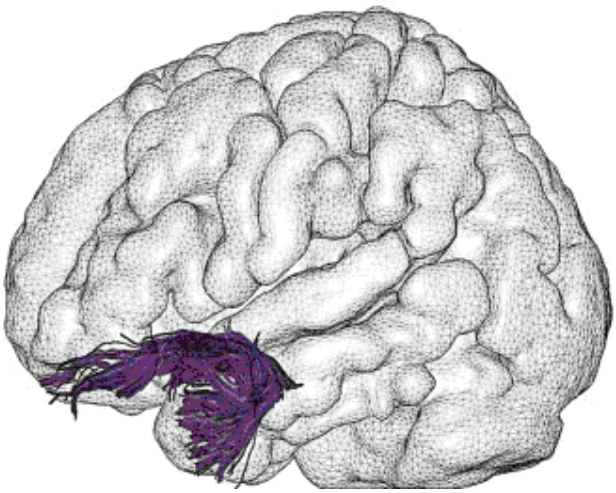

Figure 1.4. The uncinate fasciculus. From Catani and Thiebaut de Schotten (2008) (p.1112).

A ventral route for language may have been conceptualised as long ago as the late 19th Century (Weiller et al., 2011). However, it is only in recent years that evidence for this route has begun to amass (e.g., Frey et al., 2008; Friederici, 2009; Leclercq et al., 2010; Parker et al., 2005; Saur et al., 2008). Several white matter pathways are likely to contribute to the ventral language route, including the uncinate fasciculus (UF), shown in Figure 1.4, which connects the anterior temporal lobe with the ventrolateral prefrontal cortex (Wise, 2003). Recent work has also pointed to the involvement of the inferior fronto-occipital fasciculus (IFOF) in the ventral language route (Duffau et al., 2005, 2009; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). The IFOF, which it has been claimed, may only exist in humans (Catani & Thiebaut de Schotten, 2008; Catani, 2007; Forkel, Thiebaut de Schotten, & Dell'Acqua, 2010), connects the occipital lobe with frontal and temporal cortices (Catani et al., 2002; Forkel et al., 2010; Gloor, 1997; Martino, Brogna, Robles, Vergani, & Duffau, 2010), and can be seen in Figure 1.5. A third ventral association tract that has been implicated in language processing, which runs in close proximity to the UF and IFOF, is the inferior longitudinal fasciculus (ILF) (Catani et al., 2002; Catani & Mesulam, 2008a; Duffau et al., 2009; Frey et al., 2008), which is shown in green in Figure 1.6. Studies have also suggested that the ventral

language route connecting temporal and frontal language areas is likely to go via the extreme capsule, as shown in Figure 1.7 (indeed the ventral route is occasionally referred to as the extreme capsule fibre system) (Frey et al., 2008; Glasser & Rilling, 2008; Parker et al., 2005; Saur et al., 2008).

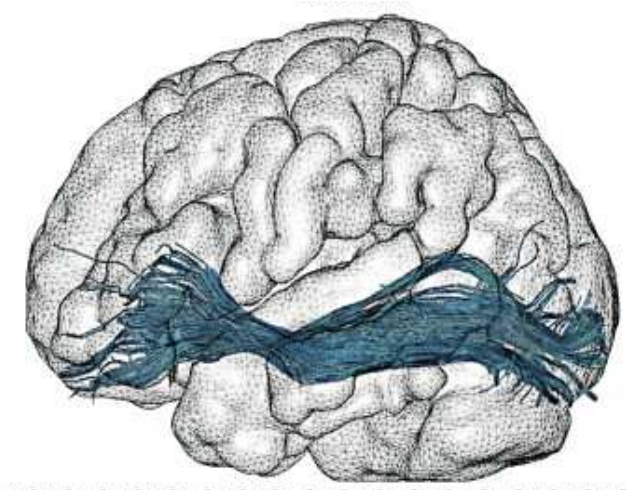

Figure 1.5. The inferior fronto-occipital fasciculus. Taken from Catani and Thiebaut de Schotten (2008) (p.1114).

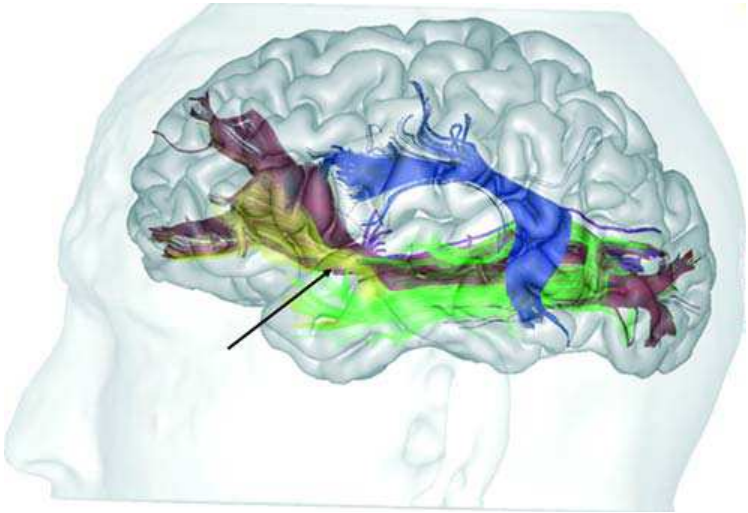

Figure 1.6. The inferior longitudinal fasciculus (green), inferior fronto-occipital fasciculus (purple), uncinate fasciculus (yellow), and arcuate fasciculus (blue). This figure, from Duffau et al. (2009) (p.387), shows tracts potentially involved in the ventral language route (and their relationship to the arcuate fasciculus, part of the dorsal route).

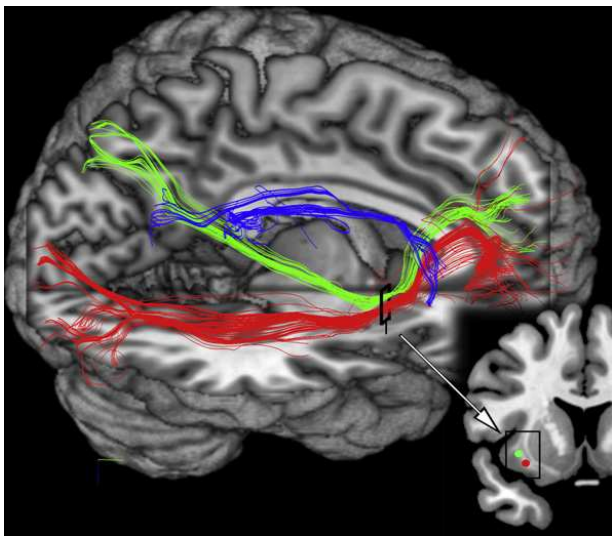

Figure 1.7. Tractography image from Axer, Klingner, and Prescher (2012) (p.11) showing two branches of the inferior fronto-occipital fasciculus (red and green) passing through the extreme capsule (black square). The arcuate fasciculus is also shown (blue).

Neuroimaging evidence suggests that the ventral route plays a crucial role in semantic processing, including language comprehension (i.e., converting inputs such as speech and writing to meaning) (Duffau et al., 2005; Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Duffau et al., 2009; Friederici, 2009; Saur et al., 2008; Wise, 2003). This aligns with neurocognitive models of language processing, such as that proposed by Hickok and Poeppel (2004, 2007), in which the ventral language system allows access to semantic information, whilst the dorsal language system maps directly between speech perception and production. A semantically related role for the ventral route is indicated by the fact that its constituent pathways are connected to the anterior temporal lobe, a region which has frequently been implicated in semantic processing (Crinion, Warburton, Lambon Ralph, Howard, & Wise, 2006; Mummery et al., 1999; Mummery et al., 2000; Pobric, Jefferies, & Lambon Ralph, 2007; Schwartz et al., 2009; Visser, Jefferies, & Lambon Ralph, 2009). Semantic deficits have been demonstrated in individuals with anterior temporal lobe damage associated with various aetiologies including anterior temporal lobectomy for temporal lobe epilepsy (Lu et al., 2002),

herpes simplex virus encephalitis (Kensinger, Siri, Cappa, & Corkin, 2003), and the neurodegenerative condition semantic dementia (Jefferies & Lambon Ralph, 2006).

Turken and Dronkers (2011) used diffusion imaging and resting-state functional imaging data in healthy participants to assess which white matter pathways were associated with regions found previously to relate to language comprehension deficits in a VLSM study of individuals with stroke aphasia (Dronkers et al., 2004). They found evidence of involvement of all of the aforementioned ventral pathways, the ILF, IFOF, and UF, although they noted that the fact that these paths were connected to regions that emerged in their VLSM analysis did not prove that those paths support language comprehension *per se* (Turken & Dronkers, 2011). Duffau and colleagues have repeatedly shown that intra-operative subcortical electrical stimulation of ventral white matter pathways elicits semantic paraphasias in naming (Duffau et al., 2005, 2008, 2009; Leclercq et al., 2010; Mandonnet et al., 2007). Their results have led them to conclude that whilst the ventral route may include multiple tracts, the IFOF constitutes the crucial ventral tract underlying semantic aspects of language (Duffau et al., 2005, 2009; Mandonnet et al., 2007). It should, however, be borne in mind that this conclusion is based on performance on tasks involving visual input (i.e., picture naming) (Duffau et al., 2009).

The emerging picture from the aforementioned work is that of a language network supported by the co-operation of dual pathways, a dorsal route concerned with phonological processing and a ventral route subsuming semantic processing (Saur et al., 2008; Ueno, Saito, Rogers, & Lambon Ralph, 2011). Whilst the dorsal and ventral routes have been attributed distinct language functions, it is worth bearing in mind that the two routes are unlikely to be entirely independent, with intact language processing likely depending upon parallel processing in, and interaction between, the two routes (Cloutman, 2012; Ueno et al., 2011; Weiller et al., 2011; Wise, 2003). A very recent

study has looked at the relationship between damage to the dorsal and ventral route and language deficits in acute stroke aphasia. Kümmerer et al. (2013) assessed voxel-level relationships between performance on comprehension and repetition subtests of the Aachen Aphasia Test (Huber et al., 1984) and lesion location on structural MR images. They then overlaid 'lesion maps' for comprehension and repetition on dorsal and ventral pathway templates derived from healthy individuals in a previous study (Saur et al., 2008). Proportion of overlap with the pathways was then calculated for the comprehension and repetition lesion maps. The authors found that repetition deficits were associated with damage in regions that primarily overlapped with the dorsal language route, whilst comprehension deficits related to damage encompassing the ventral language route (Kümmerer et al., 2013). Two questions arising from this work are, firstly, does this relationship between dorsal and ventral route damage and specific language deficits hold in chronic stroke aphasia? Secondly, does it hold when language measures are related to white matter measures derived directly from stroke aphasic participants?

Evidence from a recent study using FA as a measure of tract integrity suggests that similar relationships are seen in chronic stroke aphasia with measures of white matter integrity from these same participants. A study involving a case-series of 24 individuals with chronic stroke aphasia found that FA levels in the dorsal route related to phonological performance, whilst semantic performance related to FA within the ventral route (Rolheiser, Stamatakis, & Tyler, 2011). In **Chapter 6** the PCA-derived behavioural measures previously mentioned are related to whole-brain FA maps and ACM, in order to systematically investigate how variations in different abilities in chronic stroke aphasia relate to variations in both local (FA) and, more importantly, global (ACM) connectivity within the dorsal and ventral routes, and beyond.

Using a brain-wide measure such as ACM, which can reflect abnormalities in connectivity to a voxel arising from changes distal from that voxel, meant that changes remote from the lesion could also be taken into account when assessing brain-behaviour relationships. This could include long-range decreases in connectivity, arising from processes such as Wallerian degeneration, or potentially adaptive increases in connectivity reflecting neural plasticity. A study examining the influence of melodic intonation therapy, an intensive speech therapy, on speech production and underlying structural connectivity in six chronic stroke aphasic individuals claimed to identify increases in right hemisphere AF tract volume and number of tracts post-therapy using probabilistic tractography (Schlaug, Marchina, & Norton, 2009). The authors argued that improved spoken language performance shown by their participants was related to the structural changes in the right hemisphere AF. In the present work, potentially adaptive changes in connectivity are identified in the analyses considered in **Chapters 4** and **6**.

Research Aims

By combining detailed behavioural and neuroimaging data from a group of individuals with chronic stroke aphasia in novel ways, the work presented in this thesis aims to aid better understanding of patterns of intact and spared performance in stroke aphasia. The first specific aim of this thesis was to investigate whether connectivity data could help better understand lesion-symptom relations, by employing ACM in a small number of case examples of individuals with chronic stroke aphasia (**Chapter 3**). Following on from that work, the question of whether ACM could provide some useful information at a group level was explored. Differences in connectivity between a group of individuals with stroke aphasia and a group of controls were firstly explored, followed by an examination of differences in connectivity between controls and groups of

participants with different aphasia subtypes. This was achieved by conducting VBM analyses on ACM data from stroke aphasic and control participants (**Chapter 4**).

As outlined previously, aphasic categories, such as those derived from classification systems like the BDAE are limited in terms of their ability to describe participants' abilities and to localise language performance to underlying lesion locations. This work aimed to define more robust, continuous measures of behavioural performance to more accurately describe aphasic participants' language abilities, and to use to relate to imaging data. To this end, PCA was used to define continuous behavioural measures, which were then used to plot participants' position in 'aphasic space' and to correlate with their lesion location using VBCM (**Chapter 5**). Finally, bringing together the work from previous chapters, the optimised behavioural measures were used to relate participants' language abilities to the integrity of their white matter pathways. By correlating the PCA-derived behavioural measures with T1-weighted, FA, and ACM measures using VBCM, this work aimed to assess how abnormalities in the dorsal and ventral language routes related to variations in behavioural performance in chronic stroke aphasia (**Chapter 6**).

Acknowledgement of Contribution of Other Authors

Dr Anna Woollams, Professor Matt Lambon Ralph, and Professor Geoff Parker supervised the work documented in this thesis and assisted in producing the final version of each chapter of the thesis. Dr Karl Embleton is a Research Associate within the School of Psychological Sciences and was the project advisor. Dr Embleton provided helpful guidance on many aspects of imaging acquisition and analysis, particularly the diffusion imaging documented in Chapters 3, 4, and 6. I conducted all recruitment, scanning, and behavioural testing of participants for the work presented in this thesis. I also analysed all of the neuroimaging and behavioural data presented. For all chapters of the thesis, I

produced initial drafts which were then developed further with guidance from my supervisors to produce the final versions.

CHAPTER 2

KEY METHODOLOGICAL CONSIDERATIONS RELEVANT TO THE THESIS

The purpose of this chapter is to provide an overview of some key methodological issues that have been taken into consideration in the course of this project, and how they have motivated decisions to employ specific approaches to data collection and analyses. The specific acquisition sequences employed will first be described.

MRI Acquisition Sequences

All scans were acquired on a 3 tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil.

T1-Weighted Sequence

The sequence employed to obtain high resolution structural images was a T1-weighted inversion recovery sequence with 3D acquisition, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1 mm, acquired voxel size 1.0 mm x 1.0 mm x 1.0 mm, matrix size 256 x 256, FOV = 256 mm x 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5. This is a widely used sequence which allows acquisition of images that are of high enough resolution to produce voxel sizes that allow examination of detailed brain features. This provided detailed structural scans for relation to behavioural data, using voxel-wise techniques.

Diffusion-Weighted Sequence

Diffusion-weighted images were acquired using a pulsed gradient spin echo echo-planar imaging sequence implemented with TE = 54 ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed resolution 1.875 mm x 1.875 mm, slice thickness 2.1 mm, 60 contiguous

slices, 43 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8 ms, δ = 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5.

For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity *k*-space traversal, and hence reversed phase and frequency encode direction, allowing correction for geometric distortion (Embleton, Haroon, Morris, Lambon Ralph, & Parker, 2010). A co-localised T2-weighted turbo spin echo scan with 0.94 mm x 0.94 mm in-plane resolution and 2.1 mm slice thickness was also obtained for use as a structural reference scan in distortion correction (Embleton et al., 2010). Reasons for using a distortion correction technique are detailed later in this chapter.

A key decision in selection of the diffusion-weighted sequence was the number of non-collinear gradient directions to acquire data from. Whilst data only need to be acquired from six non-collinear directions to characterise a diffusion tensor (Basser et al., 1994; Conturo et al., 1999), it has been argued that using larger numbers of gradient directions may be beneficial (Jones, 2004). So, although in clinical settings diffusion data are usually acquired using the minimum number of directions necessary, research studies frequently acquire data from many more than directions than six, particularly when tractography analyses are to be carried out. However, scan duration increases as data are acquired from more directions, meaning that there is a trade-off between number of directions data are acquired from and reasonable scan times. A 43-direction sequence was deemed appropriate for use in this work, allowing acquisition of high quality diffusion data for subsequent tractography-based analyses, within a scan time that was tolerable for a clinical population.

Acquisition time for the diffusion MRI data was approximately 28 minutes, although this varied slightly based on the participant's heart rate due to the fact that

cardiac gating was employed. Cardiac gating was incorporated in the diffusion sequence in order to ameliorate artefacts arising from pulsatile brain movements that can affect tractography results (Jones & Pierpaoli, 2005).

Spatial Normalisation

In order to compare images from different participants using any statistical technique, the images need first to be aligned in a common stereotactic space (Ashburner & Friston, 2000; Brett, Leff, Rorden, & Ashburner, 2001; Rorden & Karnath, 2004). As brain morphometry of individuals varies in terms of size, overall shape, ventricular size, and patterns of gyri and sulci, spatial normalisation algorithms need to be applied to each image, to produce data which are comparable in shape, size and orientation (Lee et al., 2006; Rademacher, Caviness, Steinmetz, & Galaburda, 1993; Rorden & Karnath, 2004). The presence of focal lesions, such as those often seen in stroke, tends to interfere with automated normalisation algorithms (Brett et al., 2001; Crinion et al., 2007; Lee et al., 2006; Mori et al., 2008; Rorden & Karnath, 2004; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). When one attempts to subject an image of a lesioned brain to a standard spatial normalisation procedure, the normalisation algorithm attempts to minimise mismatch between a template image and the participant's image, across the entire brain, including the lesion site. This can result in significant distortion of the image (Brett et al., 2001; Crinion et al., 2007).

One way of dealing with this issue is to use 'cost-function masking' to exclude the lesioned area from the normalisation process (Andersen, Rapcsak, & Beeson, 2010; Brett et al., 2001). However, cost-function masking is time-consuming, operator-dependent, and can result in distortion outside the lesioned area (Crinion et al., 2007; Ripollés et al., 2012). Furthermore, unified segmentation-normalisation methods, such as those implemented in SPM5 onwards (Ashburner & Friston, 2005), have previously been

shown to be superior to normalisation with cost-function masking in individuals with stroke lesions (Crinion et al., 2007; cf Andersen et al., 2010). Seghier et al. (2008) have developed a modified version of unified segmentation-normalisation, specifically for use in lesioned brains. Seghier et al.'s (2008) method incorporates an extra tissue class that unexpected or abnormal voxels from within the lesion can be assigned to during the segmentation process. As well as addressing segmentation issues, the additional tissue class can optimise normalisation by acting as an 'implicit' mask (Andersen et al., 2010).

The work presented in this thesis uses the unified segmentation-normalisation method of Seghier et al. (2008) for pre-processing of all images. The method has previously been used effectively in studies involving individuals with stroke lesions (e.g., Leff et al., 2009; Price et al., 2010). A recent study that evaluated the validity of different automated procedures for normalisation of lesioned brains showed that different methods performed best depending on which outcome measure was used to evaluate effectiveness (Ripollés et al., 2012). Overall Seghier et al.'s (2008) method compared favourably to other methods, particularly on measures reflecting lesion volume changes and distortion around lesions (Ripollés et al., 2012). It is worth bearing in mind that any differences between methods are likely to be small in comparison to the size of smoothing kernels applied to data (Crinion et al., 2007; Meinzer et al., 2013). When employed in preliminary analyses of the current work, the results obtained using Seghier et al.'s (2008) method were visually inspected by a number of experienced researchers and deemed to be good, and all subsequent analyses were inspected for possible issues such as lesion shrinkage, and results were always deemed to be acceptable.

Diffusion data such as ACM and FA maps were generated in native diffusion space. In order to subject these images to group-level analyses, they too needed to be normalised. Seghier et al.'s (2008) method was also used for normalisation of diffusion data. Before normalising the diffusion data, careful checks were made to ensure that

participants' T1-weighted images and their diffusion images were accurately co-registered. By using the same normalisation procedure across imaging types (T1-weighted, FA, and ACM), a level of consistency was achieved allowing more valid comparison across imaging types (which was particularly relevant in Chapter 6).

Lesion Identification

Accurate lesion identification was key to the generation of lesion overlap maps in the current work, and for deriving the lesion outlines used in Chapters 3 and 5 (Crinion, Holland, Copland, Thompson, & Hillis, 2013). Seghier et al.'s (2008) aforementioned method was used for automated lesion identification as well as normalisation. In Seghier et al.'s (2008) method a participant's lesion is defined using the modified unified segmentation-normalisation and a 'fuzzy clustering' procedure, which identifies outlier voxels that are then grouped together. This automated method was employed as it represented a more replicable, less operator-dependent, and less time-consuming approach than manual lesion identification (Fiez, Damasio, & Grabowski, 2000; Seghier et al., 2008; Wilke, de Haan, Juenger, & Karnath, 2011). Furthermore, automated approaches have been shown to be able to identify potentially indirect lesion effects, which may play a role in lesion-symptom relations and could potentially be overlooked with manual lesion identification (Wilke et al., 2011). Optimum specifications for Seghier et al.'s (2008) toolbox with data from the current project were explored, with different parameters being tested and the outcome assessed. The most accurate lesion outlines were obtained by using the toolbox's default settings, with the exception of the *U*-threshold, which was set to 0.5. The automated lesion identification procedure was employed with these settings throughout this thesis.

Lesion-Symptom Mapping

In Chapter 4 traditional VBM is used to identify differences in ACM between controls and stroke aphasic participants, and between controls and participants with different subtypes of stroke aphasia. Whilst traditional VBM is a useful method for identifying statistical relationships between brain and behaviour, particularly in a relatively novel measure such as ACM, more sophisticated methods such as incorporating continuous behavioural data into the model, have been developed. As noted in Chapter 1, such methods include VLSM (Bates et al., 2003) and VBCM (Tyler et al., 2005a). The VBCM method (Tyler et al., 2005a) was used to relate participants' behavioural performance to their lesion locations in Chapters 5 and 6. VBCM is similar to VLSM but enables a more fine-grained analysis of lesions by correlating continuous behavioural measures to continuous intensity values, rather than binary values, in every brain voxel. The VBCM approach has recently been employed in a study relating stroke aphasic individuals' scores on language assessments to FA maps (Rolheiser et al., 2011). It has also been used in studies of comprehension and production in stroke aphasia (Geva et al., 2012; Leff et al., 2009) and of object recognition and inflectional morphology in individuals with brain damage resulting from aetiologies such as stroke, herpes simplex virus encephalitis, and aneurysm (Taylor, Stamatakis, & Tyler, 2009; Tyler, Marslen-Wilson, & Stamatakis, 2005b).

Whilst VBCM and VLSM are both able to capture the fact that behavioural deficits may be graded in extent, VBCM is also able to capture potential gradations in brain damage. Using continuous behavioural and brain measures offers increased sensitivity and statistical power in lesion analyses (Tyler et al., 2005a), although the binary brain measures used in VLSM may have increased sensitivity when relationships between lesions and behaviour are non-linear (Geva et al., 2012). Whilst the focal lesions in stroke aphasia may mean that most brain voxels are either lesioned or non-lesioned, as

captured by the VLSM model, there may be some more subtle gradations in perilesional areas. Functioning of perilesional tissue has been shown to play an important role in naming performance and in treatment-induced language improvements in stroke aphasia (e.g., Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Meinzer & Breitenstein, 2008; Meinzer et al., 2008). VBCM was therefore deemed an appropriate technique for relating participants' continuous performance measures to their imaging data.

Processing of Diffusion-Weighted Data

Diffusion-weighted data were submitted to a number of processing steps in order to generate FA maps and ACMs. Firstly, all diffusion data were distortion-corrected using the procedure described by Embleton et al. (2010) (see below for further details). FA maps were then produced by fitting a single diffusion tensor to each voxel in the distortion-corrected diffusion-weighted data. The values in each voxel of the FA map vary from zero to one and represent the magnitude of anisotropy within each voxel. In brain regions where diffusion is equal in all directions, such as cerebrospinal fluid, FA values will be closer to zero. In areas where diffusion is more anisotropic, i.e., it occurs preferentially in one direction, such as within white matter fibres (particularly those which are parallel to one another), FA values will be higher (Basser & Pierpoali, 1996).

ACMs were generated by submitting the distortion-corrected diffusion-weighted data to the model-based bootstrap of constrained spherical deconvolution (Haroon, Morris, Embleton, &, Parker, 2009) (see below for further details). This process produced probability density functions, which provide estimates of fibre orientation(s) within voxels, as well as quantifying the uncertainty within those estimates (Haroon et al., 2009). These PDFs served as the input for the probabilistic index of connectivity (PICo) tractography algorithm (Parker, Haroon, & Wheeler-Kingshott, 2003), which was used to generate ACMs. ACMs were produced by launching ten probabilistic

tractography streamlines from every voxel in the brain. As such, the seed region given to the PICo algorithm from which to launch streamlines, consisted of a binary mask of the entire brain. Having launched ten probabilistic streamlines from every brain voxel, the number of streamlines passing through each voxel was then recorded. The values in the ACM therefore represent the relative connectivity of each brain voxel to every other brain voxel, with higher values representing a greater number of probabilistic streamlines passing through a voxel.

Distortion Correction

A major disadvantage of commonly used diffusion-weighted acquisition sequences is that they can result in significant geometric distortion in the phase encode direction in regions close to air-tissue boundaries (Embleton et al., 2010; Jezzard & Balaban, 1995). Such distortions are typically more severe at 3 tesla than 1.5 tesla, as they are proportional to the strength of the magnetic field employed (Alexander, Lee, Lazar, & Field, 2007; Mori et al., 2008). Regions susceptible to such distortion include, for example, anterior areas of the temporal lobes and inferior areas of the frontal lobes, in which distortion can give rise to erroneous and faulty tractography. For reliable tractography results to be obtained this distortion needs to be corrected (Alexander et al., 2007; Embleton et al., 2010). In this thesis work diffusion-weighted acquisition sequences were employed that allowed application of a distortion correction procedure described by Embleton et al. (2010). Embleton et al.'s (2010) method also reduces the effects of eddy currents, another source of distortion that can affect diffusion imaging results.

A General Introduction to Tractography

A brief introduction to tractography will now be provided, before further discussion of issues relating specifically to the processing of diffusion data in the correct work. Tractography is a diffusion-based method which yields information regarding the trajectories of white matter tracts, which is then used to algorithmically reconstruct continuous three-dimensional (3D) tracts (Catani & Mesulam, 2008a; Clayden, Storkey, & Bastin, 2007; Jones, 2008). Tracts are reconstructed by firstly selecting initial 'seed points' from which to begin tracking. The orientation of the diffusion tensor is estimated and the tracking algorithm then moves in the direction of least hindrance to diffusion (i.e., greatest diffusivity) into the next voxel. This process is then repeated with the algorithm moving along a continuous path, generated by piecing together voxel-by-voxel tensor orientation estimates (Catani et al., 2002; Conturo et al., 1999; Jones, 2008; Mori, Crain, Chacko, & van Zijl, 1999; Parker et al., 2002; Parker, Haroon, & Wheeler-Kingshott, 2003; Poupon et al., 2000). The crucial assumption underlying tractography is that the principal direction of diffusion is equivalent to the orientation of the WM tracts in a voxel (Ciccarelli et al., 2003, 2008; LeBihan et al., 2001). Two threshold values are commonly applied to constrain the tractography process, an FA threshold and an angular threshold. The tractography algorithm will continue until it reaches a region where anisotropy falls below a given FA threshold (Catani et al., 2002; Ciccarelli et al., 2008; Jones, 2008). Thresholds are often selected which differentiate grey and white matter, although the FA threshold is not employed with all tractography algorithms (Jones, 2008). The second constraining parameter, the angular threshold, specifies the maximum angle a tract can turn between two voxels. This parameter aims to eliminate generation of implausible pathways, although there is no general agreement as to what the angular threshold should be (Ciccarelli et al., 2008; Jones, 2008).

Several different types of tractography algorithms have been developed, all of which can be described as either deterministic or probabilistic (e.g., Batchelor et al., 2001; Conturo et al., 1999; 2008; Mori et al., 1999; Parker et al., 2002; Parker et al., 2003; Poupon et al., 2000). Each of these methods has its own advantages and disadvantages (Jones, 2008), for example deterministic tractography has been argued to be relatively simple and provide easily interpretable results (Bassett et al., 2011) but is limited by the fact that it cannot represent branching fasciuli and it provides no information regarding the confidence that can be associated with a reconstructed pathway, unlike probabilistic tractography (Jones, 2008). There is currently no objective way to compare the success of different algorithms at tracking white matter in the human brain, and consequently there is no agreement as to which method yields optimum results (Ciccarelli et al., 2008; Hubbard & Parker, 2009).

False positives, i.e., reconstruction of non-existent tracts, and false negatives, i.e., failing to identify existing tracts, may occur in tractography results. Issues such as potential presence of multiply oriented fibre orientations within a voxel (as discussed below) and the fact that results depend upon implementation of thresholds, such as those for terminating tracking, on which there is no consensus regarding optimum values, can contribute to the occurrence of false positives and negatives. Careful analysis of such results is therefore required, taking into account established neuroanatomical knowledge, to evaluate the validity of tractography findings (Ciccarelli et al., 2003; Parker et al., 2002).

A particular issue for tractography techniques is the role of distance effects. There is uncertainty, which is non-uniform throughout the brain, associated with orientation estimates conducted for each voxel (Jones, 2003, 2008). This uncertainty accumulates with increasing distance from the seed region, meaning that the frequency with which voxels are visited by streamlines propagated in a probabilistic tractography algorithm

decreases with increasing distance from the seed region (Jones, 2008; Morris et al., 2008). For this reason, frequency of connection is generally higher for regions closer to the seed region than for more remote regions, meaning that it is hard to define a threshold of connection probability that indicates presence or absence of a tract (Morris et al., 2008).

Crossing Fibres

The resolution of diffusion-weighted imaging is at the level of voxels, which are far greater in size than the diameter of individual axons. This means that only bundles rather than individual axons can be visualised (Ciccarelli et al., 2008; Lee et al., 2006). The tensor model that is commonly used to generate diffusion metrics such as FA and to provide orientation data to tractography, estimates the orientation of diffusion tensors based on averages across these axon bundles. This does not pose a problem if the axons have the same orientation, i.e., they are organised in parallel. However, in many brain regions this is not the case and in such regions, where fibres may cross, touch, merge, or diverge, tractography algorithms tend to perform poorly (Catani et al., 2002; Ciccarelli et al., 2008; Johansen-Berg & Behrens, 2006; Jones, 2008; Pierpaoli et al., 2001; Schmahmann & Pandya, 2008).

More detailed orientation data, which afford improved tractography results in regions of multiple, differentially oriented fibre tracts, can be obtained using more sophisticated models than the tensor model (Basser, 2002; Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Catani et al., 2002; Parker & Alexander, 2005; Tournier et al., 2008; Tournier, Calamante, & Connelly, 2007; Tournier, Calamante, Gadian, & Connelly, 2004; Tuch, 2004; Tuch et al., 2002; Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005). Although these methods are more computationally demanding and require longer processing times (Ciccarelli et al., 2008), all diffusion data in the current

thesis were processed using such a technique. The method employed was the model-based bootstrap of constrained spherical deconvolution (Haroon et al., 2009), a method based on the constrained spherical deconvolution (CSD) technique devised by Tournier et al. (2007, 2008). The CSD method has been shown to be able to resolve fibre populations that are separated by smaller angles than that achievable with other methods such as *q*-ball imaging (Tuch, 2004) and to improve estimates of fibre orientations present in each voxel (Haroon et al., 2009; Tournier et al., 2007, 2008).

Anatomical Connectivity Mapping

As noted in Chapter 1, this work employed ACM (Embleton et al., 2007) to investigate abnormalities in white matter tracts across the entire brain in individuals with stroke aphasia. Unlike standard tractography, in which streamlines are launched from a particular seed region defined by the researcher, in ACM multiple probabilistic streamlines are launched from every voxel in the brain. The output in ACM is a whole-brain connectivity map, in which each voxel value reflects the number of streamlines that have passed through that voxel. In this way ACM values reflect how connected that voxel is to every other grey and white matter voxel throughout the brain (Embleton et al., 2007). Whilst the ACM value within a voxel reflects its relative level of connectivity, it does not reflect the spatial distribution of the tracts from which that connectivity is received (Bozzali et al., 2011). Thus, whilst ACM benefits from the ability to demonstrate changes in connectivity that can arise due to distant changes in brain structure, it is limited by the fact that it cannot directly indicate the source of such connectivity changes.

Figure 2.1 shows an example ACM from a healthy older control participant and Figure 2.2 shows an example of an ACM from a stroke aphasic participant. ACM was employed in this work because it offers brain-wide connectivity information, with voxel

values able to reflect abnormalities in connectivity that may arise due to local structural brain changes or to changes remote from the voxel. This information was deemed to be potentially illuminating in the study of aphasia, where language deficits could arise as a result not only of damage to cortical areas and proximal white matter pathways important to language, but also as a result of reduced connectivity to such areas caused by damage elsewhere in the brain.

Further, because ACM values are computed for every voxel in the brain, *a priori* regions of interest (ROIs) to seed tractography from did not need to be defined. If specific ROIs had been identified, it is probable that at least some participants would have had lesions to the intended seed point, meaning that tractography could not be seeded from the specified region for all participants. Furthermore, seeding tractography from the whole-brain rather than a smaller ROI meant that abnormalities that arose anywhere throughout the brain would be identified, including abnormalities in connectivity to areas as remote as the contralesional hemisphere, which could reflect either decreased or in fact increased connectivity. In the ensuing chapters ACM results are compared to those from analysis of FA maps. FA was chosen as a comparison metric because it is a widely used measure, which provides local information regarding white matter integrity to compare to the more global connectivity information gained in ACM. Whilst T1-weighted measures can reflect changes in concentration in grey and white matter, FA offers increased sensitivity to variations in white matter microstructure compared to T1-weighted imaging (Klingberg et al., 2000; Stamatakis, Shafto, Williams, Tam, & Tyler, 2011). FA is particularly suited to investigations of white matter properties because white matter is more anisotropic than grey matter or cerebrospinal fluid (Basser & Pierpaoli, 1996).

When used in concert with FA maps, ACM can reveal brain regions where white matter pathways may appear to be undamaged but connectivity has been affected due to

damage elsewhere. Conversely, ACM can also confirm that structural connectivity through a particular pathway has been retained. However, as noted previously, ACM values do not convey any information regarding which brain regions connectivity has been derived from. As such, information obtained from an individual's ACM should be interpreted within the context of their FA map (and/or T1-weighted scan). In this way, an FA map can be used to identify regions of damage to cortical pathways, whilst ACM can provide additional information regarding the state of connectivity within such pathways. More detail regarding how the information obtained from ACM is complementary to that in FA is given in subsequent chapters.

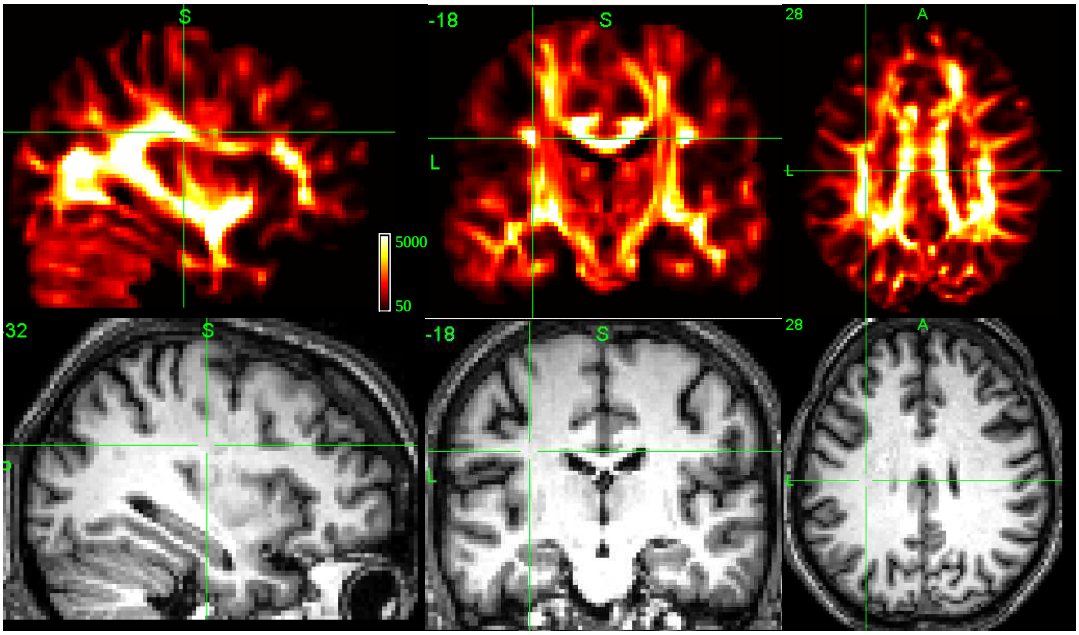

Figure 2.1. Example of a control participant's normalised Anatomical Connectivity Map (top row) and T1-weighted scan (bottom row).

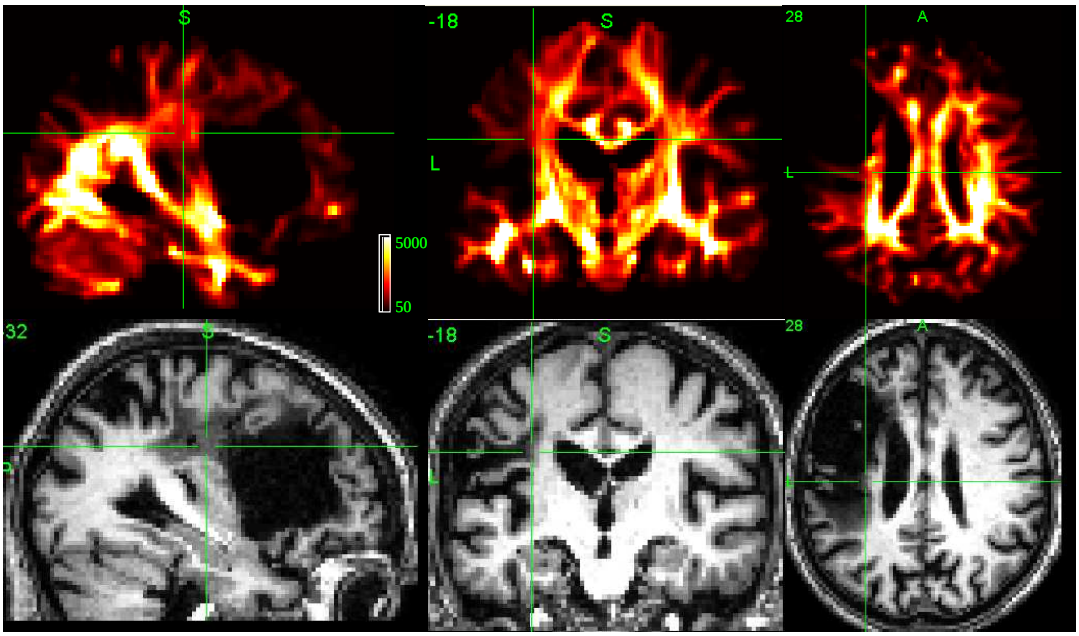

Figure 2.2. Example of a stroke aphasic participant's normalised Anatomical Connectivity Map (top row) and T1-weighted scan (bottom row).

In summary, this work employed a normalisation procedure designed for use in lesioned brains (Seghier et al., 2008), a distortion correction technique that affords improved visualisation of brain regions such as inferior anterior temporal regions (Embleton et al., 2010), a bootstrapped CSD method that enables resolution of multiple intra-voxel fibre populations in diffusion data (Haroon et al., 2009), and a whole-brain probabilistic tractography method (ACM) (Embleton et al., 2007). Combining neuroimaging data acquired and processed using these approaches with detailed, continuous behavioural data in chronic stroke aphasia renders this a novel and innovative piece of research.

CHAPTER 3

IMAGING DISCONNECTION: IMPROVING LESION-SYMPTOM MAPPING IN CHRONIC STROKE APHASIA USING ANATOMICAL CONNECTIVITY MAPPING

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Abstract

Objective: This study aimed to investigate whether a recently developed measure reflecting structural connectivity of brain white matter could help to explain variations in aphasic symptoms in individuals with chronic stroke aphasia. **Method:** Performance on a battery of language assessments was related to magnetic resonance imaging data including data from a diffusion-weighted imaging technique called Anatomical Connectivity Mapping (ACM). Participants with a variety of left hemisphere lesions were considered: two with similar anterior lesions, two with similar posterior lesions, and one with a more ventral lesion. **Results:** Differences between participants on language assessments were more understandable when information in their ACM was taken into account. In both the anterior and posterior cases, severity of language impairment appeared to relate to extent of disruption to connectivity in the dorsal language route. The fifth participant, whose language deficits were more semantic in nature, appeared to relate to disruption in ventral route connectivity. **Interpretation:** This work illustrates that information regarding white matter connectivity can help to improve the accuracy of lesion-symptom mappings in individuals with chronic stroke aphasia. Phonological deficits related more to dorsal route connectivity abnormalities, whilst semantic deficits related more to ventral route connectivity abnormalities, in line with contemporary models of language processing. ACM represents a useful, whole-brain tool for evaluating disruptions in connectivity in chronic stroke aphasia.

Introduction

Lesion-symptom mapping studies have played a key role in the advancement of knowledge regarding brain-language relationships. Important insights achieved using such an approach include seminal findings by Carl Wernicke and Paul Broca (Blunk et al., 1981; Broca, 1861; Eggert, 1977; Hillis, 2007; Naeser & Hayward, 1978) and the lesion-symptom mapping approach continues to be widely employed in the study of stroke aphasia today (Bates et al., 2003; Dronkers & Ogar, 2004; Geva et al., 2012; Leff et al., 2009; Rorden & Karnath, 2004; Schwartz et al., 2011; Tyler et al., 2005a). However, classical associations founded on lesion-symptom mapping, between posterior lesions and comprehension deficits and anterior lesions and production deficits, have been challenged by cases of aphasic individuals who do not show the expected concordance between lesions and deficits (Basso et al., 1985; Vignolo et al., 1986; Willmes & Poeck, 1993). In addition, individuals with seemingly similar cortical lesions can demonstrate different behavioural profiles, and conversely, individuals with similar performance on behavioural tasks can have lesions that do not appear to encompass common cortical regions (Caplan, Hildebrandt, & Makris, 1996; Wilson & Saygin, 2004). One potential contributor to shortcomings in lesion-symptom mapping is a failure to appreciate the impact of damage to white matter pathways on the functioning of large-scale neural networks subserving language processing (Blank, Scott, Murphy, Warburton, & Wise, 2002; Catani & ffytche, 2005; Catani & Mesulam, 2008; Mesulam, 1990; Parker et al., 2005; Warburton et al., 1999). The current work aimed to evaluate whether taking white matter connectivity information into account could help improve lesion-symptom mapping in individuals with chronic stroke aphasia.

The emerging picture from recent neuroimaging work is that language function relies upon at least two white matter pathways connecting temporal and inferior frontal cortices, a dorsal route via the arcuate fasciculus (AF) (Ciccarelli et al., 2008; Glasser &

Rilling, 2008; Rilling et al., 2008) and a more ventral route (e.g., Parker et al., 2005; Saur et al., 2008). Evidence for the existence of a ventral language route has emerged primarily from tractography (e.g., Anwander, Tittgemeyer, Von Cramon, Friederici, & Knösche, 2007; Duffau, 2008; Frey, Campbell, Pike, & Petrides, 2008; Parker et al., 2005; Saur et al., 2008), and intra-operative electro-stimulation studies (e.g., Diehl et al., 2010; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Duffau, 2008; Leclercq et al., 2010). Various candidate fasciculi have been suggested as constituting the ventral language route, including the uncinate fasciculus (UF) (McDonald et al., 2008; Wise, 2003), inferior fronto-occipital fasciculus (IFOF) (Duffau et al., 2005, 2009; Mandonnet et al., 2007), and inferior longitudinal fasciculus (ILF) (Catani & Mesulam, 2008a; Mummery et al., 1999), although these need not be mutually exclusive (Duffau et al., 2009) and most accounts agree that the ventral route passes through the region of the extreme capsule (EmC) (Frey et al., 2008; Glasser & Rilling, 2008; Parker et al., 2005).

In terms of roles of the two language routes, evidence suggests that the dorsal route is involved in phonological processing, providing a direct bi-directional route between speech perception and production (Bernal & Altman, 2010; Hickok & Poeppel, 2004, 2007; Leclercq et al., 2010; Saur et al., 2008; Weiller et al., 2011). The dorsal route has also been implicated in syntactic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Friederici, 2009). The ventral route, meanwhile, has been associated with semantic processing, providing a bi-directional route between perception and production that is mediated by meaning (Friederici, 2009; Hickok & Poeppel, 2004, 2007; Leclercq et al., 2010; Saur et al., 2008). Despite evidence for a degree of specialisation, both routes are likely to work in parallel to achieve most language tasks in healthy individuals (Cloutman, 2012; Ueno et al., 2011; Weiller et al., 2011; Wise, 2003).

Dorsal and ventral white matter pathways appear, therefore, to be involved in language processing in healthy individuals. But what are the implications of damage to the dual route system? Can recent findings regarding the intact language system help us to better understand the impairments shown by individuals with stroke aphasia? Given that white matter pathways play an important part in normal language function, taking into account the effect of stroke on white matter pathways important to language processing may help to better explain individuals' performance on language tasks and, consequently, some of the previously outlined exceptions in expected lesion-symptom mappings. Whilst the repetition deficits characteristic of conduction aphasia have long been associated with AF damage (Breier et al., 2008; Catani & ffytche, 2005; Catani & Mesulam, 2008; Geschwind, 1965a, 1965b; Schlaug, Marchina, & Norton, 2009; cf. Anderson et al., 1999; Selnes, van Zijl, Barker, Hillis, & Mori, 2002), it is only very recently that work has looked at the relationship between damage to other white matter pathways and aphasic symptoms. A recent study of a large cohort with acute stroke aphasia found that repetition deficits were associated with damage in regions likely to overlap with the dorsal language route, whilst comprehension deficits related to damage encompassing the ventral language route (Kümmerer et al., 2013). This study employed a method wherein behavioural performance was related to lesion location in a voxel-level analysis. Resulting lesion maps were then overlaid on templates of white matter pathways from healthy individuals, in order to infer which pathways may have been impacted upon by stroke damage. A similar approach was employed in a sample of chronic stroke aphasics in which phonological errors in naming were found to relate to integrity of the dorsal language route (Schwartz et al., 2012).

A study of chronic stroke aphasics in which behavioural performance was related directly to white matter measures obtained from participants (rather than indirectly inferred by reference to white matter effects predicted on the basis of the lesion on

standard imaging), was conducted by Rolheiser, Stamatakis, and Tyler (2011). Their study looked at the relationship between fractional anisotropy (FA), a diffusion imaging metric that is sensitive to alterations in local white matter microstructure, and performance on different behavioural assessments. Phonological task performance was found to relate to dorsal route FA, whilst semantic performance related to ventral route FA (Rolheiser et al., 2011). Together these findings accord with the notion of the dorsal route underpinning phonological performance and the ventral route subserving semantic performance (e.g., Hickok & Poeppel, 2004, 2007; Saur et al., 2008; Weiller et al., 2011). A similar relationship has also been observed in the context of primary progressive aphasia, a focal form of neurodegenerative dementia marked by deterioration in language function (Acosta-Cabronero et al., 2011; Agosta et al., 2010; Galantucci et al., 2011).

Advances in research into the structure and function of, and effects of pathology on, white matter have been enabled by developments in diffusion-weighted imaging over the past two decades. Imaging of white matter has evolved from the original diffusion tensor model (Basser, Mattiello, & LeBihan, 1994) to more complex models of the diffusion process, based on techniques such as *q*-ball imaging (e.g., Tuch, 2004) and spherical deconvolution (e.g., Tournier et al., 2008; Tournier, Calamante, & Connelly, 2007; Tournier, Calamante, Gadian, & Connelly, 2004), which allow resolution of multiple fibre populations within a single voxel. Diffusion metrics available to researchers have diversified from FA and mean diffusivity (MD) to tractography-derived measures of tract length and fibre number (Calamante, Tournier, Jackson, & Connelly, 2010; Correia et al., 2008; Pannek et al., 2011), allowing investigation of different aspects of brain connectivity. The current work employed a recently developed technique for investigating structural connectivity called Anatomical Connectivity Mapping (ACM) (Embleton et al., 2007). ACM is a probabilistic tractography-based technique that allows visualisation of whole-brain connectivity by launching multiple probabilistic trajectories

from every voxel in the brain[2]. ACM has the potential to be particularly informative in investigations of white matter changes in chronic stroke aphasia, as one might expect to see connectivity abnormalities in pathways that extend beyond lesion boundaries. Appreciation of the location and severity of such abnormalities may, therefore, improve lesion-symptom mappings, by providing a better understanding of extent of damage.

The aim of the current study was to use ACM to better understand how brain damage relates to language performance in a group of individuals with chronic stroke aphasia. Each participant's scores on a range of language tests were related to connectivity information in their ACM, as well as their high resolution T1-weighted structural scan and FA map. Whilst diffusion metrics such as FA can provide insights into the microstructural integrity of a particular voxel within a white matter tract, ACM allows us to investigate how changes throughout the brain impact upon longer range connectivity. To illustrate the utility of this approach, we first present the results of "pseudoneurosurgery", in which we establish the sensitivity of ACM to focal damage involving key language processing tracts. We then present data from a case-series of five chronic stroke aphasic participants. Two of these have similar anterior lesions, two have similar posterior lesions, and one has a ventral lesion. Consideration of how these particular lesions have affected connectivity of the dorsal and ventral pathways explains the striking differences in their behavioural profiles.

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[2] In this work 'connectivity' will be used as a shorthand for the information extracted using probabilistic tractography, which is a proxy for true anatomical connectivity. Tractography, like other neuroimaging methods, has limitations, and these include being affected by issues such as false positives, false negatives, and distance effects (Johansen-Berg & Behrens, 2006; Jones, 2008; Morris et al., 2008). Therefore, whilst diffusion MRI tractography-derived connectivity and 'true' anatomical connectivity are strongly linked, the two cannot be considered to be equivalent.

Methods

Participants

Data from five chronic stroke participants are presented here. Participants' gender, age, education, time post-stroke, stroke aetiology, and diagnosis according to assessment on the Boston Diagnostic Aphasia Examination (Goodglass et al., 2000) are given in Table 3.1. All were right handed, as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971), had English as their first language, and had no history of neurological condition except a single left hemisphere stroke. Ethical approval for the study was granted by the North West Multi-centre Research Ethics Committee, UK. Written informed consent was obtained from all participants.

Table 3.1

Participant Information

Initials	**Gender**	**Age (years)**	**Education (years)**	**Time Post-Stroke (months)**	**Stroke Aetiology**	**Aphasia Type**
PE	Female	73	16	22	I	C/W
EB	Male	61	17	12	I	Anomia
DS	Male	72	11	105	I	Anomia
KW	Male	81	10	24	I	Broca's
KS	Male	59	12	12	H	TSA

Abbreviations: I = ischaemic, H = haemorrhagic, TSA= transcortical sensory aphasia, C/W = Conduction/Wernicke's

Behavioural Assessments

In addition to the BDAE, participants were tested on a battery of language assessments, which are detailed in Table 3.2. The battery was designed to assess participants' phonological and semantic performance. A small battery of cognitive tests was also conducted with participants, details of which are given in Supplementary Information. Testing was carried out in participants' homes over several sessions. Participants' performance was scored based on their first response for all assessments, apart from sentence comprehension. For the sentence comprehension tasks participants were given two points for each prompt correct response and one point for delayed correct responses or self-corrections, as per the scoring system for the Comprehensive Aphasia Test (CAT) (Swinburn, Porter, & Howard, 2005). Responses on naming assessments needed to be produced within five seconds of presentation to be marked as correct. Minor dysfluencies in responses were accepted. Presentation of spoken stimuli was repeated if requested by participants.

Magnetic Resonance Imaging (MRI) Data Acquisition

All images were acquired on a 3.0 tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil.

Structural MRI Data Acquisition

High resolution structural scans were acquired using a T1-weighted inversion recovery sequence with 3D acquisition, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1 mm, acquired voxel size 1.0 x 1.0 x 1.0 mm^3, matrix size 256 x 256, FOV

= 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

Diffusion Data Acquisition

A pulsed gradient spin echo (PGSE) echo planar imaging (EPI) sequence was used to acquire diffusion-weighted data, implemented with TE = 54 ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed in-plane resolution 1.875 x 1.875 mm^2, slice thickness 2.1 mm, 60 contiguous slices, 43 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8ms, δ = 13.1ms), 1 at b = 0, SENSE acceleration factor = 2.5 (because the sequence was cardiac gated, the TR was dependent on the individual's heart rate). Each diffusion-weighted volume was acquired entirely before starting on the next diffusion weighting, resulting in 44 temporally spaced volumes with different direction diffusion gradients. For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity *k*-space traversal, and hence reversed phase and frequency encode direction (Embleton et al., 2010). Diffusion-weighted acquisitions were cardiac-gated using a peripheral pulse unit on the participant's index finger, aimed at reducing artefacts associated with pulsatile brain movements (Jones & Pierpaoli, 2005). Cardiac gating meant that the duration of the diffusion-weighted scan was dependent on the participant's heart rate, but was approximately 28 minutes. Cardiac gating was not used for participants DS and KS due to arrhythmia. A co-localised T2-weighted turbo spin echo scan with 0.94 x 0.94 mm in-plane resolution and 2.1 mm slice thickness was also obtained as a structural reference scan for use in the distortion correction procedure (Embleton, Haroon, Morris, Lambon Ralph, & Parker, 2010).

MRI Data Analysis

Processing of Structural T1-Weighted Data

Structural T1-weighted scans were normalised and segmented using a modified unified segmentation-normalisation procedure developed by Seghier et al. (2008), implemented in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Seghier et al.'s (2008) software was also used to generate automated outlines of participants' lesions (see Supplementary Information). Figures 3.2, 3.3, and 3.4 include normalised T1-weighted scans from each stroke aphasic participant, with their automated lesion outline overlaid.

Processing of Diffusion Data

Diffusion data were first subjected to a distortion correction procedure (Embleton et al., 2010) implemented in MATLAB, which reduces artefacts arising from magnetic field inhomogeneities in regions near air-tissue boundaries, such as the anterior temporal lobes. This procedure also corrects for distortions caused by eddy currents (Embleton et al., 2010). FA maps were generated for each participant by fitting a single diffusion tensor to each voxel in the distortion-corrected diffusion-weighted data. The distortion-corrected diffusion-weighted images were also processed using the model-based bootstrap of constrained spherical deconvolution (Haroon, Morris, Embleton, & Parker, 2009; see also Jeurissen, Leemans, Tournier, & Sijbers, 2008), a method based on the constrained spherical deconvolution (CSD) technique devised by Tournier et al. (2007, 2008). The application of model-based residual bootstrapping to CSD allowed quantification of the uncertainty in the inferred fibre orientation, producing probability density functions (PDFs) suitable for use in probabilistic tractography (Haroon et al., 2009). The PDFs yielded by the bootstrapped CSD process were used to produce ACMs

(Embleton et al., 2007). ACMs were generated using the probabilistic index of connectivity (PICo) tractography algorithm (Parker, Haroon, & Wheeler-Kingshott, 2003). Ten tractography streamlines were launched from every voxel in each participant's brain and the frequency of intersection of each streamline with each brain voxel recorded. The output from the ACM represents the relative connectivity of each brain voxel to every other white or grey matter voxel in that brain.

Results

Pseudoneurosurgery

"Pseudoneurosurgery" was carried out by applying small masks to the ACM tractography process, so that streamlines could not pass through or be launched from the voxels within the mask. These masks were placed in selected parts of the dual route white matter language system of a control participant's brain. The aim was to ascertain which regions demonstrated reduced connectivity as a result of damage to specific parts of white matter pathways.

The control participant on whose brain pseudoneurosurgery was conducted was a 72 year old right-handed female, with 16 years of education and no neurological history. Masks were drawn as regions of interest (ROIs) in MRIcro (http://www.cabiatl.com/mricro) and then included as explicit masks when generating ACMs in PICo. Only one ROI mask was used per ACM, so an ACM was generated with one mask included, then another ACM was generated with a different mask included, and so on. The masks used are shown in Figure 3.1a (for more details of the masks see Supplementary Information). The resulting ACMs were compared back to the control participant's original ACM, run without any masking. As well as comparing the two ACM outputs visually, in order to clearly demonstrate regions in which connectivity was reduced after 'lesioning', the 'lesioned' ACM was subtracted from the 'unlesioned' ACM using the Imcalc function in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). The resultant subtraction maps are shown as a composite in Figure 3.1b and individually in Figures 3.1c to 3.1f.

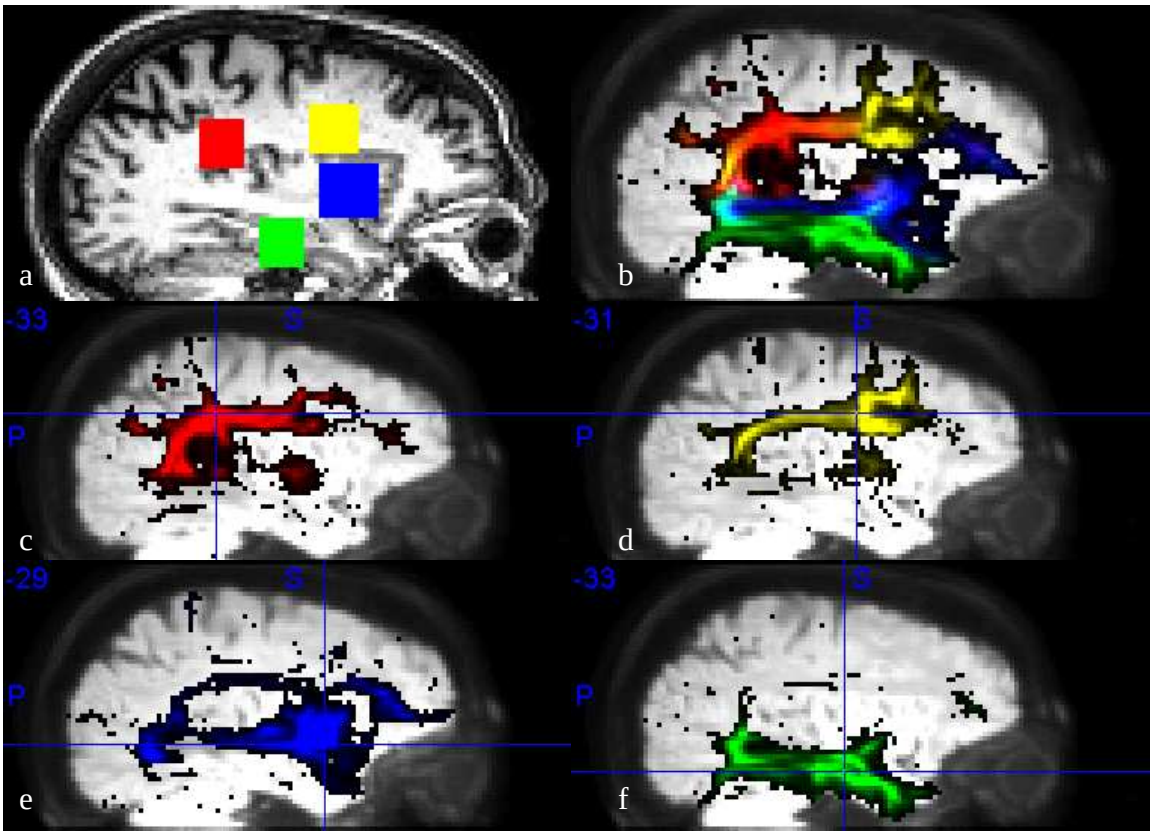

Figure 3.1. a) Location of masks used as 'lesions' in "pseudoneurosurgery". The AF lesion (red), SLF lesion (yellow), EmC lesion (blue), and the ILF lesion (green). b) Composite image showing results of pseudoneurosurgery with the AF (red), SLF (gold), EmC (blue), and ILF (green) lesion masks. Regions of reduced connectivity after applying the c) AF lesion; d) SLF lesion; e) EmC lesion; f) ILF lesion. Crosshairs indicate the location of the relevant simulated lesion. Subtractions are thresholded from 100 – 2000.

Inclusion of the 'AF lesion' mask resulted in reduced connectivity along the dorsal pathway, particularly at the posterior end of the pathway, including the component that arches around the posterior end of the Sylvian fissure into the temporal lobe, as can be seen in Figure 3.1c. The 'SLF lesion' simulation led to reduced connectivity in the region of the mask itself, unsurprisingly, and then along the dorsal route posterior to the mask. As Figure 3.1d shows, reductions in the posterior part of the dorsal route were, however, less extensive than those seen in the 'AF lesion' simulation. Inclusion of the

‘EmC lesion’ resulted in reduced connectivity in the area of the EmC and, to a lesser extent, the anterior part of the dorsal route and posterior part of the ventral route, as shown in Figure 3.1e. Finally, presence of the ‘ILF lesion’ led to reduced connectivity in the region of the mask itself and along the inferior and posterior component of the ventral route, as is evident in Figure 3.1f. The ILF lesion did not appear to impact on connectivity along the dorsal route or the more anterior and superior aspect of the ventral route in the region of the EmC.

These simulated and constrained lesions along the white matter pathways known to be implicated in intact and impaired language processing demonstrate the sensitivity of ACM to disruption distal from the area of the lesion. The simulations captured important areas of the language network, with each simulation probing different parts of the dual route system. ACM therefore has the potential to further our understanding of brain-behaviour relationships in chronic stroke aphasia. Having established the sensitivity of the method to constrained simulated lesions, we then employed ACM to investigate connectivity changes in individuals with real stroke lesions and chronic stroke aphasia.

Behavioural Assessment Results

Participants’ scores on the battery of language tests are given in Table 3.2. For participants’ scores on additional cognitive measures, see Supplementary Information.

Table 3.2

Participants' Scores on Language Assessment Battery

Assessment \ Participant	PE	EB	KW	DS	KS
Minimal Pairs Nonwords (PALPA 1)[a] (/72)	**56**	68	**54**	**57**	68
Minimal Pairs Words (PALPA 2)[a] (/72)	62	71	**47**	**56**	69
Repetition Nonword Immediate (PALPA 8)[a] (/30)	**4**	25	**0**	**17**	22
Repetition Nonword Delayed (PALPA 8)[a] (/30)	**1**	**16**	**0**	**11**	24
Repetition Word Immediate (PALPA 9)[a] (/80)	**36**	80	**3**	**70**	75
Repetition Word Delayed (PALPA 9)[a] (/80)	**33**	80	**0**	74	76
Reading Aloud Nonword (PALPA 8)[a] (/30)	**5**	26	**0**	23	**0**
Reading Aloud Word (PALPA 31)[a] (/80)	**41**	**78**	**2**	**78**	**7**
Word-to-Picture Matching - Spoken[b] (/64)	62	63	**61**	64	**46**
Word-to-Picture Matching - Written[b] (/64)	64	64	**59**	64	**43**
Picture Naming (64-item naming)[b] (/64)	**13**	**52**	**1**	**57**	**20**
Picture Naming (BNT)[c] (/60)	**7**	**40**	**0**	49	**8**
Camel and Cactus Test - Written[b] (/64)	57	59	56	57	-
Camel and Cactus Test - Pictures[b] (/64)	**54**	58	57	58	**44**
Synonym Judgement[d] (/96)	**76**	91	**79**	90	**81**
Sentence Comprehension – Spoken[e] (/32)	**16**	**23**	**27**	28	**27**
Sentence Comprehension – Written[e] (/32)	**12**	**20**	**23**	27	-

Scores in bold indicate performance more than two standard deviations below the mean performance of a group of 13 healthy control participants, similar in age and education level to the stroke aphasic participants. Assessment sources: (a) the Psycholinguistic Assessment of Language Processing (PALPA) (Kay, Lesser, & Coltheart, 1992); (b) the Cambridge Semantic Battery (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000); (c) the Boston Naming Test (Kaplan et al., 1983); (d) the 96-item synonym judgement test (Jefferies, Patterson, Jones, & Lambon Ralph, 2009); (e) the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2005).

Neuroimaging Results

Abnormalities in participants' ACMs were interpreted by comparison between their left hemisphere ACM and that of an individually age- and education-matched control participant. Whilst attempts were made to match controls and participants closely, and visually the results would appear to be closely matched enough for a qualitative comparison between participants and controls, it has previously been shown that the structure of white matter pathways can vary between individuals (Bassett, Brown, Deshpande, Carlson, & Grafton, 2011; Johansen-Berg, 2010; Lawes et al., 2008; Scholz, Klein, Behrens, & Johansen-Berg, 2009). Therefore, we also compared participants' left hemisphere ACM and FA results with their own right hemisphere results and found the same pattern of results. Whilst differences have also previously been observed between left and right hemisphere pathways (Büchel et al., 2004; Catani et al., 2007; Iturria-Medina et al., 2011; Parker et al., 2005), meaning that this comparison also has limitations, the fact that the same results appeared using both control left hemispheres from healthy individuals, and participants' own undamaged hemispheres, suggests that the results obtained were reliable.

Posterior Cases

Participant PE

On examination of participant PE's T1-weighted scan, which is shown in Figure 3.2, one might expect her to present with severely impaired comprehension as well as production deficits, given that her lesion includes the classic Wernicke's area. However, this was not the case, her comprehension was relatively spared (at least at a single word level). This is in contrast to a significant impairment on any task requiring spoken output, including repetition and reading aloud of words and nonwords, and picture naming. PE's language performance makes sense though, in the context of her ACM. Examination of

her ACM shows that connectivity through her left hemisphere dorsal route has been severely affected by her stroke lesion. Whilst the lesion itself only impacts upon the posterior end of the dorsal route (as shown on her T1-weighted scan and FA map), connectivity along her dorsal route has been severely diminished. This closely resembles the pattern of reduced connectivity observed when the 'AF lesion' was applied in the pseudoneurosurgery simulations (i.e., dorsal route connectivity remote from the area of damage is reduced in both cases).

PE's impaired performance on all tasks requiring spoken responses makes sense in the context of severely reduced dorsal route connectivity, given that the dorsal route has been associated with phonological processing (Hickok & Poeppel, 2004, 2007; Saur et al., 2008; Weiller et al., 2011). The fact that PE's performance on minimal pairs, repetition, and reading tasks was markedly worse for nonword items than word items would also be predicted from her reduced dorsal route connectivity. Both dorsal and ventral routes are likely to be involved in processing of real words in the intact language system, but for nonwords the ventral route via meaning is unlikely to offer much support in this process, so processing of nonwords depends more heavily upon the dorsal route. PE's sentence-level comprehension was also mildly impaired, consistent with previous studies that have suggested a role for the dorsal route in syntactic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Friederici, 2009). The ACM also shows that PE's ventral route is relatively spared (although a little diminished at its posterior extent), which would predict relatively intact single word comprehension, which PE demonstrated.

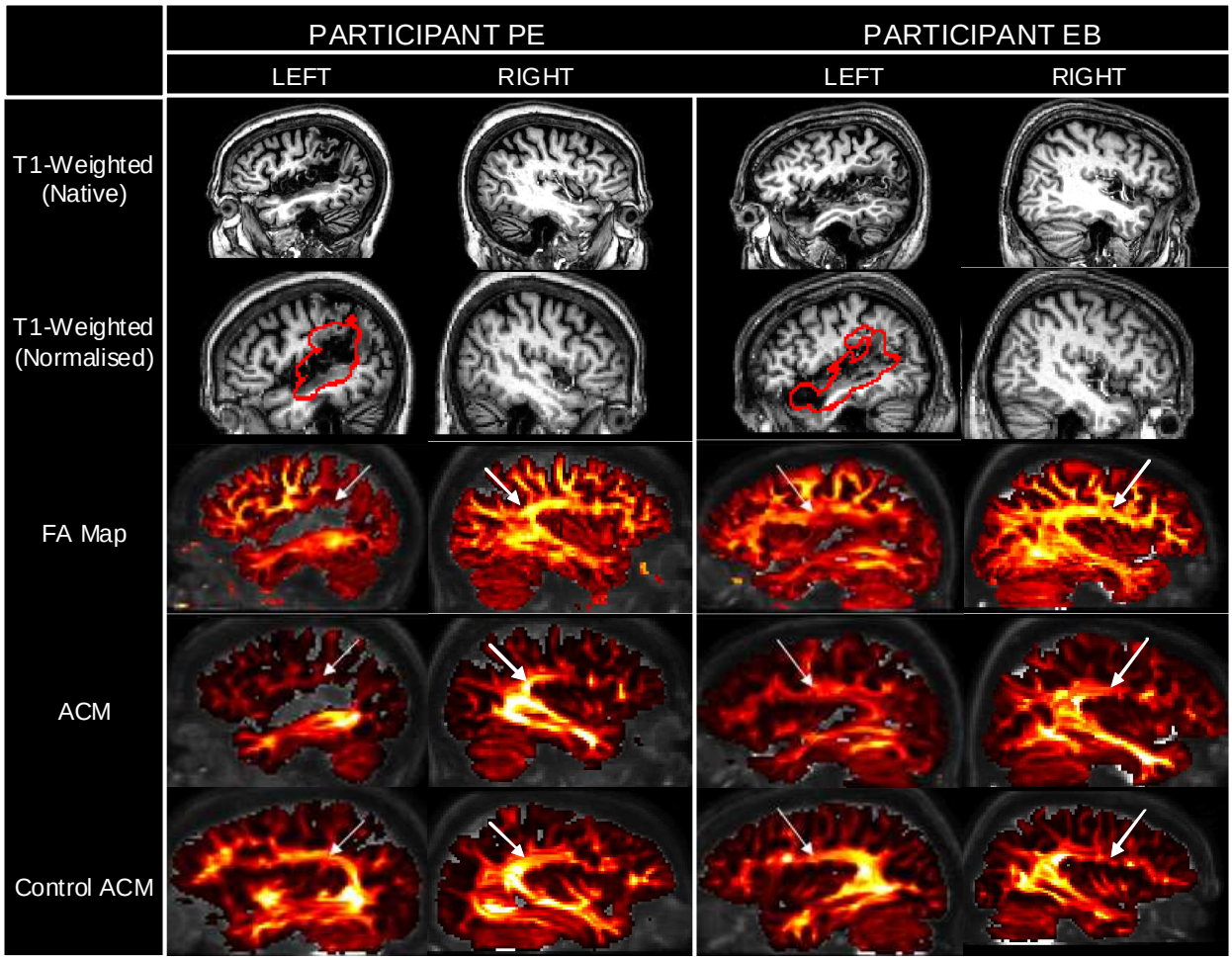

Figure 3.2. Imaging results for posterior cases PE (left) and EB (right). T1-weighted scan (top row); normalised T1-weighted scan with lesion outline shown in red (second row); FA map (third row); ACM (fourth row); ACM from matched healthy control participant (bottom row). Healthy control participant for PE = female, 72 years old, 16 years of education. Healthy control participant for EB = male, 63 years old, 17 years of education. All images are shown in native space apart from the normalised T1-weighted images. Arrows indicate features of interest referred to in text on FA and ACM images.

Participant EB

As can be seen in Figure 3.2, EB's lesion, although not identical to PE's, was similar in location and extent. Yet, EB's performance fell within normal limits for the majority of language assessments. EB showed a very mild impairment on delayed nonword repetition and reading aloud words. He showed a moderate impairment on

naming tasks and slightly impaired spoken and written sentence comprehension, although for the sentence-level tasks he answered correctly on all but one spoken sentence task and all but two written sentence tasks but dropped points due to slow responses. His performance on all other tests was relatively spared. Examination of EB's ACM reveals diminished connectivity along the dorsal route and a very slight reduction in ventral route connectivity. The fact that EB's performance was mildly impaired on a demanding phonological task, delayed nonword repetition, is likely to reflect the fact that his dorsal route connectivity is diminished rather than totally eliminated (i.e., disconnected). EB's slightly impaired naming could reflect both dorsal route effects and the slight reduction in ventral route connectivity. The fact that EB performed well on most assessments reflects that fact that the majority of his dual stream language system remains connected, even if this connectivity is slightly diminished. As with participant PE, the extent of EB's reduction in dorsal route connectivity was more evident on examination of his ACM than his T1-weighted scan or FA map.

Comparison of participants PE and EB

Our posterior case examples, PE and EB, had largely overlapping lesion locations as seen on the T1-weighted scans. The consequences of their lesions also looked more similar than different in the FA maps. Both of their lesion locations would predict a fluent, Wernicke-like aphasia. Whilst both are fluent, neither presented with a significant comprehension impairment. Furthermore, their performance on language tasks was very different. Not only did EB perform better than PE on all tasks that both fell outside normal limits on, but PE also demonstrated severely impaired performance on tasks that EB performed to within normal limits, including immediate word and nonword repetition, delayed word repetition, and nonword reading. This difference in language impairment might be difficult to explain on the basis of T1-weighted scans alone, but is

clearly understandable when differences evident on ACM are taken into account. Whilst EB's ACM shows evidence of slightly reduced connectivity along the dorsal route and very slightly reduced ventral route connectivity, PE's ACM shows connectivity that is diminished, to zero at some points, along the dorsal route (as well as a small amount of ventral route reduction in connectivity). In other words, PE's ACM reveals disconnection, whilst EB's shows a reduction in connectivity.

Anterior Cases

Participant KW

Participant KW showed slightly impaired performance on the receptive phonology task, minimal pairs (for words and nonwords), although the severity of this impairment was far less than his impairment on all tasks requiring spoken responses. He was unable to repeat or read aloud words or nonwords, or to name pictured items. However, his relatively spared semantic performance is evident from his scores on the word-to-picture matching, camel and cactus, synonym judgement, and sentence comprehension tasks, which were either within normal limits or only mildly impaired. While damage to regions of the dorsal pathway is evident in KW's FA map, as seen in Figure 3.3, its severity only becomes fully apparent on examination of his ACM, which shows dorsal route connectivity to have diminished to the point that it is non-existent until the most anterior extent of the path. Again, KW's performance reflects the white matter connectivity changes evident on his ACM. The fact he was severely impaired on all tasks requiring spoken responses fits with the fact that his dorsal route connectivity is severely affected and his relatively good performance on semantic assessments, including comprehension assessments, is to be expected given the fact that connectivity through his ventral route is relatively high. KW's lesion location encompassed the location of the mask used for the 'SLF lesion', and as with the participant PE, similarities in regions of

reduced connectivity between the simulation and participant KW's ACM can be seen. Both the 'SLF lesion' simulation and participant KW's ACM reveal reduced connectivity along the dorsal route but, interestingly, in both cases connectivity is retained at the most anterior extent of the dorsal route, suggesting that this region receives connectivity from white matter pathways other than the remainder of the dorsal route.

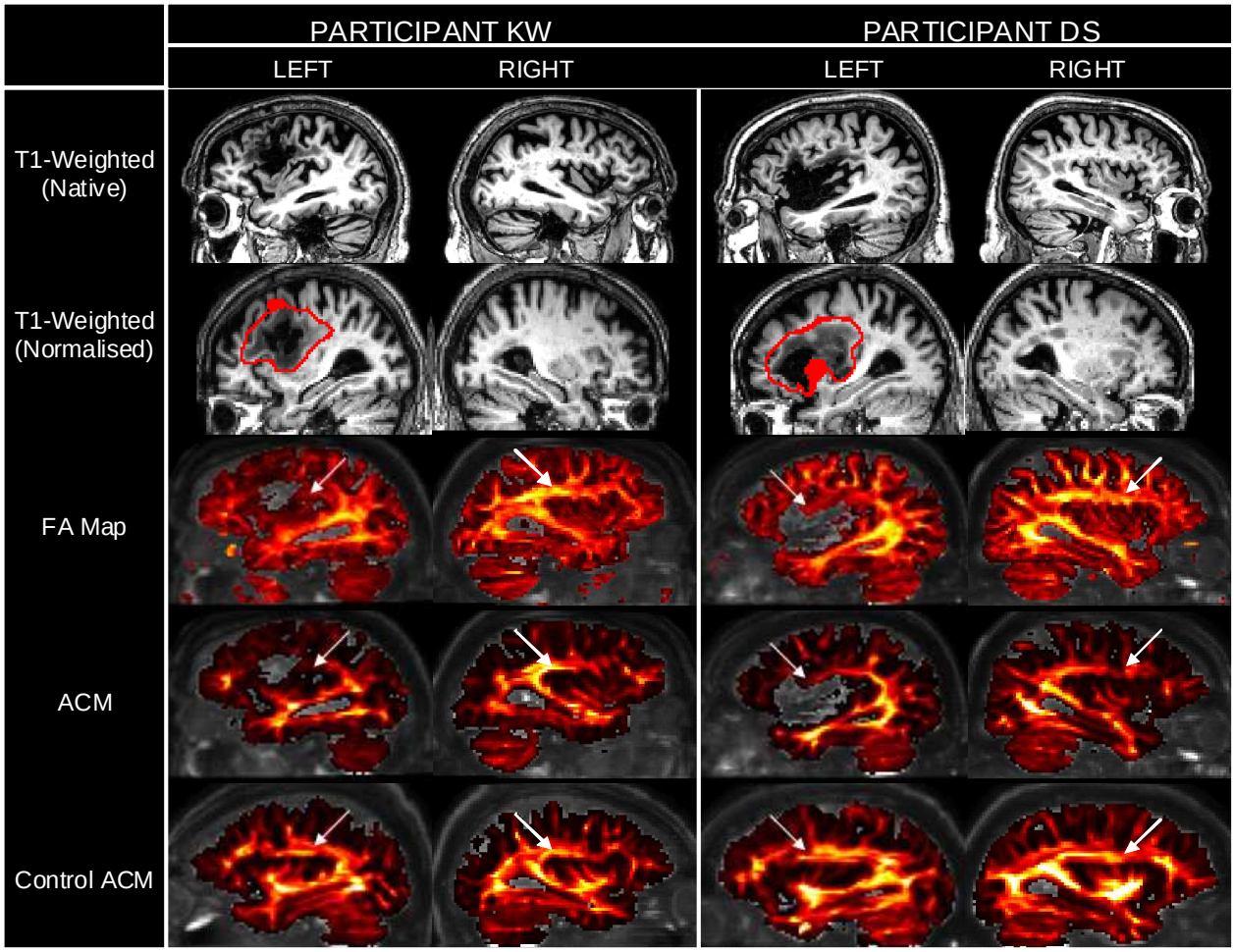

Figure 3.3. Imaging results for anterior cases KW (left) and DS (right). T1-weighted scan (top row); normalised T1-weighted scan with lesion outline shown in red (second row); FA map (third row); ACM (fourth row); ACM from matched healthy control participant (bottom row). Healthy control participant for KW = male, 79 years old, 12 years of education. Healthy control participant for DS = male, 77 years old, 10 years of education. All images are shown in native space apart from the normalised T1-weighted images. Arrows indicate features of interest referred to in text on FA and ACM images.

Participant DS

Participant DS demonstrated mildly impaired performance on minimal pairs, immediate word repetition, and one of the two naming assessments. He also showed very mildly impaired word reading, and moderately impaired immediate and delayed repetition of nonwords. However, DS was able to perform spoken and written word-to-picture matching, both camel and cactus tests, synonym judgement, and both sentence comprehension tasks within normal limits. DS' mild language impairments, which are most notable on the phonologically demanding task, delayed nonword repetition, are likely to reflect reduced connectivity and integrity of his dorsal route, which is evident on his FA map and more strikingly on his ACM, as shown in Figure 3.3. The connectivity of the posterior part of DS' dorsal route appears to be relatively intact, which is in keeping with the fact that his phonological deficits are relatively mild. His good performance on the semantic assessments is consistent with his largely intact ventral route connectivity.

Comparison of Participants KW and DS

Like the posterior case examples presented earlier, these two anterior participants have largely overlapping lesion locations, as seen on T1-weighted scans. However, their language performance differs significantly. Not only was KW impaired on tasks that DS was not, but in all tasks on which both were impaired, KW scored at or close to floor-level, whilst DS' scores were only mildly impaired. These differences in language profile can be understood more clearly by examining both participants' ACMs. KW's dorsal route connectivity has been effectively eliminated, whereas DS' ACM shows a reduction in connectivity at only the most anterior point of the dorsal route. This may explain why KW showed such a severe phonological output deficit, which was absent in DS. KW and

DS scored similarly on semantic assessments, reflecting the fact that connectivity in most of the ventral route is relatively intact in both cases.

Extrasylvian Case

Participant KS

The anterior and posterior participant pairs presented above illustrate how differences in dorsal route connectivity relate to variations in language performance in chronic stroke aphasic individuals with similar lesion locations. The final case to be presented, participant KS, serves to illustrate the impact of white matter connectivity changes in an inferior posterior part of the ventral pathway.

Recent work has provided evidence for the involvement of several white matter pathways in the ventral language route. This includes anterior structures such as the UF and extreme capsule fibre system (Anwander et al., 2007; Parker et al., 2005; Saur et al., 2008; Schmahmann et al., 2007; Wise, 2003), as well as pathways which extend from posterior to anterior regions such as the IFOF (Duffau et al., 2005, 2009). An additional, more posterior, tract that may contribute to the ventral language pathway is the ILF. Although it has often been associated with vision (Catani, Jones, Donato, & ffytche, 2003), the role of the ILF has been said to be unclear (Catani et al., 2003; Mandonnet et al., 2007). There is increasing evidence, however, that the region where the ILF terminates anteriorly is more multimodal and semantic in nature (Matsumoto et al., 2004; Mummery et al., 1999; Sharp, Scott, & Wise, 2004; Visser & Lambon Ralph, 2011), and that the ILF may therefore be part of the ventral language route (Saur et al., 2008; c.f. Mandonnet et al., 2007). The ILF's potential role in language may have previously been underappreciated for two reasons, firstly that it falls outside of mid cerebral artery (MCA) territory and is therefore damaged less often in MCA stroke (Phan et al., 2005),

and secondly, that it is subject to susceptibility artefacts which particularly affect the anterior temporal lobe in MRI (Devlin et al., 2000; Embleton et al., 2010).

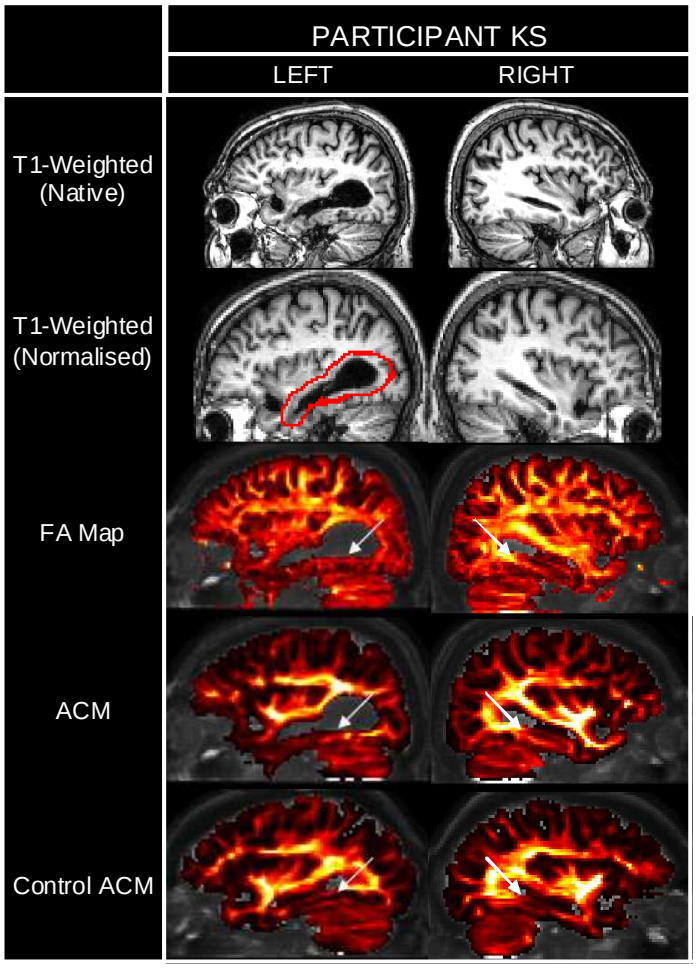

Figure 3.4. Imaging results for extrasylvian case KS. T1-weighted scan (top row); normalised T1-weighted scan with lesion outline shown in red (second row); FA map (third row); ACM (fourth row); ACM from matched healthy control participant (bottom row). Healthy control participant = male, 59 years old, 11 years of education. All images are shown in native space apart from the normalised T1-weighted images. Arrows indicate features of interest referred to in text on FA and ACM images.

Participant KS has a lesion that falls outside the classic perisylvian language area but impacts upon the most inferior and posterior aspect of the ventral route, including both

the ILF and IFOF, as can be seen in Figure 3.4. He presented with transcortical sensory aphasia (TSA), meaning his speech was fluent and he was able to repeat, but his comprehension was impaired. His lesion is located at the temporo-parieto-occipital junction of the left hemisphere, a region often associated with TSA (Alexander, Hiltbrunner, & Fischer, 1989) and semantic impairments following stroke (Noonan, Jefferies, Corbett, & Lambon Ralph, 2010). KS performed well on phonological tasks such as word and nonword repetition, and minimal pairs. However, his performance was impaired on spoken and written word-to-picture matching, spoken sentence comprehension, the picture version of the camel and cactus test, picture naming, and reading aloud. KS' good performance on phonological tasks would be predicted by the location of his cortical lesion, and the fact that on his FA map and ACM it can be seen that connectivity through the dorsal route is largely unaffected. KS' impaired performance on tasks involving semantics is also to be expected when the results of his FA map and ACM are considered. The connectivity through the posterior part of his ventral route has been seriously affected, which would predict a semantic impairment. The location of the diminished connectivity is right at the posterior, inferior part of the ventral route. As well as showing regions of diminished connectivity, ACM can reveal where connectivity is still intact. So in the example of KS, if his FA map only was considered, whilst one can see that the dorsal route appears to be structurally intact, whether connectivity though that route has been affected by stroke lesion cannot be assessed. Based on assessment of his ACM, the fact that normal connectivity seems to be maintained through the dorsal route can be confirmed.

Areas of reduced connectivity on KS' ACM are closely mirrored by those resulting from inclusion of the 'ILF lesion' in the "pseudoneurosurgery" simulations. In both cases reduced connectivity can be seen along the inferior and posterior component of the ventral route. Furthermore, in both cases connectivity along the dorsal route and the more

anterior and superior parts of the ventral route in the region of the EmC appear to be relatively intact.

Discussion

Taking into account white matter connectivity abnormalities can help us better understand the language profiles of chronic stroke aphasics, in terms of both spared and impaired features. Here, we introduced the use of ACM as a means to chart disruptions to connectivity in this participant group for the first time. Initially, we used "pseudoneurosurgery" to establish the consequences of constrained lesions to key left hemisphere dorsal and ventral language pathways upon long range connectivity as measured by ACM. Having established the sensitivity of this measure to these simulated lesions, we then considered the effects of real stroke lesions upon ACM in light of the language processing of a small case-series of chronic stroke aphasic participants.

We have presented aphasic individuals with posterior lesions which largely overlap, but whose behavioural performance is divergent. Participant PE was impaired on all tasks requiring spoken output, whilst participant EB's language deficits were relatively mild, with notable deficits only emerging on more demanding phonological tasks. On examination of their ACM data, it is clear that PE presents with much more extensive dorsal route connectivity reductions than EB, which may help explain their differing language profiles. Similarly, our anterior cases, KW and DS, both showed large anterior lesions on their T1-weighted scans. Yet KW was severely impaired on all tasks involving spoken word (and nonword) production, whilst DS showed milder language deficits which were most appreciable in the phonologically demanding delayed nonword repetition task. Again, the key difference on the ACM would appear to be extent of dorsal route connectivity changes, with KW showing evidence of far greater dorsal route connectivity abnormalities than DS. Finally we presented the case of KS, a participant whose lesion falls largely outside the classic perisylvian language network, yet who presented with language impairment. Whilst KS' performance on tasks of input and output phonology was within normal limits, his semantic performance was not. On

examination of his ACM it was clear that KS had reduced connectivity through the ventral pathway.

What ACM has revealed regarding white matter connectivity changes and language performance in this group is in line with what would be expected from the literature on the dual route language system in healthy brains. Reduced dorsal route connectivity appeared to impact on phonological processing, with smaller amounts of change influencing higher level phonological tasks (participants EB and DS), and more substantial connectivity changes impacting on all tasks requiring a spoken response (participants KW and PE). The current findings, therefore, support the involvement of the dorsal route in phonological processing (Bernal & Altman, 2010; Hickok & Poeppel, 2004, 2007; Leclercq et al., 2010; Saur et al., 2008; Weiller et al., 2011). There were only two sentence-level assessments in the battery, so strong claims regarding syntactic processing cannot be made. However, the fact that all participants with dorsal route damage showed some degree of impairment on sentence comprehension tasks is consistent with the idea that the dorsal route may play a role in syntactic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Friederici, 2009). Unlike the first four participants described, participant KS showed no reduction in dorsal route connectivity in his left hemisphere. However, a marked reduction in connectivity in the posterior and inferior component of his left hemisphere ventral route was evident on his ACM. This reduced connectivity was associated with impaired performance on assessments involving semantics, which is in line with the idea that the ventral route plays an important role in semantic processing (Friederici, 2009; Hickok & Poeppel, 2004, 2007; Leclercq et al., 2010; Saur et al., 2008). Whilst the dorsal and ventral routes have been associated with phonological and semantic processing, respectively, it is important to note that both routes are likely to play a part in most language tasks in the intact language system (Cloutman, 2012; Weiller et al., 2011). This is reflected by the fact that patterns

of impaired and intact task performance in stroke aphasia are usually relative rather than absolute, which was evident in our participant group.

Understanding individuals' white matter connectivity changes could potentially influence the type of speech and language therapy delivered to them. If information was available regarding regions where a participant had remaining white matter connectivity, therapy could be directed at utilising those intact resources. For example, in participants PE and KW, whose dorsal route connectivity is severely reduced but who have good ventral route connectivity, therapy could be devised to make more use of the intact ventral route, for example through enhanced reliance on semantics to drive speech (Laine & Martin, 2012; Nickels & Best, 1996; Raymer et al., 2008; Stinear & Ward, 2013). With individuals such as EB and DS, who have some remaining dorsal route connectivity, as well as relatively intact ventral route connectivity, both phonology and semantics could be employed in therapy. For individuals such as KS, who have intact dorsal route connectivity, but ventral route deficits, a more phonologically-based therapy might be more appropriate. If both dorsal and ventral routes are affected, for example in a case of global aphasia, therapy that encourages the use of right hemisphere pathways might potentially be employed. Melodic intonation therapy, for example, which has been argued to rely more on right hemisphere regions, has been associated with increases in the right hemisphere homologue of the dorsal route in chronic stroke aphasia (Schlaug et al., 2009).

The current work demonstrates that whole-brain connectivity mapping, ACM, can be a useful tool in the study of chronic stroke aphasia. ACM has previously been shown to be sensitive to changes in white matter connectivity in other clinical conditions, such as Alzheimer's disease (Bozzali et al., 2011, 2012). As discussed above, the results we have obtained using ACM have related well to the behavioural data from our participants, as well as previous research. ACM allows unbiased tracking of the entire

brain, without the need for *a priori* hypotheses regarding the location of connectivity changes. ACM offers different information regarding white matter to that available in FA maps. Whilst FA and related measures such as MD may be taken to reflect local microstructure of white matter tracts (Basser & Pierpaoli, 1996), ACM reflects global connectivity and can reveal connectivity reductions that can arise from both damage to close by or remote brain regions. This is particularly useful information when we are interested in syndromes such as different types of aphasia, where individuals' language performance may not only reflect local damage to cortical and white matter areas, but also distal changes in connectivity resulting from this damage, as was particularly clear for participant PE in the current work. In addition to revealing areas that appear to be intact on FA maps, but which are receiving reduced connectivity due to distal damage, ACM is also able to offer confirmatory evidence that pathways have maintained normal structural connectivity after damage. Considering connectivity information from ACM, alongside information regarding white and grey matter integrity from T1-weighted scans and FA maps, can improve the accuracy of lesion-symptom mapping by accounting for unexplained variance in participants' performance.

Conclusions

Information regarding white matter connectivity can complement cortical lesion site information when attempting to understand the differing performance of chronic stroke aphasic individuals on language tasks. Changes in different parts of the dual pathway language system impact differently on language performance of individuals with stroke aphasia, with reduced connectivity in the dorsal route being associated primarily with phonological impairment and reduced connectivity in the ventral route being linked to semantic deficits. Through using ACM to explore whole-brain connectivity, we were able to detect disruption to connectivity distal to both simulated

and real lesion sites. This information allowed us to explain behavioural variation between individual chronic stroke aphasic participants, thereby improving the accuracy of lesion-symptom mapping and furthering our understanding of the neural mechanisms that support language processing. As a whole-brain connectivity mapping approach, ACM would be ideally suited to investigating whether there is any evidence for potentially positive changes in participants' white matter connectivity and, if so, how these relate to behavioural performance. This could be particularly illuminating if ACM were combined with detailed behavioural assessment in a longitudinal study charting individuals with stroke aphasia from the acute to the chronic stage.

Supplementary Information

Additional Cognitive Assessments

Participants completed a small battery of additional cognitive assessments, which included: the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997), Raven's Coloured Progressive Matrices – sets A, AB, and B (Raven, 1962), Elevator Counting – with and without distraction (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), forward and backward digit span (Wechsler, 1987), and Corsi span (Milner, 1971).

Lesion Outlines

Participants' lesion outlines were generated using Seghier et al.'s (2008) automated lesion identification procedure, implemented with default settings apart from the *U* threshold, which was set at 0.5. In addition to the stroke aphasic participants' data, data from 21 control participants were included in the lesion identification procedure. The control group included 11 males and 10 females. All were right-handed and had no history of neurological illness. The control group's mean age was 69.62 years (SD = 6.18) and mean number of years in education was 12.80 years (SD = 2.73).

Pseudoneurosurgery Masks

The masks were drawn as ROIs on the control participant's native, 'unlesioned' ACM. The 'AF lesion', which was a volume of 810 voxels was located at the posterior end of the dorsal route in a superior temporo-parietal region. The 'SLF lesion' was 800 voxels located over the anterior dorsal route, in the frontal lobe. The 'EmC lesion' was 528 voxels, located in the anterior part of the ventral route, inferior and slightly anterior to the SLF lesion, underlying the insula. Finally, the 'ILF lesion', which was 1080

voxels, was placed in the posterior portion of the ventral route. It was the most inferior mask and was located in the posterior anterior temporal lobe.

Table 3.3

Participants' Scores on Additional Cognitive Assessments

Participant / **Assessment**	**PE**	**EB**	**KW**	**DS**	**KS**
Brixton Spatial Rule Anticipation Task (/55)	**23**	44	28	40	29
Raven's Coloured Progressive Matrices (/36)	29	36	29	26	31
Elevator Counting - without distraction (/7)	**5**	6	**2**	6	**5**
Elevator Counting – with distraction (/10)	**3**	10	**2**	**3**	9
Forward Digit Span (/8)	**2**	6	**4**	**4**	8
Backward Digit Span (/7)	2	4	3	2	4
Corsi Span (/7)	6	6	4	5	6

Scores given in bold fall outside the normal range, based on published norms. Norms were unavailable for the Raven's Coloured Progressive Matrices.

CHAPTER 4

BREAKING AND MAKING CONNECTIONS: MAPPING WHOLE-BRAIN CONNECTIVITY IN CHRONIC STROKE APHASIA

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Abstract

Aphasia is a common long-term consequence of brain lesions arising from stroke. We used a recently introduced method called Anatomical Connectivity Mapping to go beyond perilesional changes and increase our understanding of disruption and adaptation in chronic stroke aphasia. Results revealed extensive disturbance of key left hemisphere language pathways, including the arcuate fasciculus, paralleled by an increase in the strength of connections in the homologous tract in the right hemisphere.

Main Text

Aphasia, an impairment which can affect language production and/or comprehension, is often seen after a left hemisphere stroke. Unfortunately, many stroke survivors experience some level of language dysfunction chronically ranging from mild word-finding difficulties to severe impairments of expressive and receptive language. Brain changes supporting recovery of function may not only take place in the cortex but may also involve long-range white matter association pathways. Recent advances in diffusion imaging have allowed investigation of the brain's white matter pathways *in vivo*. The emerging picture from this research is that normal language function is subserved by at least two pathways connecting anterior and posterior cortical left hemisphere language areas, a dorsal and a ventral language pathway (e.g., Parker et al., 2005; Saur et al., 2008). The goal of our study was to apply a recently introduced measure, Anatomical Connectivity Mapping (ACM), to identify areas of disruption or adaptation in a representative group of chronic stroke aphasic participants, with differing levels and types of language impairments.

We considered differences between stroke aphasic participants and controls on high resolution T1-weighted magnetic resonance imaging (MRI), and fractional anisotropy (FA), a commonly used diffusion MRI metric that is sensitive to alterations in local white matter microstructure. We contrasted results obtained using these more commonly used measures with those obtained using ACM, a recently developed whole-brain probabilistic tractography method that provides information regarding how strongly connected each grey and white matter voxel is to every other voxel in the brain (Embleton, Morris, Haroon, Lambon Ralph, & Parker, 2007; see also Bozzali et al., 2011; Cercignani, Embleton, Parker, & Bozzali, 2012). In ACM the value in each voxel represents connectivity by quantifying the number of probabilistic tractography trajectories that reach that voxel. ACM offers a whole-brain method for investigating

changes in white matter connectivity and this study is the first time it has been employed in a stroke aphasic group. We used these three image types to assess whether ACM offers any additional insights over and above those provided by common measures of local grey and white matter integrity, T1-weighted imaging and FA.

We recruited 31 individuals with chronic stroke aphasia from a single left hemisphere stroke (see Figure 4.1 for lesion overlap map) and a group of 19 control participants of comparable age and education and compared T1-weighted, FA, and ACM data between groups using voxel-based morphometry (VBM). For each image type statistical comparisons were conducted between stroke aphasic participants and controls in each brain voxel. Firstly we looked at which brain regions showed reduced values in stroke aphasic participants relative to controls on each image type. As Figure 4.2 shows, tissue concentration was lower for the stroke aphasic participants on T1-weighted imaging in widespread left hemisphere regions, mainly covering middle cerebral artery territory. Reduced white matter integrity, as indicated by lower FA values, was seen in the stroke aphasic participants in a region largely overlapping with the T1-weighted cluster. The ACM results showed lower connectivity values in stroke aphasic participants throughout the left hemisphere white matter language network, including both dorsal and ventral pathways, with more specific delineation of the affected connecting structures than in either the T1-weighted or FA results.

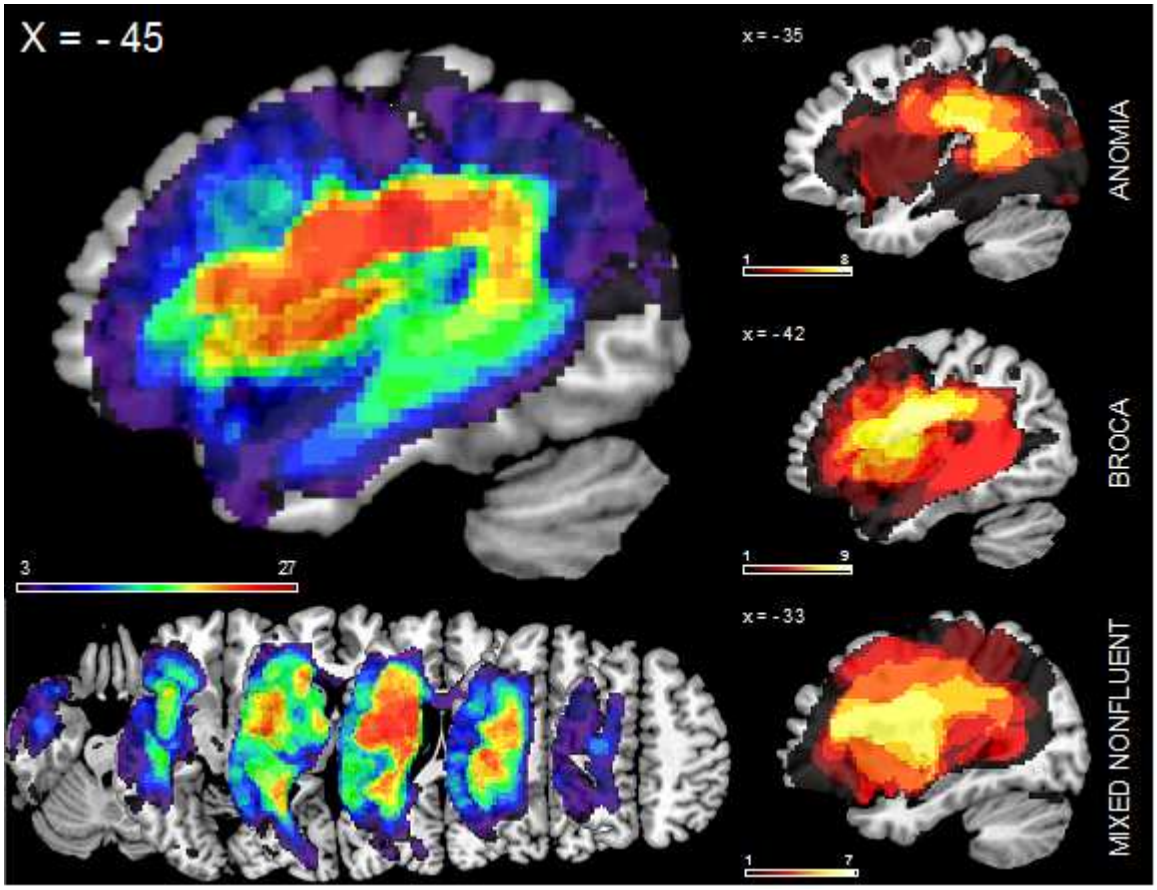

Figure 4.1. Lesion overlap map showing the distribution of stroke aphasic participants' lesions (*N* = 31). Colour scale indicates number of participants with lesion in that voxel. All imaging data are presented in neurological convention. Smaller maps on the right show lesion overlap of subgroups entered into VBM follow-up analyses: anomic (*n* = 9), Broca's (*n* = 8), and mixed nonfluent (*n* = 6).

Our stroke aphasic participants were a heterogeneous group who varied in the precise nature of their language impairments. The subtypes offered by standardised measures like the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983; Goodglass, Kaplan, & Barresi, 2000) offer a way to capture differences in behavioural profiles. We therefore conducted VBM analyses for any BDAE subgroups in our sample with an $n > 5$ (Figure 4.2), these consisted of nine anomic aphasics (with word-finding difficulties but relatively fluent speech and intact comprehension), eight Broca's aphasics (with nonfluent speech but relatively intact comprehension) and six mixed nonfluent aphasics (with nonfluent speech and mildly impaired comprehension) (see Figure 4.1 for

subgroup lesion overlap maps). The T1-weighted results showed a large overlap between subgroups, particularly the two nonfluent subgroups. The anomia subgroup showed abnormally low values in T1-weighted, FA, and ACM analyses in more posterior and inferior regions than the nonfluent groups. The differences between the subgroups were more pronounced in ACM, particularly with the anomic subgroup showing much smaller regions of lower ACM. This was particularly apparent in the degree of dorsal route involvement in the anomic subgroup relative to the other subgroups. The difference between Broca's and mixed nonfluent aphasics was also most notable in the ACM analyses, with the larger cluster for mixed nonfluent aphasics aligning with the fact that mixed nonfluent aphasics tend to have more extensive language impairment than Broca's aphasics.

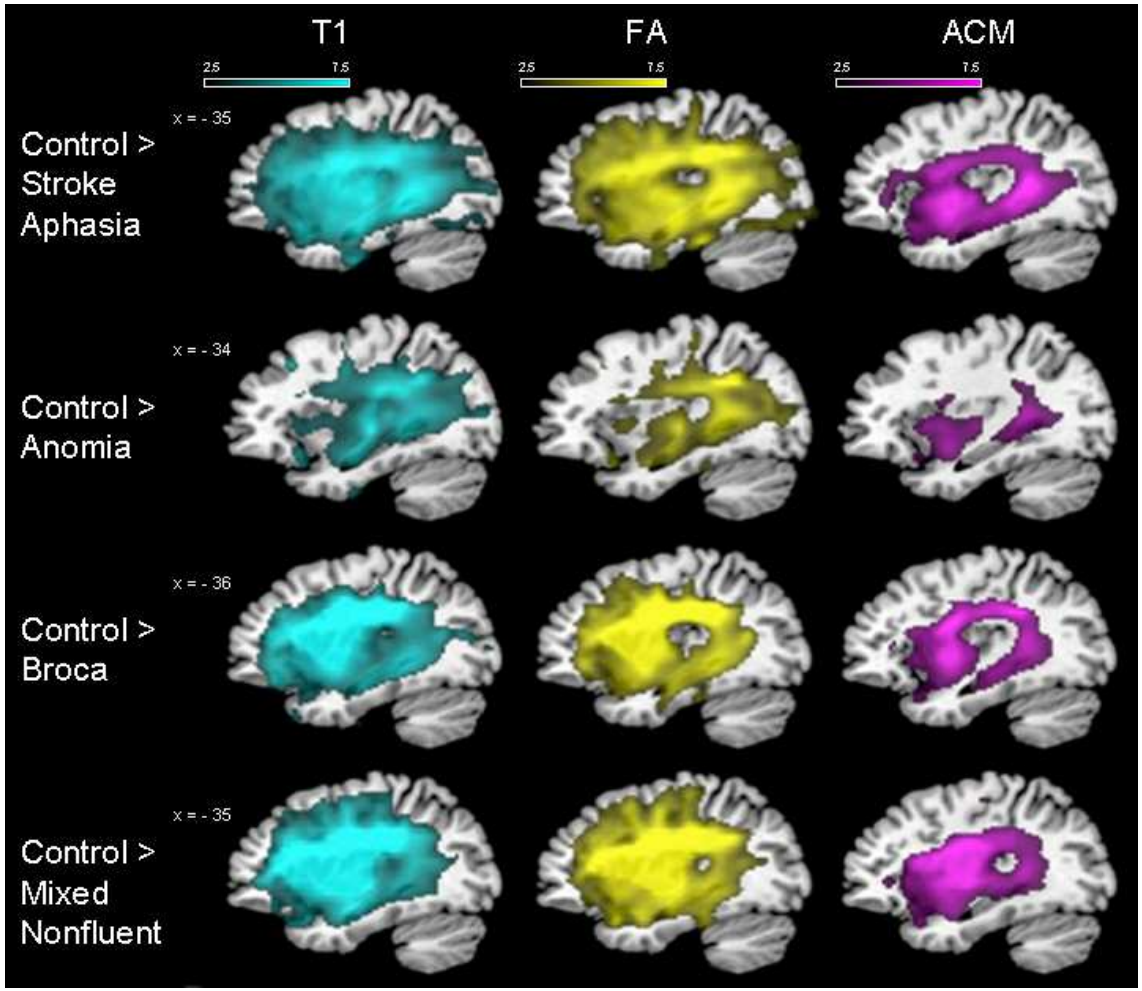

Figure 4.2. Clusters of significantly higher values in controls (n = 19) than all stroke aphasic participants (n = 31) (top row), and participants with anomia (n = 9) (second row), Broca's aphasia (n = 8) (third row), and mixed nonfluent aphasia (n = 6) (bottom row). All results are shown at $p < .001$ voxel-level, $p < 0.05$ FWE-corrected cluster-level. Cluster sizes (voxels): control > stroke aphasia = 56444 (T1), 55663 (FA), 25186 (ACM); control > anomia = 25522 (T1), 18272 (FA), 7057 (ACM); control > Broca = 36716 (T1), 32566 (FA), 16571 (ACM); control > mixed nonfluent = 40998 and 291 (T1), 43857 (FA), and 20301 (ACM). Image threshold (t) 2.5 – 7.5.

In order to explore potential positive adaptive changes, we also examined the reverse contrasts, as represented by areas of higher T1-weighted tissue concentration, FA, and ACM in stroke aphasic participants than controls. In the T1-weighted and FA analyses no significant clusters emerged. However, in the ACM analyses a cluster showing higher connectivity in the stroke aphasic group than the control group was found in the right hemisphere (see Figure 4.3). When we examined the same contrast (stroke aphasic > control) within aphasic subgroups, we found no clusters showing increased connectivity relative to controls in the nonfluent subgroups. The anomia subgroup showed a higher connectivity cluster that overlapped with the location of the cluster for the whole stroke aphasic group but was smaller (328 voxels, $p < .001$ voxel-level, $p < .05$ FWE-corrected cluster-level). The cluster of higher connectivity was largely located within the right hemisphere arcuate fasciculus (see Figure 4.3), the homologue of an important pathway in the left hemisphere language network (Parker et al., 2005) that was almost universally damaged to some extent in our sample. Our results contrast with the contralesional hemisphere changes in connectivity (as measured using network analysis) in a group of nine individuals with chronic subcortical stroke lesions (Crofts et al., 2011). The specificity of our results in terms of their location suggests that they reflect genuine consistent increases in connectivity.

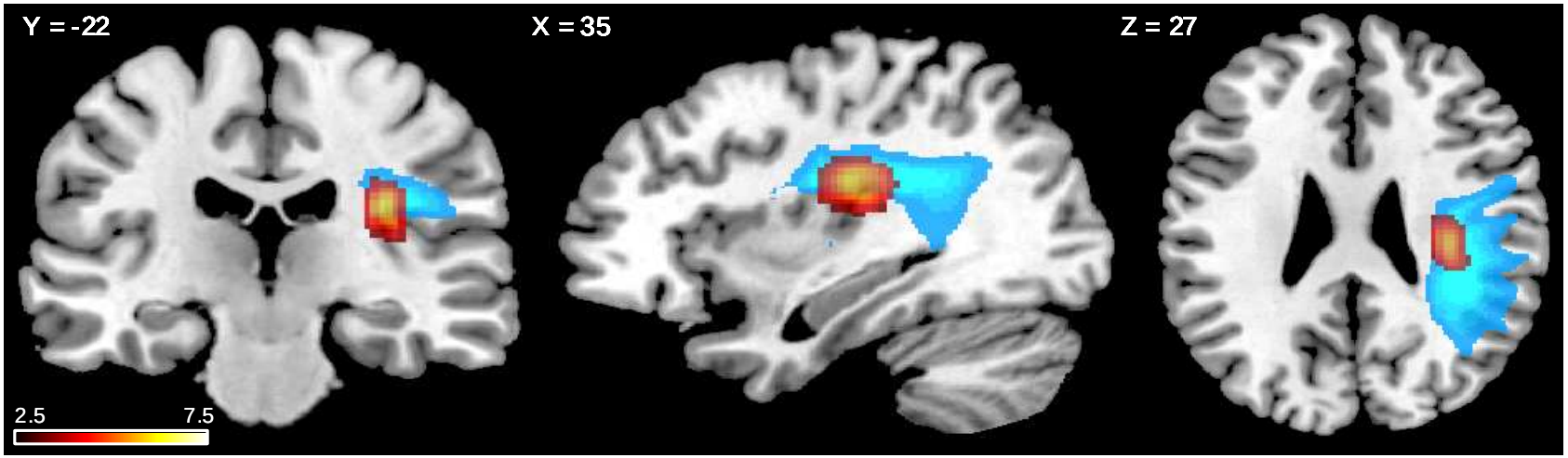

Figure 4.3. Cluster of higher anatomical connectivity in the chronic stroke aphasic group than the control group. The cluster is shown in the hot colour scale overlaid on the right hemisphere arcuate fasciculus from Catani et al.'s (2012) tractography-based atlas (http://www.natbrainlab.com/) in cyan. Results are shown at $p < .001$ voxel-level, $p < 0.05$ FWE-corrected cluster-level. Cluster size: 669 voxels. Image threshold (t) 2.5 – 7.5.

This study is the first to identify increased connectivity in chronic stroke aphasia in the right arcuate fasciculus, a homologue of a left hemisphere white matter pathway known to support language in healthy individuals (e.g., Parker et al., 2005; Saur et al., 2008). This effect appears to be driven by those participants with a diagnosis of 'anomic' aphasia, the least severe subgroup within the cohort. Given the increased right hemisphere connectivity we have identified in chronic stroke aphasic participants was most apparent in the mildest participants, this difference may represent positive adaptive changes contributing to language recovery. This is consistent with a previous study that found therapy-induced increases in the number of fibre tracking trajectories in chronic stroke aphasia along the right arcuate using targeted tractography (Schlaug et al., 2009). The mechanisms supporting these changes are not yet clear, but could potentially result from dendritic branching, synaptogenesis, or development of new white matter connections (Crofts et al., 2011).

In the current study right hemisphere changes were only found using the recently introduced technique of ACM and were not evident on voxel-level analyses of T1-weighted scans or FA maps. Our FA analyses yielded a similar pattern of results to the T1-weighted analyses. Although the two metrics capture different things it is unsurprising that the gross between-group differences were similar, as our participants had clear lesions and both measures reflect local structural changes. We have shown that ACM can be used to identify regions of both reduced and increased white matter connectivity following stroke, and as such it represents an exciting new way of understanding language processing deficits. Given its ability to reveal changes at a network level, ACM may be particularly illuminating in longitudinal studies of language recovery.

Online Methods

The study had ethical approval from the North West Multi-centre Research Ethics Committee, UK. Informed consent was obtained from all participants.

Participants

Participants in the stroke aphasic group were included if they had chronic aphasia, that is that they had an enduring impairment in producing and/or understanding spoken language and were at least 12 months post-stroke at time of scanning and assessment (*N* = 31). All participants were recruited on the basis that they reported one left hemisphere stroke (ischaemic or haemorrhagic). Exclusion criteria included: having any contraindications for scanning, being pre-morbidly left handed, having had more than one full stroke, or having any other significant neurological conditions. All participants' first language was English. For details of stroke aphasic participants, see Table 4.1 in Supplementary Information. A lesion overlap map depicting the lesion locations of the cohort is provided. The control group consisted of 19 healthy older adults (8 females, 11 males). The mean age and years of education of the control group are given in Table 4.1.

Behavioural Testing

As part of a larger battery of language assessments, the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983; Goodglass et al., 2000) was completed with all stroke aphasic participants. This allowed participants to be allocated to subgroups (e.g., 'Anomia', 'Broca' etc). The BDAE is a widely used aphasia assessment which enables classification of individuals into aphasia subgroups based on performance on tests assessing language capacities such as fluency, comprehension, and repetition.

Neuroimaging Acquisition

All scans were acquired on a 3.0 tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. A T1-weighted inversion recovery sequence with 3D acquisition was employed, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1 mm, acquired voxel size 1.0 mm x 1.0 mm x 1.0 mm, matrix size 256 x 256, FOV = 256 mm x 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

Diffusion-weighted images were acquired using a pulsed gradient spin echo (PGSE) echo planar imaging (EPI) sequence implemented with TE = 54 ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed resolution 1.875 mm x 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 43 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8 ms, δ = 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5. To minimise artefacts associated with pulsatile brain movements (Jones & Pierpaoli, 2005) the sequence was cardiac gated using a peripheral pulse unit. Acquisition time for the diffusion MRI data was approximately 28 minutes, although this varied slightly based on the participant's heart rate. Each diffusion-weighted volume was acquired entirely before starting on the next diffusion weighting, resulting in 44 temporally spaced volumes with different direction diffusion gradients. For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity *k*-space traversal, and hence reversed phase and frequency encode direction (Embleton et al., 2010). A co-localised T2-weighted turbo spin echo scan with 0.94 mm x 0.94 mm in-plane resolution and 2.1 mm slice thickness was also obtained as a structural reference scan for use in distortion correction (Embleton et al., 2010).

Neuroimaging Pre-processing

Participants' T1-weighted scans were normalised and segmented using a modified unified segmentation-normalisation procedure (Seghier et al., 2008) implemented in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Images were also smoothed with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Diffusion data were corrected for susceptibility- and eddy current-induced distortion using the distortion correction procedure described in (Embleton et al., 2010) implemented in MATLAB. The distortion-corrected diffusion-weighted images were subsequently processed using the model-based bootstrap of constrained spherical deconvolution (Haroon et al., 2009), a method based on constrained spherical deconvolution (CSD) (Tournier et al., 2007) (Tournier et al., 2008). Bootstrapped CSD produced probability density functions (PDFs) that were used as input to the tractography process used to generate ACM (Embleton et al., 2007). The probabilistic index of connectivity (PICo) tractography algorithm (Parker et al., 2003) was used for tractography, with ten probabilistic tractography streamlines launched from every voxel in each brain. FA maps were generated for each participant by fitting a single diffusion tensor to each voxel in the diffusion-weighted data. Each participant's T1-weighted image, ACM, and FA map were co-registered and normalised to MNI space using Seghier et al.'s (2008) method.

Neuroimaging Analysis using Voxel-Based Morphometry (VBM)

VBM analyses were conducted in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/), with each image type (T1-weighted, FA, ACM) analysed separately. Statistical comparisons between groups were conducted

on every brain voxel of the smoothed and normalised images. For the stroke aphasia-control comparisons these groups were simply all stroke aphasic participants compared with all controls. Analyses based on BDAE subtypes were conducted for any subtype with an $n > 5$. In these analyses the groups were the particular aphasic subgroup compared with the whole control group. The resulting images show clusters of voxels in which one group showed significantly higher values than the other group. All results are presented at $p < .001$ uncorrected at the voxel-level, $p < 0.05$ family-wise error (FWE) corrected at the cluster level. All results are displayed overlaid on the Ch2better template in MRIcron (Rorden, Karnath, & Bonilha, 2007).

To ensure that the output of the ACM analyses were not a result of stroke aphasic participants having a different number of seed voxels to controls owing to differences in overall brain size, we calculated the number of voxels in each participant's right hemisphere (the contralesional hemisphere for stroke aphasic participants). We then re-ran the ACM VBM with number of right hemisphere voxels as a covariate, but the pattern of significant results did not change.

Supplementary Information

Table 4.1

Participant Background Information

Participant	Age (years)	Gender	Years of Education	Time post-stroke (months)	BDAE Classification
1	62	M	11	110	Anomia
2	73	F	16	22	Wernicke/Conduction
3	81	M	10	56	Anomia
4	72	M	11	106	TMA
5	61	M	17	12	Anomia
6	81	M	10	24	Broca
7	59	M	12	12	TSA
8	59	M	11	103	Broca
9	49	M	17	42	Broca
10	63	M	11	13	Global
11	49	F	12	69	Anomia
12	69	M	11	39	Global
13	70	F	11	84	Anomia
14	73	M	11	190	Mixed Nonfluent
15	64	M	11	26	Mixed Nonfluent
16	68	M	11	142	Global
17	77	M	11	66	Mixed Nonfluent
18	60	M	12	23	Anomia
19	60	M	12	44	Wernicke
20	47	M	12	18	Broca
21	55	M	11	131	Broca
22	84	M	12	25	Anomia
23	48	M	12	33	Broca
24	55	M	13	31	Mixed Nonfluent

Participant	Age (years)	Gender	Years of Education	Time post-stroke (months)	BDAE Classification
25	64	F	14	181	Mixed Nonfluent
26	72	M	11	23	Anomia
27	45	F	12	12	Broca
28	78	M	12	76	Broca
29	65	M	11	81	Anomia
30	65	M	11	128	Mixed Nonfluent
31	66	M	12	59	Wernicke
Mean (SD)	64.30 (10.50)	N/A	11.97 (1.76)	63.90 (50.55)	N/A
Control Mean (SD)	68.21 (5.99)	8 F 11 M	13.07 (2.77)	N/A	N/A

CHAPTER 5

CAPTURING MULTIDIMENSIONALITY IN STROKE APHASIA: MAPPING COMPONENT ABILITIES ONTO NEURAL STRUCTURES

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Summary

Stroke aphasia is a multidimensional disorder in which there is continuous variation along multiple different underlying abilities, with the precise profile of impairments differing from individual to individual. We present a novel approach to teasing apart different aspects of aphasic performance that allows us to most effectively isolate their neural bases. Principal components analysis (PCA) was used to extract core factors underlying performance of 31 participants with chronic stroke aphasia on a detailed battery of behavioural assessments. The PCA revealed three key factors, with phonology explaining the most variance, followed by semantics, and then cognition. The use of rotated PCA rendered participants' scores on these three factors orthogonal and therefore ideal for use as simultaneous continuous predictors in a voxel-based correlational methodology (VBCM) analysis of high resolution structural scans. Phonological processing ability related to left temporo-parietal regions including Heschl's gyrus, mid to posterior middle and superior temporal gyri and superior temporal sulcus, as well as a region of white matter underlying the primary auditory cortex corresponding to part of the dorsal language pathway. The semantic factor related to left anterior to mid middle temporal gyrus, inferior temporal gyrus, and fusiform gyrus, as well as a region of white matter overlapping with the location of the ventral language pathway. Interestingly, the cognitive factor was not consistently correlated with the structural integrity of any particular region, as might be expected in light of the widely distributed nature of the regions that support executive functions. The phonological and semantic processing areas identified align well with those identified using other methodologies such as functional neuroimaging and transcranial magnetic stimulation. Our novel use of PCA allowed us to characterise participants' behavioural performance more robustly and accurately than if we had used raw scores on assessments or

diagnostic classifications. The rotation used in the PCA allowed the resulting cognitive factors to be considered simultaneously in our VBCM analysis, hence the regions that emerged are those relating uniquely to the ability of interest. In addition to improving our understanding of lesion-symptom mapping in stroke aphasia, our approach could also be used to clarify brain-behaviour relationships in other neurological disorders.

Introduction

Although aphasia is a common consequence of middle cerebral artery stroke, individual patterns of preserved and impaired language abilities are highly variable, meaning that these individuals form a very heterogeneous clinical group. The major determinant of individual performance profiles in stroke aphasia is the location and extent of their lesion. In attempting to relate stroke aphasic performance to underlying neural damage, however, three challenges emerge: 1) mapping performance on neuropsychological tests to underlying abilities; 2) consideration of co-occurring deficits within individual participants; and 3) identification of the neural regions that uniquely support a given ability. The current study aimed to unpack the nature of the behavioural impairments in stroke aphasia and to locate their neural substrates using a novel approach to overcome these challenges. Our approach applies data reduction techniques to detailed neuropsychological assessments to identify independent underlying abilities that can then be directly related to the neural regions that support them. Use of this technique allows the multidimensional nature of stroke aphasia to be taken into account in the imaging analysis, which in turns permits us to identify brain areas key for a given function more accurately than analyses based upon individual tests or diagnostic classifications.

Previous behavioural research has identified dissociable semantic and phonological aspects of aphasic performance. Lambon Ralph, Moriarty, and Sage (2002) found that a large proportion of variance in naming accuracy and error types could be accounted for by the integrity of phonological and semantic representations in a case-series of 21 individuals with aphasia. Using computational modelling, Schwartz, Dell, Martin, Gahl, and Sobel (2006) demonstrated that a model in which lesions were either applied to phonological or semantic components could account for a large proportion of variance in behavioural performance of 94 participants with aphasia. In addition to phonological and semantic factors, general cognitive ability has been found to affect

aphasic performance. A recent study found that the success of anomia therapy in a case-series of 33 aphasic participants was reliably predicted by two overarching factors, their phonological ability and their cognitive ability (Lambon Ralph, Snell, Fillingham, Conroy, & Sage, 2010).

At a neuroanatomical level, the distinction between phonological and semantic aspects of aphasic performance could reflect a) differences in extent of damage to dorsal (phonological) versus ventral (semantic) white matter language pathways (e.g., Hickok & Poeppel, 2004, 2007; Kümmerer et al., 2013; Saur et al., 2008; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011) or b) integrity of perisylvian (phonological) versus extrasylvian (semantic) brain regions (Ardila, 2010; Henry, Beeson, Stark, & Rapcsak, 2007; Price, Moore, Humphreys, & Wise, 1997). In keeping with these proposals, speech production performance has been found to correlate with lesions to perisylvian grey and white matter (Borovsky, Saygin, Bates, & Dronkers, 2007; Schwartz, Faseyitan, Kim, & Coslett, 2012) and semantic errors in naming performance have been associated with lesions to the anterior to mid MTG and temporal pole (Schwartz et al., 2009) and electro-stimulation of ventral white matter pathways (e.g., Duffau et al., 2005).

Here we present a novel approach to isolating different cognitive abilities underlying chronic aphasic performance and to identifying their neural substrates. Detailed behavioural data from a case-series of individuals with relatively heterogeneous stroke aphasic profiles are entered into a Principal Components Analysis (PCA). This data reduction technique allows extraction of the underlying factors which best explain the variation in the set of data. PCA derived factor scores therefore reflect participants' core abilities from their raw scores on a range of behavioural assessments. The type of PCA used in the current study uses varimax rotation, meaning that the extracted factors are more easily interpretable (in terms of their psychological meaning as indicated by loadings of the underlying tests) and that they are orthogonal to one another. This latter

feature allows us to simultaneously enter participants' scores on each factor into a voxel-wise analysis with their structural neuroimaging data. This yields a set of statistical parametric maps showing brain regions where tissue concentration relates to core language abilities, such as phonological or semantic ability.

Using PCA factor scores as predictors of lesion data offers a number of important advantages over analyses based upon individual tests or diagnostic classifications. The PCA approach capitalises on the additional reliability offered by multiple tests, whilst at the same time incorporating an assumption that any particular test involves a variety of underlying abilities. To take the example of picture naming, a widely used neuropsychological assessment, additional sensitivity can be obtained by using more than one test as different versions vary in difficulty (e.g., the Boston Naming Test versus the 64-item Cambridge Naming Test). Both measures cannot, however, be entered as predictors in an imaging analysis as they will be correlated, introducing issues around collinearity. Moreover, it is obvious that picture naming tests draw on both phonological and semantic processing, hence the functional role of neural regions simply associated with picture naming is not clear. By combining multiple behavioural assessments with PCA, we obtain the additional sensitivity of multiple tests, each of which can load onto more than one underlying factor, thereby reflecting their multifaceted nature. By then applying varimax rotation to our PCA, we achieve factor scores that are orthogonal, avoiding the problem of collinearity.

As the orthogonal factor scores generated by PCA can be entered simultaneously as predictors in an imaging analysis, this permits identification of the key neural regions supporting a given function more accurately than analyses based upon diagnostic classifications. Aphasic subtypes derived from classification systems such as the Boston Diagonostic Aphasia Examination (BDAE) (Goodglass et al., 2000) or the Western Aphasia Battery (Kertesz, 1982) are clearly useful clinical tools for capturing an

individual's performance profile. However, they are limited in their capacity to identify specific brain regions uniquely associated with core language abilities. Figure 5.1 shows areas of significantly lower tissue concentration in subsets of our participants with different aphasia classifications compared to controls using a standard voxel-based morphometry (VBM) approach (see Supplementary Information for Details). It is clear from Figure 5.1 that while the location of lesions associated with different subtypes is sensible and accords with what we know concerning the functional neuroanatomy of language processing, there is nevertheless a large proportion of overlap between subtypes. Through entering all the orthogonal factors identified in a rotated PCA simultaneously, this shared overlap is removed and the areas uniquely associated with a particular underlying cognitive ability are revealed.

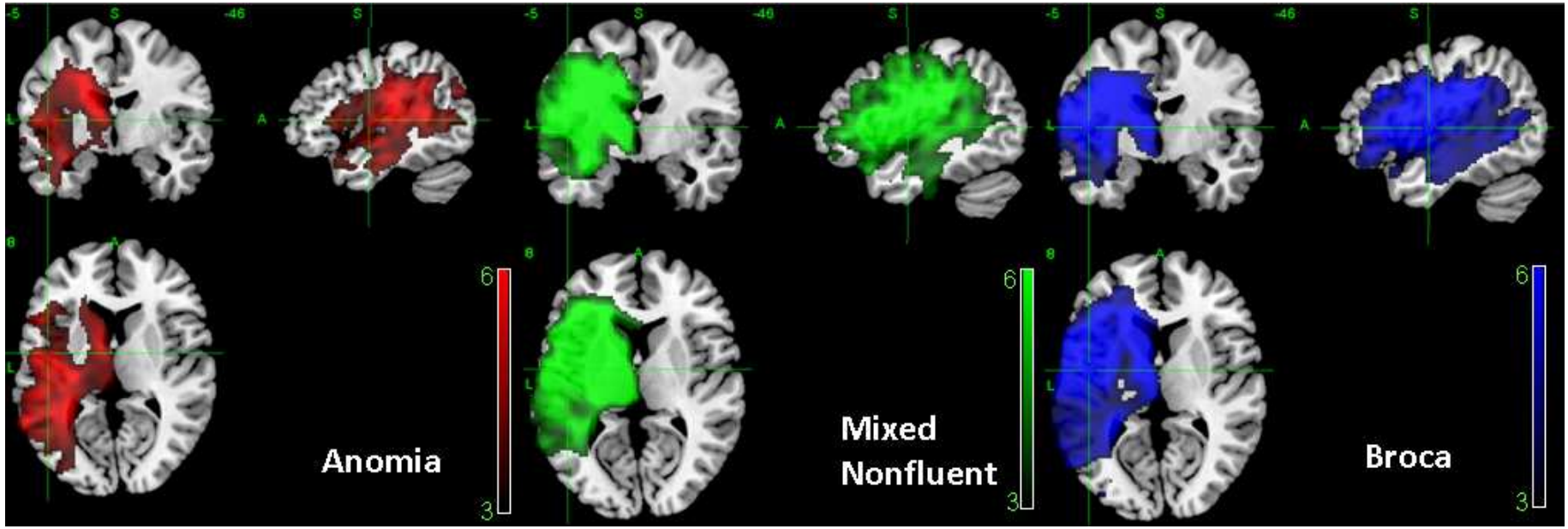

Figure 5.1. Results of VBM analysis comparing tissue concentration of aphasic participants with anomic (n = 9), Broca's (n = 8), and mixed nonfluent (n = 6) aphasia to healthy older controls (n = 19). Image threshold (t) 3.0 – 6.0. Results are presented at $p < 0.001$ voxel-level, $p < 0.001$ FWE-corrected cluster-level. Analyses were not conducted for aphasic subgroups with $n < 5$ participants (global = 3, TMA = 1, TSA = 1, Wernicke's = 2, Wernicke's/Conduction = 1). For details of the VBM procedure, see Supplementary Information. All neuroimaging results are shown overlaid on the Ch2better template in MRIcron (Rorden, Karnath, & Bonilha, 2007).

Our approach therefore marries two lines of investigation which have co-existed in the aphasia literature, the aforementioned behavioural studies which have sought to characterise the underlying factors determining aphasic performance, and the lesion-symptom mapping literature, which has provided valuable insights into the neurological correlates of aphasic symptoms. Lesion-symptom mapping has, in recent years, primarily advanced via the use of voxel-level statistical analyses which compare the tissue integrity of different individuals. The fact that analyses are carried out over the whole-brain and without the need for *a priori* hypotheses regarding regions of tissue difference means that voxel-wise methods are a relatively unbiased way of determining lesion-symptom mappings (Ashburner & Friston, 2000; Draganski & May, 2008; although see Jones, Symms, Cercignani, & Howard, 2005). Furthermore, the very fact that analyses are carried out at the voxel-level means a relatively high degree of anatomical accuracy can be achieved using such methods (Rorden & Karnath, 2004).

Many studies employing the VBM methodology (as utilised in generation of Figure 5.1) split participants into subgroups, for example into individuals who perform within normal limits and those who perform outside normal limits on a given assessment. This produces a statistical parametric map illustrating regions of significantly differing tissue concentrations between groups (Ashburner & Friston, 2000). A variation on the VBM approach which has been widely used in studies of stroke aphasia in recent years is voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003). In VLSM continuous scores on a behavioural measure are compared between individuals with and without lesions to that particular voxel. The output of a VLSM analysis is a statistical parametric map showing which brain voxels are significantly related to performance on the given behavioural measure (Bates et al., 2003; Saygin et al., 2004). The VLSM approach, therefore, affords a more graded measure of all participants' performance than the dichotomy imposed by more traditional VBM. The method employed in the current study

is voxel-based correlational methodology (VBCM) (Tyler et al., 2005a). VBCM, like VLSM, uses continuous behavioural measures to correlate with lesion data. However, VBCM also employs continuous measures of tissue concentration rather than binary values for each brain voxel. Rather than classifying each brain voxel as lesioned or non-lesioned, in VBCM the signal intensity value for each voxel is used as the brain measure to correlate with continuous behavioural measures.

In the current study participants were not recruited on the basis of having specific aphasia types or symptoms. Our aim was to obtain a representative cohort of individuals with chronic stroke aphasia, and as such, our sample was necessarily heterogeneous in terms of their behavioural profiles. Voxel-wise analysis methods require variance in both the behavioural measures used as predictors and the integrity of brain tissue across different regions. In this sense, the variability across individuals in terms of their behavioural performance and their lesion location increases the power of the design, over and above the additional power offered by the larger numbers recruited via a general rather than selective strategy. Through combining data obtained from a detailed neuropsychological assessment of each participant using rotated PCA, we aimed to extract the key underlying dimensions of variation. We then used these factors as simultaneous predictors in a VBCM analysis to effectively isolate the neural regions uniquely associated with each of these multiple cognitive dimensions.

Materials and Methods

Participants

Participants were recruited from the North West of England via Speech and Language Therapy services and presentations at stroke groups. Participants were included if they had chronic stroke aphasia, that is that they had an enduring impairment in producing and/or understanding spoken language and were at least 12 months post-stroke at time of scanning and assessment (N = 31). All participants were recruited on the basis that they reported one left hemisphere stroke, either ischaemic or haemorrhagic. Participants were excluded if they had any contraindications for scanning, were pre-morbidly left handed, had had more than one full stroke, or had any other significant neurological conditions. All participants had English as their first language. For demographic details of participants, see Table 5.1. Informed consent was obtained from all participants prior to participation under approval from the North West Multi-centre Research Ethics Committee, UK.

Table 5.1

Participant Background Information

	Initials	**Age (years)**	**Gender**	**Years of Education**	**Time post-stroke (months)**	**BDAE Classification**
1	JM	62	M	11	110	Anomia
2	PE	73	F	16	22	Wernicke/Conduction
3	HN	81	M	10	56	Anomia
4	DS	72	M	11	106	TMA
5	EB	61	M	17	12	Anomia
6	KW	81	M	10	24	Broca

	Initials	Age (years)	Gender	Years of Education	Time post-stroke (months)	BDAE Classification
7	KS	59	M	12	12	TSA
8	BS	59	M	11	103	Broca
9	DM	49	M	17	42	Broca
10	LM	63	M	11	13	Global
11	AL	49	F	12	69	Anomia
12	ES	69	M	11	39	Global
13	JMf	70	F	11	84	Anomia
14	JSa	73	M	11	190	Mixed Nonfluent
15	BH	64	M	11	26	Mixed Nonfluent
16	ESb	68	M	11	142	Global
17	WM	77	M	11	66	Mixed Nonfluent
18	TJ	60	M	12	23	Anomia
19	DB	60	M	12	44	Wernicke
20	GL	47	M	12	18	Broca
21	AG	55	M	11	131	Broca
22	JJ	84	M	12	25	Anomia
23	KK	48	M	12	33	Broca
24	KL	55	M	13	31	Mixed Nonfluent
25	ER	64	F	14	181	Mixed Nonfluent
26	JSb	72	M	11	23	Anomia
27	DCS	45	F	12	12	Broca
28	JSc	78	M	12	76	Broca
29	LH	65	M	11	81	Anomia
30	JA	65	M	11	128	Mixed Nonfluent
31	DBb	66	M	12	59	Wernicke

Neuropsychological Assessments

In addition to the BDAE (Goodglass et al., 2000; Goodglass & Kaplan, 1983), a battery of language assessments was administered to assess participants' input and output phonological processing, semantic processing, and sentence comprehension, as well as more general cognitive function. Assessments were conducted with participants over several testing sessions, with the pace and number determined by the participant.

The language assessments included a variety of subtests from the PALPA (Kay et al., 1992): same-different auditory discrimination using nonword minimal pairs (PALPA 1); same-different auditory discrimination using word minimal pairs (PALPA 2); immediate repetition of nonwords (PALPA 8); delayed repetition of nonwords (PALPA 8); immediate repetition of words (PALPA 9); and delayed repetition of words (PALPA 9). A number of tests from the Cambridge 64- items Semantic Battery (Bozeat et al., 2000) were also included: the spoken word-to-picture matching task, the written word-to-picture matching task; the picture version of the Camel and Cactus Test; and the picture naming test. In order to increase sensitivity to mild naming deficits, the 60-item Boston Naming Test (BNT) (Kaplan et al., 1983) was also used. Similarly, to increase sensitivity to subtle semantic deficits, a 96-trial synonym judgement test with words presented in spoken and written form (Jefferies, Patterson, Jones, & Lambon Ralph, 2009) was also used. In order to capture syntax level deficits, the spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT; Swinburn, Porter, & Howard, 2005) was included. The additional cognitive tests included forward and backward digit span (Wechsler, 1987); the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997); and Raven's Coloured Progressive Matrices (Raven, 1962).

Analysis of Neuropsychological Assessment Data

On language assessments, apart from the CAT sentence comprehension test (Swinburn et al., 2005), participants were scored on their first response. Within the CAT two points are given for each prompt correct response and one point is given for delayed correct responses or self-corrections. For the two naming assessments participants' responses were marked correct if they were given within five seconds of presentation. Minor dysfluencies in responses were accepted as correct. Repetition of auditory stimuli was provided if requested by participants.

Principal Components Analysis

Participants' scores on all assessments were entered into a Principal Components Analysis (PCA) with varimax rotation. All participants' scores on all tests were entered into the PCA in SPSS 16.0. Factors with an eigenvalue of 1.0 and above were extracted and then rotated. Following rotation, considering the factor loadings of each test in the battery allows us to interpret what psychological process is represented by that factor. Individual participants' scores on each factor were then used as behavioural covariates in the neuroimaging analysis.

Acquisition of Neuroimaging Data

High resolution structural T1-weighted Magnetic Resonance Imaging (MRI) scans were acquired on a 3.0 tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. A T1-weighted inversion recovery sequence with 3D acquisition was employed, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1 mm, acquired voxel size 1.0 x 1.0 x 1.0 mm^3, matrix size 256 x

256, FOV = 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

Analysis of Neuroimaging Data

Participants' MRI scans were normalised and segmented using a modified unified segmentation-normalisation procedure optimised for lesioned brains (Seghier et al., 2008) implemented in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Images were also smoothed with an 8mm full-width-at-half-maximum (FWHM) Gaussian kernel. Smoothed and normalised T1-weighted images were used in the lesion analyses described below.

Voxel-Based Correlational Methodology

Brain regions where tissue concentration correlated with PCA factor scores were assessed using VBCM (Tyler et al., 2005a). The VBCM analysis, which was also implemented in SPM8, involved regressing continuous behavioural measures against tissue concentrations for each brain voxel in each participant. Aphasic participants' scores on the orthogonal factors from the PCA were simultaneously entered as the continuous behavioural covariates. The output denotes in which voxels variation in tissue concentration corresponds to the variance in a given principle component, whilst controlling for variation in the other factors. In this way, VBCM revealed areas of the brain where tissue concentration covaried uniquely with a behavioural factor.

Results

Neuropsychological Assessments

Participants' scores on the behavioural assessment battery are given in Table 5.2, with participants ordered according to their performance on the Boston Naming Test. The heterogeneity of the cohort is evident from participants' broad range of scores on the assessment battery. The diversity of both the severity and character of deficits shown by this group can be appreciated from the fact that there are individuals who perform below normal limits on all tests in the assessment battery (e.g., DBb) and those who only fall below normal limits on the more difficult, sentence level assessment (e.g., JMf). Between these two extremes lie many participants whose performance on a subset of tests is impaired, whilst other tests are performed within normal limits.

Table 5.2

Participants' Scores on the Behavioural Assessment Battery

	Nonword Repetition: Immediate	Nonword Repetition: Delayed	Word Repetition: Immediate	Word Repetition: Delayed	64-Item Naming	Boston Naming Test	Nonword Minimal Pairs	Word Minimal Pairs	Spoken Word to Picture Matching	Written Word to Picture Matching	CAT Spoken Sentence Comprehension	96 Synonym Judgement	Camel and Cactus Test: Pictures	Brixton Spatial Anticipation Test[a]	Raven's Coloured Progressive Matrices[b]	Forward Digit Span[a]	Backward Digit Span[a]	PHON F1	SEM F2	COG F3
DBb	**0.00**	**0.00**	**37.50**	**0.00**	**0.00**	**0.00**	**22.22**	**52.78**	**57.81**	**31.25**	**12.50**	**48.96**	**53.13**	**38.18**	**30.56**	**25.00**	**0.00**	-0.33	-2.32	-2.02
ES	**0.00**	**0.00**	**0.00**	**0.00**	**4.69**	**0.00**	**48.61**	**54.17**	**78.13**	**90.63**	**25.00**	**72.92**	**73.44**	**40.00**	66.67	**0.00**	**0.00**	-1.08	-0.70	-1.91
ESb	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**54.17**	**50.00**	**87.50**	**60.94**	**34.38**	**52.08**	**43.75**	**23.64**	38.89	**0.00**	**0.00**	-1.67	-0.27	-0.33
KW	**0.00**	**0.00**	**3.75**	**0.00**	**1.56**	**0.00**	**75.00**	**65.28**	**95.31**	**92.19**	**84.38**	**82.29**	89.06	50.91	80.56	**50.00**	42.86	-1.21	-0.20	0.97
BS	**3.33**	**0.00**	**5.00**	**1.25**	**3.13**	**1.67**	**65.28**	**75.00**	**92.19**	100.00	**31.25**	**78.13**	**84.38**	**38.18**	91.67	**0.00**	**0.00**	-1.94	0.27	0.68
KL	**0.00**	**0.00**	**6.25**	**0.00**	**4.69**	**1.67**	**75.00**	**77.78**	**92.19**	98.44	**28.13**	**68.75**	**78.13**	61.82	88.89	**0.00**	**0.00**	-1.81	-0.07	0.97
LM	**13.33**	**3.33**	**27.50**	**0.00**	**1.56**	**1.67**	**43.06**	**54.17**	**67.19**	**53.13**	**28.13**	**57.29**	**68.75**	**32.73**	61.11	**0.00**	**0.00**	-0.87	-1.68	-0.77
DB	70.00	**30.00**	**85.00**	**83.75**	**7.81**	**8.33**	87.50	**58.33**	**64.06**	**76.56**	**31.25**	**59.38**	**82.81**	**40.00**	86.11	**37.50**	**14.29**	0.32	-2.30	0.59
PE	**13.33**	**3.33**	**45.00**	**41.25**	**20.31**	**11.67**	**77.78**	86.11	96.88	100.00	**50.00**	**79.17**	**84.38**	**41.82**	80.56	**25.00**	28.57	-1.07	0.36	0.46
KS	73.33	80.00	93.75	95.00	**31.25**	**13.33**	94.44	95.83	**71.88**	**67.19**	**84.38**	**84.38**	**68.75**	52.73	86.11	100.00	57.14	1.73	-2.40	0.72
KK	**33.33**	**3.33**	**56.25**	**26.25**	**42.19**	**15.00**	**72.22**	95.83	**93.75**	**95.31**	**46.88**	**81.25**	**84.38**	76.36	100.00	**0.00**	**0.00**	-1.21	0.16	1.32
WM	**36.67**	**30.00**	**55.00**	**41.25**	**39.06**	**25.00**	**47.22**	**63.89**	**92.19**	**75.00**	**50.00**	**61.46**	**51.56**	**43.64**	61.11	**37.50**	28.57	-0.04	-0.53	-1.34
GL	93.33	63.33	100.00	**81.25**	**68.75**	**31.67**	98.61	97.22	96.88	**95.31**	**65.63**	**75.00**	**73.44**	58.18	91.67	**37.50**	28.57	0.62	-0.36	0.58
DCS	**40.00**	56.67	**72.50**	**68.75**	**67.19**	**43.33**	97.22	97.22	100.00	98.44	**93.75**	91.67	95.31	81.82	100.00	62.50	57.14	0.21	0.05	1.68
JSa	**30.00**	**3.33**	**75.00**	**65.00**	**62.50**	**46.67**	**75.00**	**77.78**	**92.19**	98.44	**59.38**	**81.25**	**76.56**	67.27	83.33	**50.00**	28.57	-0.32	0.31	0.23

	Nonword Repetition: Immediate	Nonword Repetition: Delayed	Word Repetition: Immediate	Word Repetition: Delayed	64-Item Naming	Boston Naming Test	Nonword Minimal Pairs	Word Minimal Pairs	Spoken Word to Picture Matching	Written Word to Picture Matching	CAT Spoken Sentence Comprehension	96 Synonym Judgement	Camel and Cactus Test: Pictures	Brixton Spatial Anticipation Test[a]	Raven's Coloured Progressive Matrices[b]	Forward Digit Span[a]	Backward Digit Span[a]	PHON F1	SEM F2	COG F3
JSc	**36.67**	63.33	**90.00**	91.25	**71.88**	**53.33**	**75.00**	86.11	98.44	98.44	**75.00**	**76.04**	**82.81**	**43.64**	77.78	62.50	42.86	0.42	0.36	-0.26
JA	**36.67**	**40.00**	**85.00**	**78.75**	**79.69**	**63.33**	90.28	95.83	100.00	98.44	**78.13**	**63.54**	87.50	61.82	80.56	**37.50**	**0.00**	-0.12	0.59	0.31
JJ	**36.67**	**23.33**	**82.50**	**73.75**	**85.94**	**63.33**	**51.39**	**80.56**	98.44	98.44	**56.25**	93.75	**53.13**	**43.64**	41.67	62.50	42.86	0.24	1.43	-2.20
JM	83.33	83.33	100.00	98.75	**81.25**	**63.33**	93.06	95.83	100.00	100.00	100.00	**82.29**	**81.25**	76.36	94.44	**50.00**	57.14	0.99	-0.05	0.86
JSb	63.33	**36.67**	**86.25**	**81.25**	**75.00**	**63.33**	**76.39**	88.89	**93.75**	**90.63**	**84.38**	**75.00**	**78.13**	60.00	86.11	62.50	28.57	0.47	0.01	0.12
ER	**53.33**	**36.67**	**70.00**	**81.25**	**71.88**	**65.00**	81.94	88.89	**95.31**	**93.75**	**56.25**	**84.38**	90.63	**41.82**	38.89	**25.00**	**0.00**	-0.24	1.34	-1.09
HN	**36.67**	**23.33**	**83.75**	**80.00**	**65.63**	**65.00**	**77.78**	**76.39**	**93.75**	**93.75**	**37.50**	**85.42**	**85.94**	**25.45**	75.00	**50.00**	42.86	-0.09	0.71	-0.69
BH	86.67	80.00	100.00	96.25	95.31	**66.67**	93.06	94.44	98.44	**93.75**	**78.13**	**83.33**	**73.44**	67.27	66.67	62.50	57.14	1.20	0.22	-0.30
EB	83.33	**53.33**	100.00	100.00	**81.25**	**66.67**	94.44	98.61	98.44	100.00	**71.88**	94.79	90.63	80.00	100.00	75.00	57.14	0.76	0.17	1.15
DM	**60.00**	**10.00**	**73.75**	**68.75**	**75.00**	**71.67**	80.56	93.06	98.44	98.44	**56.25**	95.83	98.44	50.91	91.67	**37.50**	**0.00**	-0.61	1.27	0.42
DS	**56.67**	**33.33**	**88.75**	91.25	**84.38**	**73.33**	**79.17**	**77.78**	100.00	100.00	87.50	93.75	89.06	72.73	72.22	**50.00**	28.57	0.13	1.05	0.04
AG	73.33	83.33	**77.50**	**87.50**	**87.50**	78.33	100.00	98.61	100.00	100.00	87.50	**89.58**	**75.00**	56.36	75.00	100.00	100.00	1.42	0.21	-0.06
LH	**56.67**	**50.00**	**82.50**	88.75	**81.25**	78.33	95.83	97.22	96.88	100.00	90.63	92.71	87.50	76.36	88.89	87.50	57.14	0.70	0.35	0.81
JMf	93.33	66.67	96.25	98.75	96.88	80.00	90.28	95.83	100.00	100.00	**71.88**	91.67	93.75	50.91	83.33	62.50	57.14	0.81	0.74	0.11
AL	90.00	90.00	100.00	98.75	**93.75**	88.33	91.67	100.00	100.00	100.00	**84.38**	93.75	**79.69**	60.00	91.67	87.50	85.71	1.45	0.26	0.23
TJ	93.33	83.33	98.75	92.50	95.31	95.00	87.50	98.61	98.44	100.00	**68.75**	**88.54**	**70.31**	52.73	50.00	75.00	28.57	1.14	1.03	-1.29

Scores are given as percentages. Scores in bold fall below the cut-off for normal performance. The cut-off was calculated as 2 standard deviations below the mean performance of a group of 13 control participants (see Supplementary Information for details). a. Cut-off based on published norms. b. No cut-off available. PHON = phonological factor; SEM = semantic factor; COG = cognitive factor.

Principal Components Analysis

Identifying Underlying Abilities: The rotated PCA produced a three factor solution which accounted for 82% of variance in participants' performance (F1= 61%; F2 = 14%, F3 = 7%). The factor loadings of each of the different behavioural assessments are given in Table 5.3, with individual participants' scores on each factor provided in Table 5.2. Tasks which tapped input and/or output phonology (e.g., delayed nonword repetition) loaded heavily on Factor 1, hence we refer to this factor as 'Phonology'. Factor 2 was interpreted as 'Semantics' as the assessments that loaded heavily on it were those involving processing of word meanings (e.g., spoken word-to-picture matching). The two naming assessments loaded heavily on both of these factors, as they clearly require intact phonological and semantic processing to be performed successfully. Raven's Coloured Progressive Matrices (Raven, 1962), a test of nonverbal reasoning, loaded very heavily on Factor 3. The other assessments that loaded heavily on Factor 3 all recruit general cognitive processing abilities, involving modality independent choice, discrimination or reasoning, hence it was interpreted as the 'Cognition' factor.

Capturing Global Severity: It is worth noting that when the behavioural data were entered into an unrotated PCA, all tests in the battery loaded heavily on the first unrotated factor, a factor that can be interpreted as reflecting each participant's overall level of impairment. This unrotated factor does not capture anything regarding which aspects of language processing a participant is impaired on, but just gives an overall measure of their aphasic severity. This unrotated 'severity' factor correlated highly with the phonological factor from the rotated PCA ($r = 0.766$), and to a lesser extent with the semantic and cognitive factors ($r = 0.500$ and $r = 0.405$, respectively). This suggests that

in this group of individuals with stroke aphasia, severity maps quite closely onto the level of phonological processing impairment.

Table 5.3

Loadings of Behavioural Assessments on Factors Extracted from the Rotated PCA

	Factor 1 Phonology	Factor 2 Semantics	Factor 3 Cognition
Minimal Pairs - Nonwords	**0.581**	0.302	**0.642**
Minimal Pairs - Words	**0.600**	0.498	0.472
Immediate Repetition - Nonwords	**0.868**	0.189	0.188
Delayed Repetition - Nonwords	**0.917**	0.116	0.142
Immediate Repetition - Words	**0.872**	0.247	0.122
Delayed Repetition - Words	**0.868**	0.336	0.162
64-Item Naming	**0.725**	**0.646**	0.051
Boston Naming Test	**0.688**	**0.649**	-0.094
Spoken Word to Picture Matching	0.206	**0.865**	0.259
Written Word to Picture Matching	0.129	**0.799**	0.488
96 Synonym Judgement	0.414	**0.665**	0.364
Camel and Cactus Test: Pictures	0.011	0.419	**0.731**
CAT Spoken Sentence Comprehension	**0.681**	0.339	0.413
Brixton Spatial Anticipation Test	0.357	0.241	**0.654**
Raven's Coloured Progressive Matrices	0.090	0.057	**0.938**
Forward Digit Span	**0.882**	0.139	0.132
Backward Digit Span	**0.764**	0.132	0.219

Note: Factor loadings over 0.500 are given in bold.

Relationship to Subtypes: Each participant's relative abilities across different domains can be determined by examining their scores on the three factors provided in Table 5.2, with their relationship to BDAE classifications (Goodglass et al., 2000; Goodglass & Kaplan, 1983) provided in Figure 5.2. Figure 5.2A depicts performance for those participants with a score below the median on the cognitive factor, while Figure 5.2B shows those with a score equal to or higher than the median. The majority of participants sit in the multidimensional space in the areas that would be predicted based on their BDAE aphasia subtype, which determines the colour of their datapoint. For example, all of the individuals classified as having global aphasia are plotted in the lower left

quadrant of Figure 5.2A, suggesting relatively impaired phonological, semantic, and cognitive performance. Similarly, the only participant in the cohort who was classified as having transcortical sensory aphasia (TSA) is plotted in the lower right quadrant of Figure 5.2B. This participant's factor scores map exactly on to the prototypical behavioural profiles expected from a participant with TSA, in that his performance on phonological tests is relatively spared, whilst his performance on semantic tasks is impaired.

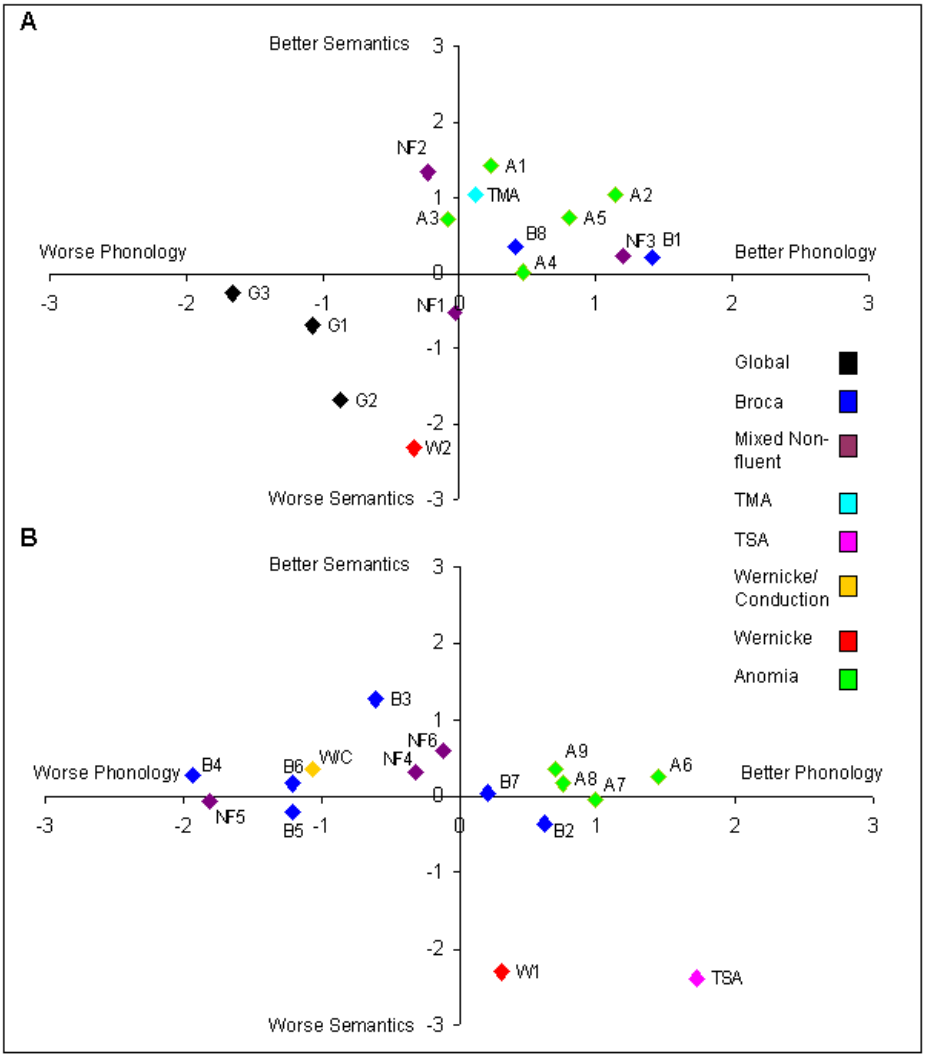

Figure 5.2. Scores of participants on phonological and semantic factors, split by performance on the cognitive factor with participants with lower cognitive scores in (A) and participants with higher cognitive scores in (B). Colour coding reflects participants' aphasia classifications. Which participant is denoted by which data point is detailed in Supplementary Information.

Whilst there is some consistency between the BDAE subtypes and the individuals' performance on the PCA factors, there is nevertheless considerable variation within these subtypes, which is evident in Figures 5.2A and 5.2B. For example, the participants classified as having Broca's aphasia show widely varying phonological performance and little variation in their semantic performance. This illustrates the fact that phonological ability can vary widely within the Broca's aphasia profile, and this difference in severity of phonological impairment is clearly relevant when it comes to considering neural bases. It would seem that labelling individuals with aphasia subtypes cannot capture this variance, whereas if participants' rotated factor scores are examined, their relative pattern of impaired and spared abilities can be better appreciated in the context of the overall group.

By plotting participants according to their factor scores it is evident that in addition to variation within aphasia subtypes, there is blurring of the boundaries between subtypes. For example, there is considerable overlap between the space occupied by individuals with Broca's aphasia and those with mixed nonfluent aphasia, demonstrating the fact that these aphasic categories are not mutually exclusive in terms of the deficits in the underlying abilities that produce them. Furthermore, for certain subtypes, such as mixed nonfluent aphasia, there does not appear to be a consistent pattern of performance. This demonstrates the heterogeneity of individuals who may receive the same diagnostic classification from systems such as the BDAE (or the Western Aphasia Battery, Kertesz [1982]), which of course limits conclusions that can be drawn about the neural bases of language processing from lesion-symptom mappings that rely on such subtypes.

Lesion Overlap: A lesion overlap map for stroke aphasic participants is provided in Figure 5.3, and covers the large left hemisphere area supplied by the middle cerebral artery (Phan et al., 2005). The maximum number of participants who had a lesion in any one voxel was 26, hence there is no area in which tissue concentration was at floor across the cohort.

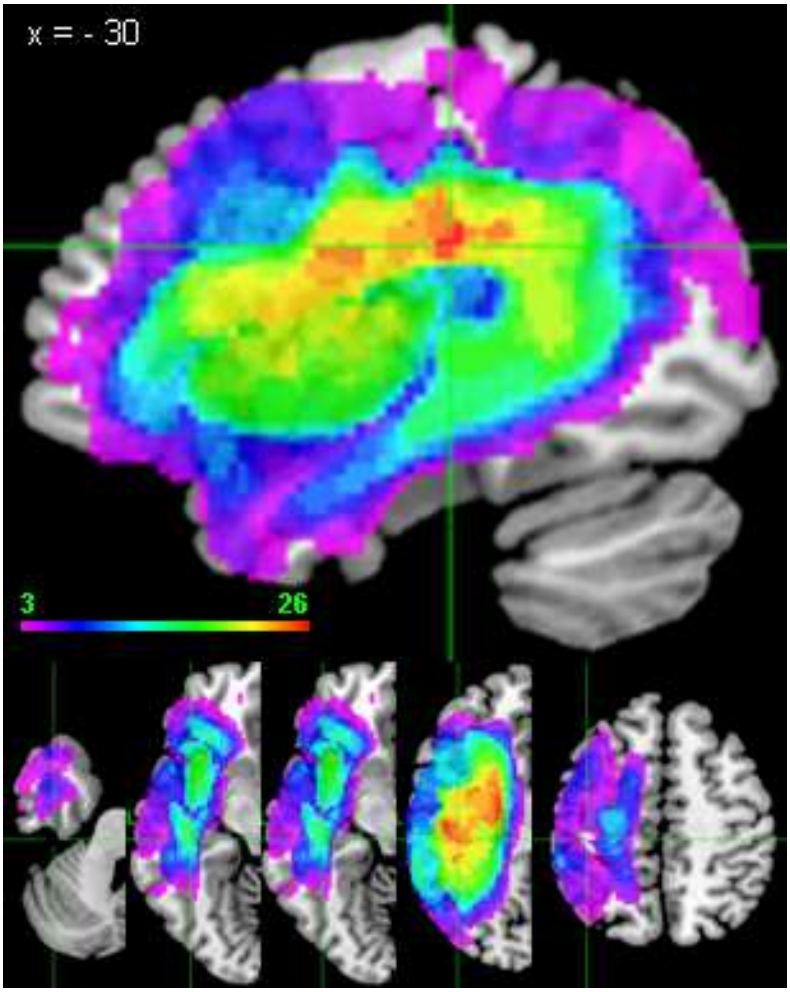

Figure 5.3. Lesion overlap map showing the distribution of participants' lesions (*N* = 31). Lesions were identified using Seghier et al.'s (2008) automated software (see Supplementary Information for details). Colour scale indicates number of participants with lesion in that voxel. Sagittal view x = -40, axial slices (left to right) z = -30, -10, 0, 30, 50.

Factor-Lesion Mapping: To ascertain which brain regions supported each underlying ability, participants' factor scores were entered simultaneously into a VBCM analysis (Tyler et al., 2005a) with their structural T1-weighted scans. The resulting maps, given in Figure 5.4, show voxels in which tissue concentration covaries uniquely with factor score. Results are given at $p < 0.001$ voxel-level, $p \leq 0.001$ family-wise error (FWE) - corrected cluster-level.

Performance on the phonological factor was correlated with voxels across a number of left hemisphere regions, principally primary auditory cortex (BA41 and 42). The cluster included the mid to posterior medial and superior temporal gyri (MTG and STG) and superior temporal sulcus (STS). It also included posterior portions of the insula, Heschl's gyrus and the planum temporale. The phonological cluster also overlapped with white matter regions, the location which appears to encompass part of the arcuate fasciculus, a key aspect of the dorsal language pathway (e.g., Catani & ffytche, 2005; Catani, Jones, & ffytche, 2005; Duffau et al., 2005; Parker et al., 2005; Saur et al., 2008; Wise, 2003).

Performance on the semantic factor was significantly related to tissue concentration in a cluster of voxels in the left hemisphere anterior temporal lobe (ATL). The cluster overlapped with the anterior to mid portion of the MTG, the inferior temporal gyrus (ITG) and part of the fusiform gyrus. With regards to white matter, the cluster included an area corresponding to part of the ventral language route, overlapping parts of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (e.g., Catani & Mesulam, 2008; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Mummery et al., 1999; Parker et al., 2005; Saur et al., 2008; Schmahmann, Smith, Eichler, & Filley, 2008; Wise, 2003).

In contrast, for correlations involving the cognitive factor, there were no clusters which survived correction for multiple comparisons.

Lesion Size: In order to ensure that our results were not merely attributable to the size of participants' lesions, each participant's lesion volume was calculated in MATLAB 2009a (Mathworks Inc., Natick, MA, USA). When lesion volume alone was regressed against participants' T1-weighted scans a large voxel cluster in left hemisphere MCA territory emerged as significant (see Figure 5.6 in Supplementary Information). The correlation between lesion volume and unrotated PCA factor score, or overall 'severity', was -0.545. Lesion volume correlated relatively weakly with phonology (r = -0.325), semantics (r = -0.260) and cognition (r = -0.411) factor scores. Including lesion volume in the VBCM model with factor scores did not markedly alter the pattern of results obtained (see Supplementary Information for results including lesion volume).

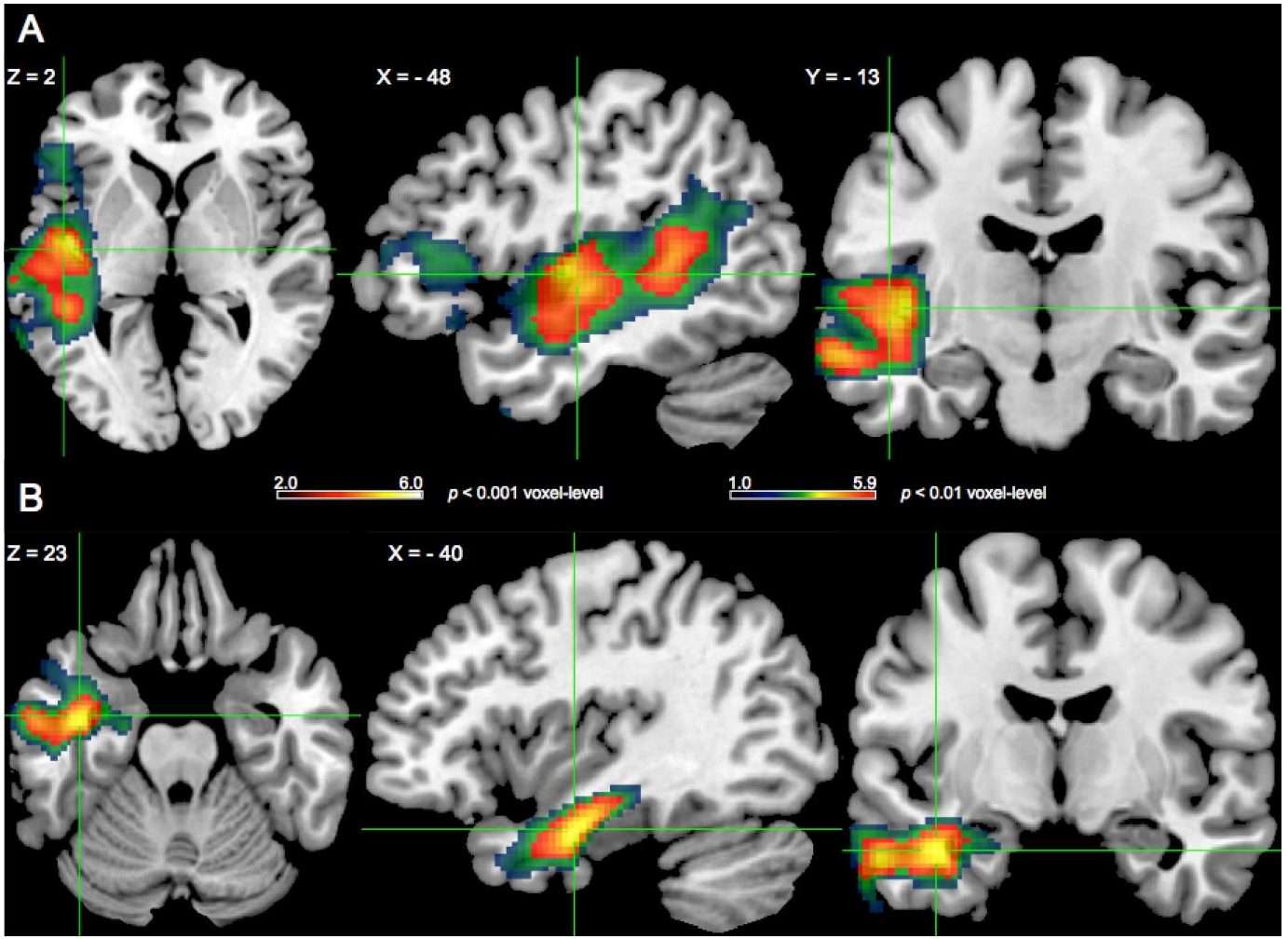

Figure 5.4. Regions found to relate significantly to phonological (**A**) and semantic (**B**) performance in VBCM analyses. Hot overlays are clusters significant at $p < 0.001$ voxel-level, $p \leq 0.001$ FWE-corrected cluster-level and which were interpreted in the text. Cluster sizes 2622 (A) and 856 (B) voxels. Image threshold (t) 2.0 – 6.0. ACTC (blue/green) overlays are clusters significant at $p < 0.01$ voxel-level, $p \leq 0.001$ FWE-corrected. Image threshold (t) 1.0 – 5.9.

Individual Cases: To facilitate interpretation of the behavioural factors and their neural correlates, four exemplar participants are presented in Figure 5.5. The exemplar participants were selected to provide contrasting pairs who score above ('high') or below ('low') the median for the group for that factor. In the first case example pair, one participant scored 'high' on both phonology and semantics (participant AL) and the other scored 'low' on both factors (participant LM), providing an illustration of general aphasia *severity*. In Figure 5.2 AL is represented by datapoint 'A6' and LM is 'G2'. As is immediately apparent on inspection of Figure 5.5, AL's lesion falls outside the key areas we have identified as supporting phonological and semantic processing, while in contrast, LM's lesion largely encompasses both areas, resulting in severe impairments.

In the second case example pair, one participant scored 'low' on phonology but 'high' on semantics (participant DM) and the other scored 'low' semantics but 'high' on phonology (participant KS), providing an illustration of the *specificity* of impairments. In Figure 5.2 DM is denoted by 'B3' and KS by 'TSA'. DM's lesion encompasses brain regions identified as correlating with phonology, with those areas shown as correlating with semantics falling largely outside the boundary of his lesion. Conversely, participant KS' lesion involves almost all of the area shown to correlate with semantics but does not significantly encroach on regions shown to correlate with phonology. Hence, when we consider individual cases, the extent to which a participant's lesion encompasses the unique areas we have identified as supporting phonological and semantic processing maps closely onto their performance on specific behavioural tests of these abilities.

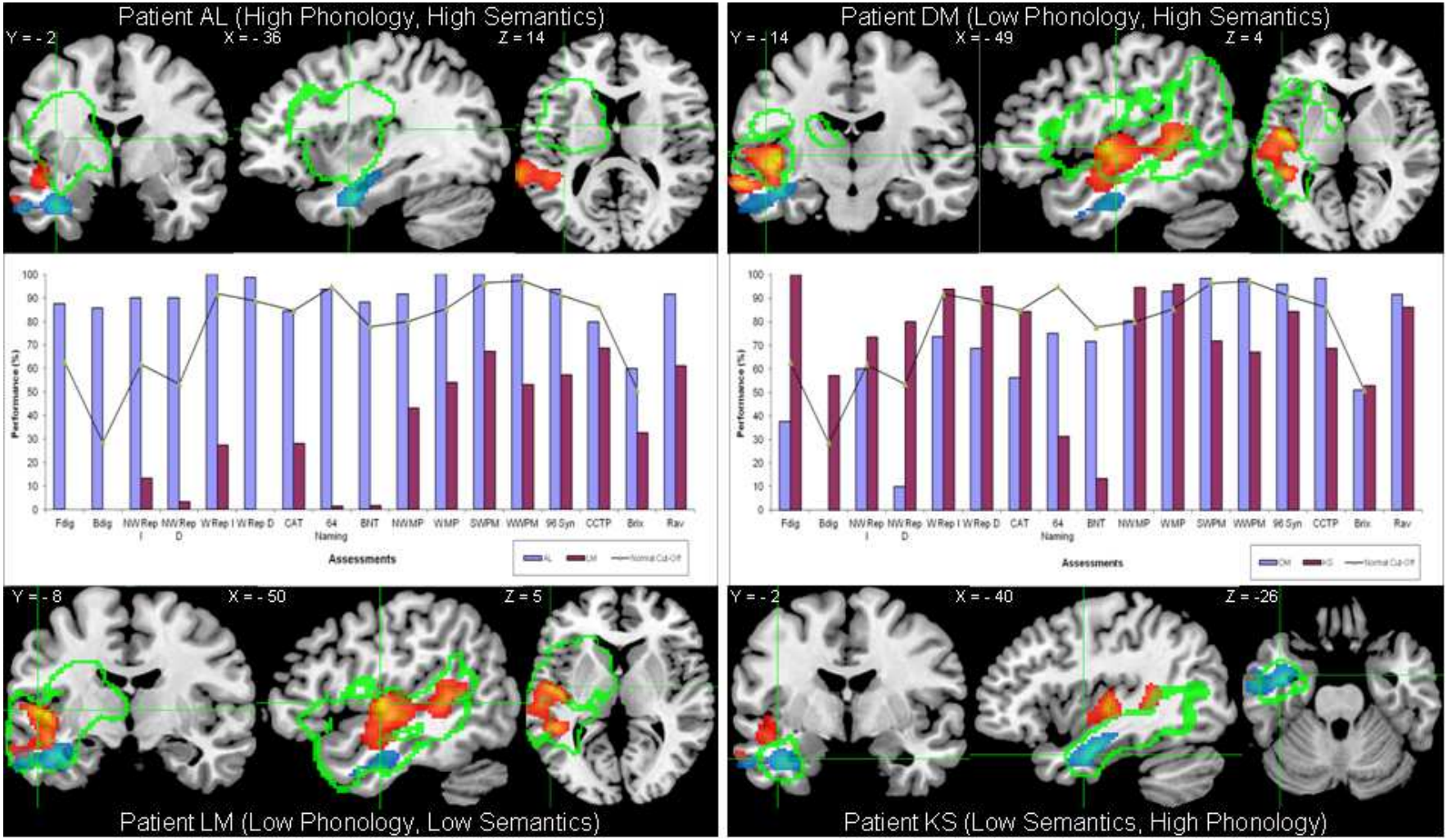

Figure 5.5. Behavioural scores and lesion data from example cases AL and LM (**A**), and DM and KS (**B**). Brain images show outlines of participant's lesions (green) overlaid on phonological (hot) and semantic (cool) clusters from the VBCM analysis. Lesion outlines were generated using Seghier et al.'s (2008) automated software (see Supplementary Information for details). Bar chart gives individuals' scores on the behavioural assessment battery, line denotes control cut-off.

Discussion

Stroke aphasia is characterised by impairments over multiple different dimensions, with considerable variation between individuals in terms of their behavioural profile. In this study, we adopted a novel approach to unpacking this variation at both the behavioural and neural level to reveal underlying abilities and their lesion correlates. We tested a representative cohort of 31 individuals with stroke aphasia on a detailed battery of cognitive tests, then used PCA to distil measures of performance that captured the key dimensions of variation. Our rotated PCA analysis revealed three factors, which corresponded to phonology, semantics, and cognition. These rotated scores have the virtue of being orthogonal to one another, allowing us to enter them simultaneously in a VBCM analysis, thereby controlling for co-occurring deficits and allowing us to identify the neural regions uniquely associated with each ability. The phonological factor, which explained the largest proportion of behavioural variance, correlated with tissue concentration in left mid to posterior STG, MTG, and STS, Heschl's gyrus, as well as the white matter underlying the primary auditory cortex, consistent with the location of the dorsal language route. The semantic factor was related to left anterior STG and MTG, parts of ITG and fusiform gyrus, and the white matter underlying those areas, which broadly corresponded with the location of the ventral language route. The third factor, cognition, which explained the least variance, did not reliably covary with any brain regions in our VBCM analysis.

The fact that the varimax rotated PCA mapped performance on a battery of neuropsychological tests onto the underlying independent factors of phonology, semantics, and cognition agrees with previous case-series studies of aphasic behaviour that have used this technique (Lambon Ralph et al., 2002, 2010). Phonological processing ability accounted for the largest proportion of variance in performance in this representative group of participants with chronic stroke aphasia. This factor was also the

most strongly correlated with the single factor emerging from an unrotated PCA that all tests loaded highly on and which provided a measure of general aphasia severity. Hence in this sample, phonological processing ability is the primary factor in determining overall severity of aphasia, with semantic and cognitive ability playing an additional role in determining the character of an individual's behavioural profile. A typical chronic stroke aphasic profile is therefore someone with a degree of phonological impairment, with or without additional semantic and/or cognitive impairment. This aligns with the clinical impression that individuals with good phonological and poor semantic processing are relatively rare in the context of stroke.

Although classifications of aphasia subtypes serve as useful clinical shorthand to describe individual performance profiles, it was clear that the current approach, based upon multiple continuous underlying dimensions of variation, offered a more refined picture of aphasic performance. Aphasia classifications such as those obtained from the BDAE (Goodglass et al., 2000; Goodglass & Kaplan, 1983) and the WAB (Kertesz, 1982) act as labels to describe prototypical positions in the multidimensional aphasic space. As was illustrated in Figure 5.2, not only can there be broad variation in the performance of participants within aphasic subtypes (see also Marshall, 2010), there can also be overlap of the boundaries between aphasic subtypes. Given these limitations of categorical aphasia types, it is unsurprising that many individuals do not fall neatly into a particular aphasia subtype (Caramazza & McCloskey, 1988; Marshall, 2010), meaning they may be underrepresented in previous research. The method we have demonstrated for capturing participants' language abilities allows extraction of key factors which describe an individual's performance profile without the need for diagnostic labels. If the underlying dimensions in our aphasic space are considered analogous to the primary colours of the RGB space, then our approach allows us to capture all shades of

performance rather than merely the prototypical colours at the extremes of the space represented by traditional aphasic classifications.

The PCA scores also offer significant advantages over categorical classifications or individual assessment scores when attempting to assess lesion-performance relationships. As Figure 5.1 demonstrates, correlating aphasic subtypes with lesion locations produces plausible yet heavily overlapping regions, which are not particularly enlightening if one is interested in using neuropsychological data to isolate the neural regions necessary for supporting a particular language function. While it is possible to correlate scores on individual tests with lesion data, these are susceptible to measurement noise and may often tap more than just the process of interest. Even if a group of tests aiming to capture a particular ability of interest is used, these cannot be entered into a lesion analysis simultaneously as they will be highly correlated, and this shared variance will be discarded. The use of rotated PCA to determine independent dimensions of variation allows us to take advantage of the reliability of multiple assessments whilst at the same time producing predictors ideal for isolation of brain regions supporting these key abilities.

Performance on the phonological factor was mainly related to tissue concentration in left hemisphere primary auditory cortex including Hechl's gyrus, mid to posterior MTG, STG, and STS, and posterior insula. These align with the areas found to be activated during phonological processing tasks in a recent review of functional neuroimaging studies (Price, 2010). Studies which included nonwords, as was the case for a number of the assessments used here, activated Heschl's gyrus and STG. STG was also found to be activated in sentence comprehension tasks, another task used here that loaded highly on the phonological factor. Tasks involving articulation were found to commonly activate STG and the temporo-parietal cortices, consistent with our results given the high loadings of repetition and naming tasks on the phonological factor.

The primary auditory and posterior temporo-parietal regions shown to relate to phonological performance in the current study also overlap with areas where peak activations were found for phonological tasks in a meta-analysis by Vigneau et al. (2006). Functional neuroimaging using positron emission tomography (PET) has also shown posterior left STS to be involved in phonological processing (Wise et al., 2001). Applying repetitive transcranial magnetic stimulation (rTMS) to posterior STG has been shown to increase error rates in language production and verbal working memory tasks (Acheson, Hamidi, Binder, & Postle, 2011).

Although the cluster we reported at a high level of statistical significance did not include inferior frontal gyrus (IFG), which has previously been implicated in studies of phonology using fMRI (e.g., Price, 2010; Vigneau et al., 2006) and rTMS (Gough, Nobre, & Devlin, 2005), when the statistical threshold is lowered our cluster does include IFG, specifically pars triangularis, as shown in Figure 5.4. The supramarginal and angular gyri have also been implicated in phonological processing in fMRI studies (Vigneau et al., 2006), and again these regions do emerge as significantly related to phonology at lower statistical thresholds in our VBCM analysis. One reason for the weaker results for these areas may be that they subserve a variety of functions, and hence would not be uniquely associated with phonological processing. This may also hold true for the absence of the anterior insula from our results, as although this area is often implicated in articulation (Dronkers, 1996; Price, 2010), it is also involved in a number of other functions (Ardila, 1999; Augustine, 1996).

Performance on the phonological factor was also significantly related to white matter underlying primary auditory cortex. This location corresponds to part of the arcuate fasciculus, believed to constitute at least part of the dorsal language route (e.g., Catani & ffytche, 2005; Catani et al., 2005; Duffau et al., 2005; Parker et al., 2005; Saur et al., 2008). This is consistent with the association of the dorsal route with phonological

processing in studies using a variety of methodologies such as intra-operative subcortical electrical stimulation (e.g., Duffau et al., 2009; Leclercq et al., 2010), diffusion-weighted imaging and tractography (e.g., Glasser & Rilling, 2008; McDonald et al., 2008) and VLSM (Bates et al., 2003).

Semantic performance was found to relate to left hemisphere ATL regions focused mainly on anterior to mid MTG, but also extending to include part of inferior temporal gyrus and fusiform gyrus. The semantic cluster also overlapped with white matter underlying these areas, sitting directly over the temporal stem which coincides with the ventral language route, likely to include parts of the inferior longitudinal, inferior fronto-occipital, and uncinate fasciculi. As with the findings for the phonological factor, our semantic cluster overlaps considerably with MTG regions found to be involved in semantics in large-scale reviews of fMRI studies (e.g., Price, 2010; Vigneau et al., 2006). Left anterior MTG semantic activations have also been shown using PET imaging (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Performance on the same synonym judgement task which loaded heavily on the semantic factor in the current study has been shown to be affected by application of rTMS to the left ATL (Lambon Ralph, Pobric, & Jefferies, 2009; Pobric, Lambon Ralph, & Jefferies, 2009). Semantic effects in picture naming have also been elicited by rTMS to the same region (Woollams, 2012). With regards to results in the white matter, the ventral language pathway has been shown to play a role in semantic processing in studies using a variety of methodologies. For example, Leclercq et al. (2010) found that stimulation of the ventral language route produced semantic paraphasias (see also Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Saur et al., 2008).

Some regions which have previously been implicated in semantic processing using other methodologies did not emerge as significant in our results. For example, inferior frontal regions, such as pars orbitalis, which have previously been implicated in

semantics in studies using fMRI (e.g., Price, 2010; Vigneau et al., 2006) and rTMS (Gough et al., 2005), did not emerge as related to the semantic factor here unless we lower our statistical threshold considerably ($p = 0.04$ voxel-level, $p = 0.003$ FWE-corrected at cluster level). It is possible that this discrepancy arises because, whilst such areas may be involved in the semantic network, producing functional activations and slowing in performance after application of rTMS, they may not be necessary to support accurate performance on semantic tasks. In terms of other areas previously associated with semantic processing such as the superior and middle frontal gyri (e.g., Price, 2010), the fact that these did not emerge in our results is not surprising as these areas lie largely outside MCA territory and therefore were not commonly lesioned in our cohort.

The fact that the third PCA factor, cognition, did not significantly relate to any lesion locations in the VBCM analysis may be indicative of the distribution of cognitive processes in the brain. Whilst linguistic processing (phonological and semantic) clearly relies on distributed neural networks (Mesulam, 1990), the kind of cognitive capacity captured by Factor 3, which can be broadly characterised as modality independent choice/control, may be even more diffusely distributed throughout the brain (Ham & Sharp, 2012; Sharp et al., 2011; Siegel, Engel, & Donner, 2011). For this reason, poor performance on tests contributing to the cognitive factor in our study may be associated with a variety of different lesion locations across participants, and hence no one location emerged as significant.

The distribution of the areas shown to significantly correlate with phonological and semantic performance is consistent with the notion that phonological deficits arise from perisylvian lesions, whilst semantic deficits are more likely to result from lesions involving extrasylvian areas (either in isolation or in addition to perisylvian damage) (Price et al., 1997; Schwartz et al., 2009). In the current cohort, participants with both phonological and semantic deficits had large lesions, which tended to involve both peri-

and extrasylvian cortex (for example, participants ES and DBb). One of our exemplar cases who had a phonological impairment in the context of good semantic processing (DM) evidenced a predominantly perisylvian lesion, while another exemplar case with a semantic impairment in the context of relatively spared phonology (KS), was characterised by an extrasylvian lesion. The current results are also consistent with a framework within which phonological deficits relate primarily to dorsal white matter damage, whilst semantic impairments are associated with ventral white matter damage (e.g., Duffau et al., 2008; Hickok & Poeppel, 2004, 2007; Kümmerer et al., 2013; Saur et al., 2008; Schwartz et al., 2012; Wise, 2003).

To conclude, the present study clearly demonstrates the utility of principle components analysis as a means to determine the key abilities underlying participants' performance and relate these to the integrity of neural structures. Our approach allows us to overcome the challenges inherent in lesion-symptom mapping with a heterogeneous population as typified here by chronic stroke aphasia. When applied to data from multiple neuropsychological tests used to obtain reliable estimates of performance across a variety of domains, PCA allows derivation of factor scores that more accurately capture individual participants' performance than traditional aphasia classifications. In line with previous case-series studies of chronic stroke aphasia, we identified the three key factors of phonology, semantics and cognition. Simultaneously entering these independent factors as predictors of neural damage takes into account an individual's profile across all component abilities and also means that the neural regions identified are uniquely associated with a given ability. Although we have applied this method in chronic stroke aphasia, it can also be utilised in the acute phase (e.g., Kümmerer et al., 2013), and would be ideally suited to mapping brain changes underlying patterns of recovery from the acute to chronic phase longitudinally. We identified a series of regions along the dorsal pathways as associated with phonological processing ability and areas along the ventral

pathway as associated with semantic processing. Our results therefore complement evidence of involvement from functional imaging by demonstrating the necessity of these peri- and extrasylvian regions to support effective processing of sound and meaning. Our general approach to lesion-symptom mapping could be utilised to understand other multifaceted neurological disorders, such as Alzheimer's disease, in future.

Supplementary Information

Voxel-Based Morphometry of Aphasia Subtypes

The VBM analyses of BDAE subtypes, results of which are given in Figure 5.1, were conducted in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Participants were divided into groups based on their BDAE classifications (for example, all participants with a diagnosis of 'anomia' were grouped together). Only groups with $n > 5$ were included in VBM analyses. Smoothed and normalised T1-weighted images from each participant in an aphasic subgroup and from a group of 19 healthy older control participants (see below for details) were entered together into the analysis in SPM8. Statistical comparisons were then carried out for every brain voxel, between the aphasic subgroup and the control group. The resulting images show clusters of voxels in which the control group had a significantly higher concentration of tissue than the aphasic subgroup.

Control Groups

Neuroimaging Healthy Controls

The healthy control group which was used in the lesion identification procedure and in the VBM analyses to compare to participants with different BDAE classifications consisted of 19 right-handed healthy older adults (8 females, 11 males). Mean age = 68.21 years (SD = 5.99), range = 59 – 80 years. Mean years of education = 13.06 years (SD = 2.77), range = 10 – 18 years.

Behavioural Data Healthy Controls

Normative data on language assessments was collected from a subset of 13 of the healthy control participants (3 females, 10 males). Mean age = 68.69 years (SD = 6.55), range = 59 – 80 years. Mean years of education = 12.55 (SD = 2.38), range = 10 – 17 years.

Table 5.4

Codes Allocated to Participants in Figure 5.2

Participant Number	**Participant Initials**	**Code Assigned in Figure 5.2**
1	JM	A7
2	PE	W/C
3	HN	A3
4	DS	TMA
5	EB	A8
6	KW	B5
7	KS	TSA
8	BS	B4
9	DM	B3
10	LM	G2
11	AL	A6
12	ES	G3
13	JMf	A5
14	JSa	NF4
15	BH	NF3
16	ESb	G1
17	WM	NF1
18	TJ	A2
19	DB	W1
20	GL	B2
21	AG	B1
22	JJ	A1
23	KK	B6
24	KL	NF5
25	ER	NF2
26	JSb	A4
27	DCS	B7
28	JSc	B8
29	LH	A9
30	JA	NF6
31	DBb	W2

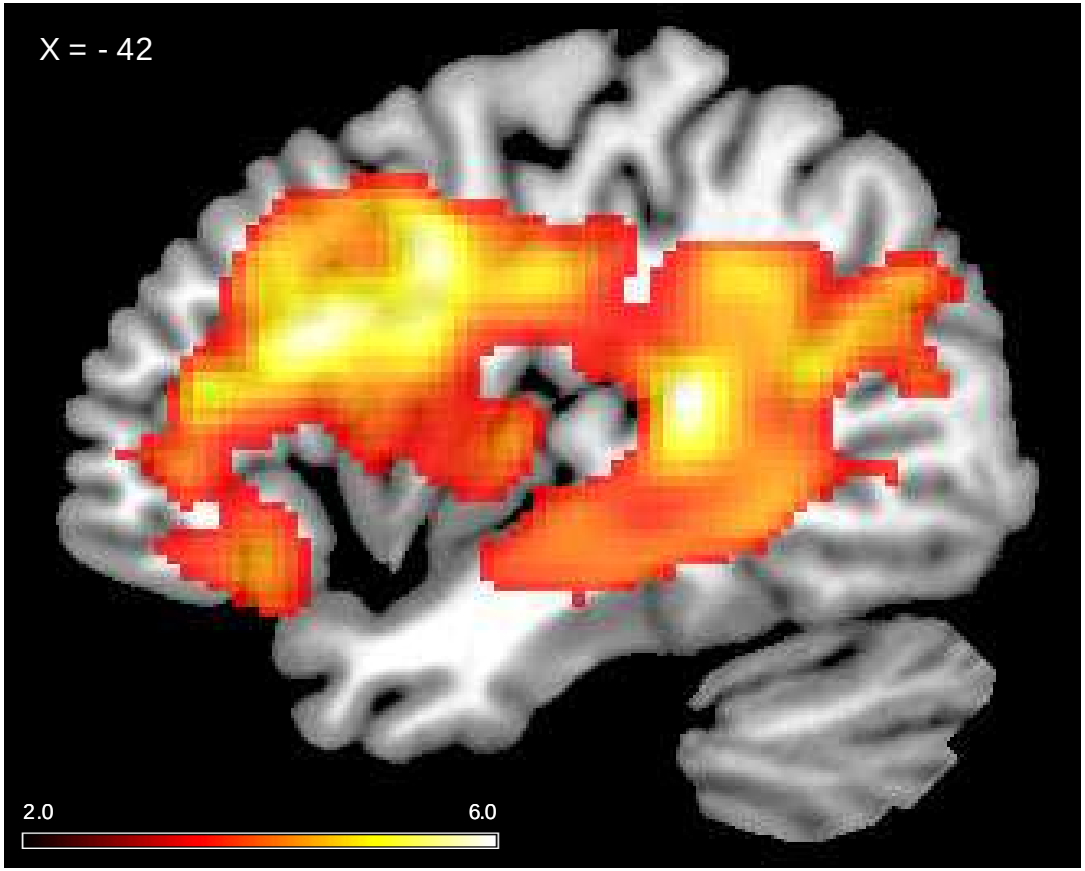

Figure 5.6. T-map showing regions found to relate significantly to lesion volume at $p < 0.001$ voxel-level, < 0.001 FWE-corrected cluster-level, cluster size 21918 voxels. Image threshold (t) 2.0 – 6.0.

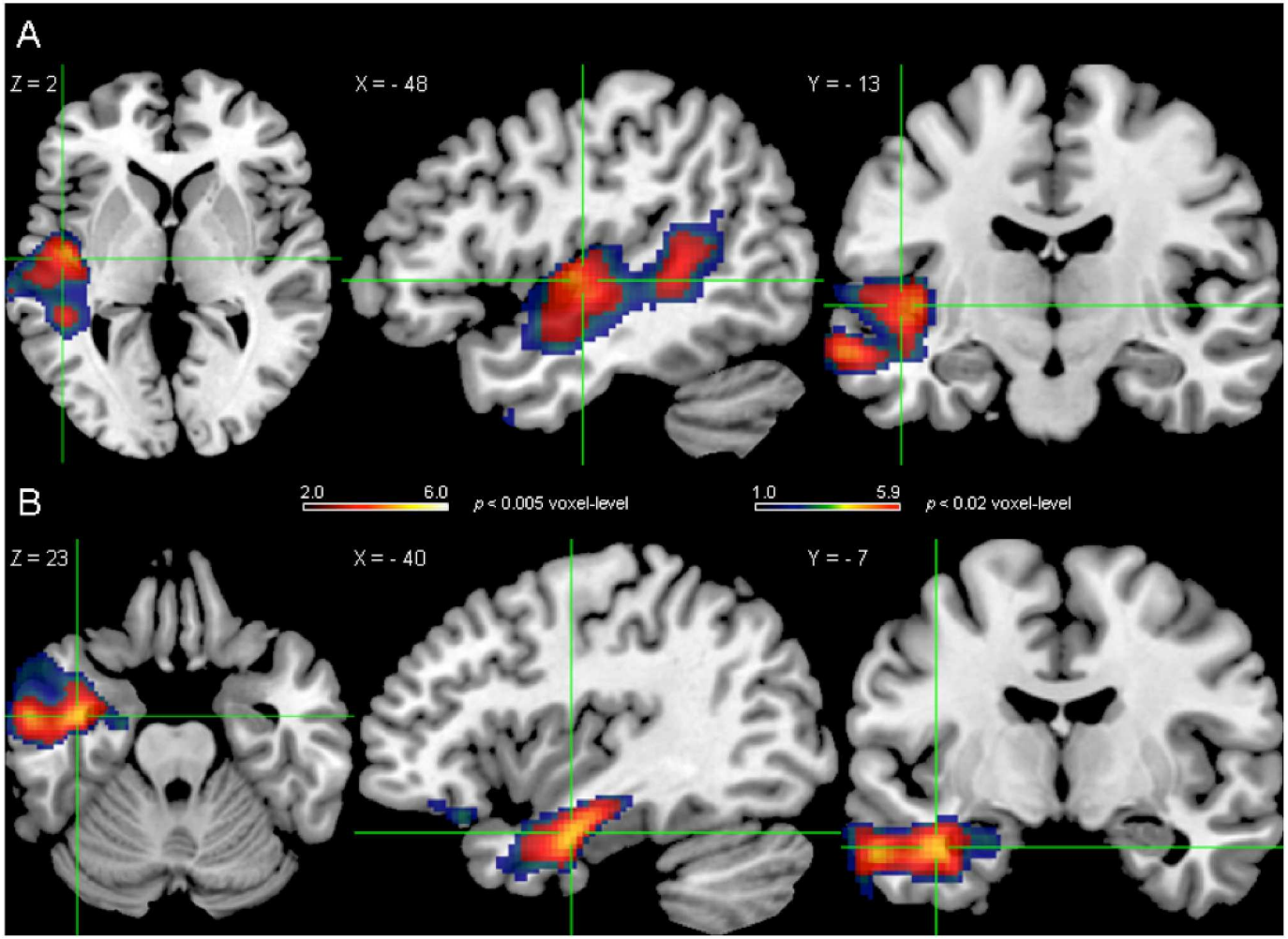

Figure 5.7. Regions found to relate significantly to phonological (**A**) and semantic (**B**) performance in VBCM analyses with lesion volume included as a covariate. Hot overlays are clusters significant at $p < 0.005$ voxel-level, $p < 0.01$ FWE-corrected cluster-level. Cluster sizes 1940 (A) and 1261 (B) voxels. Image threshold (t) 2.0 – 6.0. ACTC (blue/green) overlays are clusters significant at $p < 0.02$ voxel-level, $p < 0.03$ FWE-corrected. Image threshold (t) 1.0 – 5.9.

Automated Lesion Identification Procedure

Automated outlines of participants' lesions were generated using Seghier et al.'s (2008) modified segmentation-normalisation procedure. Data from all participants with stroke aphasia (N = 31) and all of our healthy control group (see below) (N = 19) were entered into the segmentation-normalisation. Segmented images were smoothed with an 8mm FWHM Gaussian kernel and submitted to the automated routine's lesion identification and definition modules using the default parameters apart from the lesion definition 'U-threshold', which was set to 0.5. The images generated were used to create the lesion overlap map in Figure 5.3 and the lesion outlines in Figure 5.5.

CHAPTER 6

RELATING PHONOLOGICAL, SEMANTIC, AND COGNITIVE ABILITIES TO WHITE MATTER CONNECTIVITY IN CHRONIC STROKE APHASIA

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Abstract

Deficits in language processing seen in chronic stroke aphasia vary both quantitatively and qualitatively along a number of dimensions. The current study aimed to assess how performance of individuals with chronic stroke aphasia related to changes in cortical areas and underlying white matter pathways. To do this we related participants' performance on continuous measures of phonology, semantics, and cognition, to measures of grey and white matter concentration (T1-weighted imaging), local white matter structure (fractional anisotropy, FA) and more global white matter connectivity (anatomical connectivity mapping, ACM). Phonological performance was found to relate to all imaging measures in the dorsal route and adjacent cortex. Semantic abilities correlated with local grey and white matter measures (T1-weighted and FA) and average ACM in the ventral language route and surrounding cortex in the anterior temporal lobe. Finally, cognitive performance did not show any relationship to local tissue measures but it did relate to our brain-wide connectivity measure, with good performance found to relate to increased ACM relative to controls in a right frontal area. The pattern of results obtained across the complementary imaging measures suggests that the degree to which a particular function is neuroanatomically distributed is determined by the nature of the input-output mappings involved. Moreover, our, results shed light on patterns of impaired and spared performance in chronic stroke aphasia, including potential compensatory changes in connectivity.

Introduction

Contemporary models propose that language processing is subserved by two major pathways connecting left hemisphere temporo-parietal and frontal brain regions, a dorsal route and a ventral route (e.g., Hickok & Poeppel, 2004, 2007; Parker et al., 2005; Saur et al., 2008; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011; Wise, 2003). Evidence for such a framework has emerged from work using a variety of methodologies including functional and diffusion-weighted imaging in healthy individuals (e.g., Catani, Jones, & Ffytche, 2005; Parker et al., 2005; Powell et al., 2006; Saur et al., 2008) and lesion-symptom mapping in stroke aphasic individuals using both standard structural magnetic resonance imaging and diffusion-weighted imaging (e.g., Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Kümmerer et al., 2013; Rolheiser, Stamatakis, & Tyler, 2011; Schwartz, Faseyitan, Kim, & Coslett, 2012). Support for the "dual route" model of spoken language has also emerged from studies using intra-operative electro-stimulation in individuals undergoing surgery for tumour removal, which have found results consistent with tractography work (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Duffau, 2008; Leclercq et al., 2010; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007), and also from connectionist computational modelling work (Ueno et al., 2011).

The specific white matter pathways that have been described as constituting the dorsal route are the arcuate fasciculus (specifically the parieto-frontal aspect) and the superior longitudinal fasciculus (e.g., Catani et al., 2005; Duffau, 2008; Glasser & Rilling, 2008; Makris et al., 2005; Parker et al., 2005). Evidence suggests that the ventral route is composed of several pathways, including the inferior fronto-occipital, inferior longitudinal, and uncinate fasciculi, all of which may pass through the extreme capsule (Catani & Mesulam, 2008; Duffau et al., 2009; Parker et al., 2005; Saur et al., 2008; Shinoura et al., 2010; Weiller et al., 2011; Wise, 2003). Whilst most language functions

are likely to be accomplished by the parallel working of both routes in healthy individuals, studies have found evidence to support differing specialisations for the two routes. The dorsal route has been attributed a critical role in phonological processing, whilst the ventral route has been associated with semantic processing (Duffau et al., 2009; Glasser & Rilling, 2008; Hickok & Poeppel, 2007; Kümmerer et al., 2013; Leclercq et al., 2010; Mandonnet et al., 2007; Rolheiser et al., 2011; Saur et al., 2008; Schwartz et al., 2012). It has been argued that the dorsal route is particularly key in the processing of complex syntax, although evidence has been found to suggest that successful syntactic processing requires both routes (Friederici, 2009; Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2012; Papoutsi, Stamatakis, Griffiths, Marslen-Wilson, & Tyler, 2011; Rolheiser et al., 2011).

Language deficits shown by individuals with chronic stroke aphasia vary both in terms of degree and character, with the particular profile of deficits and preserved functions varying from person to person. These patterns of relatively impaired and spared abilities may reflect differences in damage not only to cortical areas involved in language such as the inferior frontal gyrus (IFG) and temporo-parietal cortex, but also variable involvement of the white matter pathways that support normal language function. Damage to aspects of these pathways may also have effects on neural structures quite distal to the lesion, which could influence performance in either negative or positive ways.

We have previously used principal components analysis (PCA) to derive behavioural factor scores from raw scores on a large battery of language assessments with chronic stroke aphasic participants (see Chapter 5). In that study, we found that participants' performance on our battery was explained by their phonological, semantic and general cognitive abilities. Participants' scores on those behavioural factors were then used as regressors in imaging analyses using T1-weighted structural magnetic

resonance images. Phonological and semantic abilities were shown to correlate with brain regions previously identified as involved in phonology and semantics using other methods. These areas included both cortical areas and regions of white matter likely to correspond to parts of the dorsal and ventral language routes. However, PCA-derived factor scores are yet to be related directly to measures of white matter connectivity in individuals with chronic stroke aphasia.

There is increasing evidence that variations in white matter measures can index differences in behavioural performance, in both healthy and brain-damaged individuals. A commonly used white matter measure is fractional anisotropy (FA), a metric derived from diffusion-weighted imaging which reflects local microstructure. Wong, Chandrasekaran, Garibaldi, and Wong (2011) found that when healthy participants were trained on a sound-to-word learning task, FA in left temporo-parietal white matter correlated with task performance. Differences in cognitive processing speed have also been shown to relate to FA levels (Tuch et al., 2005; Turken et al., 2009) and semantic memory has been found to correlate with FA in ventral language pathways in healthy older adults (de Zubicaray, Rose, & McMahon, 2011). However, Jones, Knösche, and Turner (2012) advise caution in interpretation of FA variability in healthy individuals, noting that FA is naturally low in areas of crossing fibres. The deficits shown by individuals with the semantic variant of primary progressive aphasia, a neurodegenerative condition, have been found to relate to reductions in FA (and other related metrics such as mean diffusivity) in the ventral route (Acosta-Cabronero et al., 2011; Agosta et al., 2010; Galantucci et al., 2011). In stroke aphasia, FA within language pathways has been found to correlate with performance on measures of phonology, semantics and syntax (Breier et al., 2008; Griffiths et al., 2012; Papoutsi et al., 2011; Rolheiser et al., 2011).

Measures such as FA and mean diffusivity can reflect changes in microstructure within a particular voxel. However, another important factor to consider is changes in connectivity to a voxel that may occur as a result of more distant damage. A method that offers a greater degree of sensitivity to remote effects, which provides complementary information to that available from FA, is anatomical connectivity mapping (ACM) (Embleton, Morris, Haroon, Lambon Ralph, & Parker, 2007; see also Cercignani, Embleton, Parker, & Bozzali, 2012). ACM is a whole-brain tractography method, involving launching multiple streamlines from every brain voxel. It does not provide information on specific point-to-point connections but provides a scalar index of the degree of anatomical connectivity passing through each voxel. In addition to providing information on the degree of connectivity, ACM, unlike FA, does not show low values in voxels with multiple pathways (Jones et al., 2012). The bootstrapped constrained spherical deconvolution (Haroon et al., 2009) procedure we use to process our diffusion data allows resolution of more than one fibre population per voxel. Within voxels with more than one fibre population ACM values will tend to be high, reflecting increased connectivity, via multiple pathways, via that voxel. This is in contrast to FA, values of which would be low in such voxels. ACM has previously been used to demonstrate white matter connectivity changes in Alzheimer's disease (Bozzali et al., 2011, 2012) and to investigate relations between cognitive dysfunction and connectivity changes in multiple sclerosis (Spano et al., 2012). We have previously shown that ACM can be used to identify connectivity changes in participants with chronic stroke aphasia compared to controls and to investigate connectivity differences between participants with different subtypes of stroke aphasia (see Chapter 4).

In the current study we combine our PCA-derived continuous behavioural measures, which have previously been shown to correlate with anatomical variation on T1-weighted imaging, with complementary quantitative white matter measures, one local

(FA) and one more global (ACM). By combining these measures we aimed to provide evidence from chronic stroke aphasia for the involvement of different cortical areas and white matter pathways in phonological, semantic, and cognitive processing. In this way we aimed to gain a clearer understanding of the nature of the networks underlying healthy language processing and the relative patterns of impairment, sparing, and potentially enhancement, seen in cases of damage.

Expanding on the results of Chapter 5, in which phonology was related to temporo-parietal regions primarily focused on the primary auditory cortex and underlying white matter in T1-weighted imaging, we predicted that phonological processing ability would be related to FA and ACM variability related to the dorsal language pathway. In line with work suggesting a role for the ventral route in semantics, and the results of Chapter 5, in which semantics related to anatomical variations on T1-weighted imaging in anterior temporal regions, we predicted that semantic performance would correlate with FA and ACM changes in the ventral route. Finally, for general cognitive processing we did not find any significant clusters in T1-weighted data in Chapter 5. It was suggested that this reflected the highly distributed nature of cognitive control processes, both cortically and at a network level. Therefore, we were interested to explore whether variability in cognitive performance could be related to any changes in the white matter measures, FA and ACM.

Methods

Participants

Chronic stroke aphasic participants (N = 31) were recruited from the North West of England through presentations at stroke groups and referrals from Speech and Language Therapy services. All participants were at least 12 months post-stroke at time of scanning and assessment. Participants were recruited on the basis that they had sustained one left hemisphere stroke and had a chronic impairment of production and/or comprehension of spoken language. Exclusion criteria were: pre-morbid left-handedness, having more than one full stroke or any other significant neurological conditions, and having any contraindications for magnetic resonance imaging (MRI). Informed consent was obtained from all participants prior to participation under North West Multi-centre Research Ethics Committee approval. Participant background information is given in Table 6.1 and a lesion overlap map showing the lesion distribution of the participants is shown in Figure 6.1.

Table 6.1

Participant Information

	Initials	**Age (years)**	**Gender**	**Years of Education**	**Time Post-Stroke (months)**	**BDAE Classification**	**Phonology Score**	**Semantic Score**	**Cognition Score**
1	JM	62	M	11	110	An	0.99	-0.05	0.86
2	PE	73	F	16	22	W/C	-1.07	0.36	0.46
3	HN	81	M	10	56	An	-0.09	0.71	-0.69
4	DS	72	M	11	106	TMA	0.13	1.05	0.04
5	EB	61	M	17	12	An	0.76	0.17	1.15
6	KW	81	M	10	24	Br	-1.21	-0.20	0.97

	Initials	Age (years)	Gender	Years of Education	Time Post-Stroke (months)	BDAE Classification	Phonology Score	Semantic Score	Cognition Score
7	KS	59	M	12	12	TSA	1.73	-2.40	0.72
8	BS	59	M	11	103	Br	-1.94	0.27	0.68
9	DM	49	M	17	42	Br	-0.61	1.27	0.42
10	LM	63	M	11	13	Gl	-0.87	-1.68	-0.77
11	AL	49	F	12	69	An	1.45	0.26	0.23
12	ES	69	M	11	39	Gl	-1.08	-0.70	-1.91
13	JMf	70	F	11	84	An	0.81	0.74	0.11
14	JSa	73	M	11	190	MNF	-0.32	0.31	0.23
15	BH	64	M	11	26	MNF	1.20	0.22	-0.30
16	ESb	68	M	11	142	Gl	-1.67	-0.27	-0.33
17	WM	77	M	11	66	MNF	-0.04	-0.53	-1.34
18	TJ	60	M	12	23	An	1.14	1.03	-1.29
19	DB	60	M	12	44	We	0.32	-2.30	0.59
20	GL	47	M	12	18	Br	0.62	-0.36	0.58
21	AG	55	M	11	131	Br	1.42	0.21	-0.06
22	JJ	84	M	12	25	An	0.24	1.43	-2.20
23	KK	48	M	12	33	Br	-1.21	0.16	1.32
24	KL	55	M	13	31	MNF	-1.81	-0.07	0.97
25	ER	64	F	14	181	MNF	-0.24	1.34	-1.09
26	JSb	72	M	11	23	An	0.47	0.01	0.12
27	DCS	45	F	12	12	Br	0.21	0.05	1.68
28	JSc	78	M	12	76	Br	0.42	0.36	-0.26
29	LH	65	M	11	81	An	0.70	0.35	0.81
30	JA	65	M	11	128	MNF	-0.12	0.59	0.31
31	DBb	66	M	12	59	We	-0.33	-2.32	-2.02

Abbreviations: An = Anomia, Br = Broca, Gl = Global, MNF = Mixed Nonfluent, TMA = Transcortical Motor Aphasia, TSA = Transcortical Sensory Aphasia, We = Wernicke, W/C = Wernicke/Conduction.

Behavioural Assessments

Over several testing sessions participants completed a battery of language assessments designed to assess input and output phonological processing, semantic processing, and spoken sentence comprehension, as well as a small battery of more general cognitive tests. The assessments conducted can be seen in Table 6.2, with further details of the specific assessment sources and scoring criteria given in Supplementary Information. For descriptive purposes participants were also classified using the Boston Diagnostic Aphasia Examination (Goodglass et al., 2000; Goodglass & Kaplan, 1983). Our cohort was made up of nine individuals with anomic aphasia, eight with Broca's aphasia, six with mixed nonfluent aphasia, three with global aphasia, two with Wernicke's aphasia, one with Wernicke's/Conduction aphasia, one with transcortical sensory aphasia and one with transcortical motor aphasia. Individual participants' classifications are given in Table 6.1.

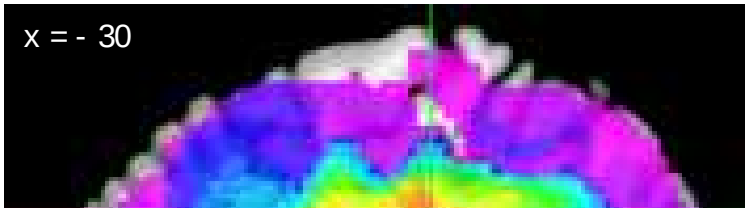

Figure 6.1. Lesion overlap map for stroke aphasic participants (N = 31). All imaging data are displayed using neurological convention. Axial slices shown at y = -30, -10, 0, 30, 50. Details of how the map was generated are given in Supplementary Information.

Principal Components Analysis

Participants' scores on all assessments in the battery were entered into a PCA with varimax rotation, for full details see Chapter 5. The rotated solution produced three orthogonal factors: 'Phonology', 'Semantics', and 'Cognition'. These three factors accounted for 82% of variance in participants' performance on the assessment battery, with phonology accounting for the most variance (61%), followed by semantics (14%), and then cognition (7%). Factor loadings of assessments are given in Table 6.2. Participants' scores on the three orthogonal factors were used as behavioural covariates for lesion analyses.

Table 6.2

Factor Loadings of Behavioural Assessments

	Phonology Factor	Semantic Factor	Cognition Factor
Minimal Pairs - Nonwords	**0.581**	0.302	**0.642**
Minimal Pairs - Words	**0.600**	0.498	0.472
Immediate Repetition - Nonwords	**0.868**	0.189	0.188
Delayed Repetition - Nonwords	**0.917**	0.116	0.142
Immediate Repetition - Words	**0.872**	0.247	0.122
Delayed Repetition - Words	**0.868**	0.336	0.162
64-Item Naming	**0.725**	**0.646**	0.051
Boston Naming Test	**0.688**	**0.649**	-0.094
Spoken Word to Picture Matching	0.206	**0.865**	0.259
Written Word to Picture Matching	0.129	**0.799**	0.488
96 Synonym Judgement	0.414	**0.665**	0.364
Camel and Cactus Test: Pictures	0.011	0.419	**0.731**
CAT Spoken Sentence Comprehension	**0.681**	0.339	0.413
Brixton Spatial Anticipation Test	0.357	0.241	**0.654**
Raven's Coloured Progressive Matrices	0.090	0.057	**0.938**
Forward Digit Span	**0.882**	0.139	0.132
Backward Digit Span	**0.764**	0.132	0.219

Note: Factor loadings over 0.500 are given in bold.

Neuroimaging

Acquisition of Imaging Data

All scans were acquired on a 3 tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. High resolution structural MRI scans were acquired using a T1-weighted inversion recovery sequence with 3D acquisition, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1 mm, acquired voxel size 1.0 mm x 1.0 mm x 1.0 mm, matrix size 256 x 256, FOV = 256 mm x 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5.

Distortion-corrected diffusion-weighted images were acquired using a pulsed gradient spin echo echo-planar imaging sequence implemented with TE = 54 ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed resolution 1.875 mm x 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 43 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8 ms, δ = 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5. Artefacts arising from pulsatile brain movements (Jones & Pierpaoli, 2005) were minimised by cardiac gating the diffusion sequence using a peripheral pulse unit placed on the participant's finger. Acquisition time for the diffusion MRI data was approximately 28 minutes, although this varied slightly based on the participant's heart rate. For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity *k*-space traversal, and hence reversed phase and frequency encode direction, allowing correction for geometric distortion (Embleton, Haroon, Morris, Lambon Ralph, & Parker, 2010). A co-localised T2-weighted turbo spin echo scan with 0.94 mm x 0.94 mm in-plane resolution and 2.1 mm slice thickness was also obtained for use as a structural reference scan in distortion correction (Embleton et al., 2010).

Pre-Processing of Imaging Data

Pre-processing of T1-weighted data was conducted in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Participants' T1-weighted scans were normalised and segmented, together with 19 age- and education-matched healthy control participants' brains (see Supplementary Information), using a modified unified segmentation-normalisation procedure (Seghier et al., 2008). The normalised images were then smoothed using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Susceptibility- and eddy current-induced distortions in diffusion data were corrected using Embleton et al.'s (2010) distortion correction method implemented in MATLAB. Distortion-corrected diffusion-weighted images were then processed using the model-based bootstrap (Haroon et al., 2009), applied to constrained spherical deconvolution (CSD) (Tournier et al., 2008, 2007). The bootstrapped CSD was used to derive probability density functions (PDFs) that were used to produce ACMs, which are whole-brain probabilistic tractography-derived connection maps (Embleton et al., 2007). ACMs quantify the total number of probabilistic paths recorded passing through each voxel of the brain, thereby providing a measure of the degree of tractography-derived anatomical connectivity passing to, from and through each voxel. ACMs were generated using the probabilistic index of connectivity (PICo) tractography algorithm (Parker et al., 2003), with ten tractography streamlines launched from every brain voxel. FA maps for each participant were generated by fitting a single diffusion tensor to each voxel within the diffusion-weighted data. Each participant's T1-weighted image, FA map, and ACM were co-registered using a rigid-body transformation and normalised to Montreal Neurological Institute (MNI) space for group-level analyses in SPM8.

Relating Behavioural and Neuroimaging Data

Voxel-Based Correlational Methodology (VBCM) (Tyler et al., 2005a) was used to identify brain regions where language abilities significantly related to brain measures. The VBCM analysis was conducted in SPM8 and involved using participants' PCA factor scores as regressors in a voxel-wise analysis. Separate analyses were carried out for each image type. Scores on each of the three orthogonal factors were entered simultaneously, and then statistical tests were conducted in each voxel to see whether scores on a particular factor significantly correlated with that voxel value. Including participants' scores on all three factors concurrently in the regression model allowed us

to identify regions where brain measures covaried uniquely with each behavioural factor. Lesion volume was also included as a covariate in the regression model. This conservative approach was intended to reduce the possibility of areas consistently associated with larger lesions being incidentally correlated with poor behavioural performance.

Results

Behavioural Assessments

Participants' scores on the PCA-derived factors are given in Table 6.1. Each participant's overall performance on the behavioural battery, in the context of the group, is characterised by their distribution of scores across the factors. Participants' scores vary from factor to factor and for each orthogonal factor there is a range of scores across participants (phonology = -1.67 to 1.73, semantics = -2.40 to 1.43, and cognition = -2.20 to 1.68). For participants' raw scores on behavioural assessments see Supplementary Information.

Voxel-Based Correlational Methodology

Phonology

As is evident from Figure 6.2, scores on the phonological factor were found to relate to highly overlapping clusters in all three imaging types, T1-weighted, FA, and ACM. As reported in Chapter 5, in the T1-weighted image analyses, phonology related to tissue concentration in the primary auditory cortex (BA 41 and 42) including Heschl's gyrus, the middle to posterior portions of the middle temporal gyrus (MTG), superior temporal gyrus (STG) and superior temporal sulcus (STS; BA 21 and 22), and a small part of the posterior insula. The cluster also overlaps with underlying temporo-parietal white matter.

In the analysis of the FA maps, correlations with phonological performance were found in areas that largely overlapped with the location of the T1-weighted cluster. This included primary auditory cortex including Heschl's gyrus, MTG, STG, STS, and temporo-parietal white matter including part of the arcuate fasciculus.

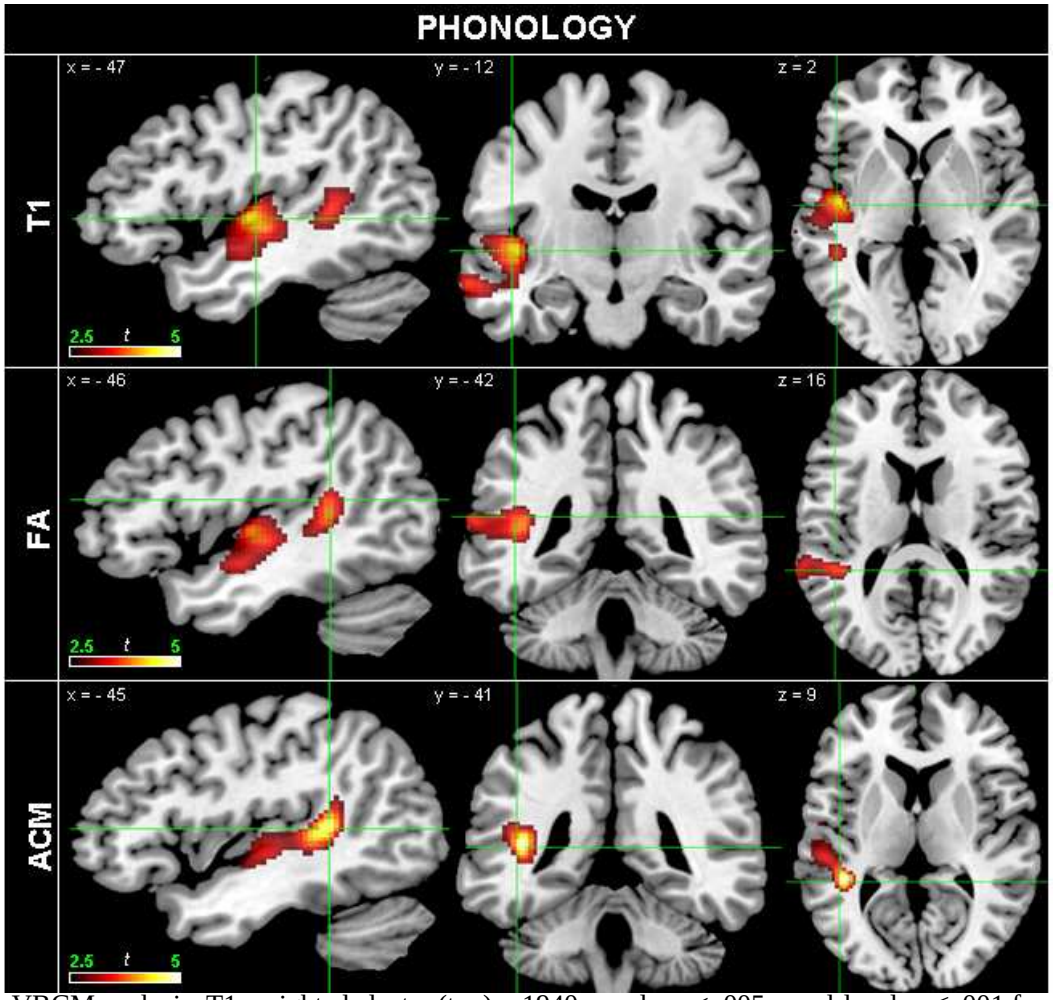

Figure 6.2. Phonological clusters from VBCM analysis. T1-weighted cluster (top) = 1940 voxels, $p < .005$ voxel-level, $p \leq .001$ family-wise error (FWE) -corrected cluster-level. FA cluster (middle) = 1748 voxels, $p < .005$ voxel-level, $p \leq .001$ FWE-corrected cluster-level. ACM cluster (bottom) = 873 voxels, $p < .005$ voxel-level, $p < .05$ FWE-corrected cluster-level.

Areas found to correlate with phonological performance in ACM coincided with those found in the FA analysis but appeared to be more localised to white matter. ACM values in STG, MTG, part of STS, primary auditory cortex and underlying white matter including the arcuate fasciculus correlated with phonological performance.

Semantics

Semantic performance was found to correlate significantly with overlapping clusters in the anterior temporal lobe in both T1-weighted image and FA analyses, as shown in Figure 6.3. The ACM analysis did not reveal any significant clusters that survived correction for multiple comparisons, nor were there any significant clusters at voxel-level p <.005 even without correction. Possible reasons for this unexpected difference between measures are discussed below.

The T1-weighted image results for semantics (also reported in Chapter 5) include correlations with tissue in inferior temporal gyrus (ITG; BA 20), fusiform gyrus (BA 36), and left anterior to middle MTG (BA 21). The cluster also encompassed significant amounts of anterior temporal white matter.

The VBCM analysis of FA and semantics revealed a significant cluster encompassing ITG (including the mid temporal pole), fusiform gyrus, MTG, parahippocampal gyrus (BA 36), hippocampus, and white matter occupying large parts of the temporal stem. This would appear to include a large section of the ventral language route, including parts of the inferior longitudinal, inferior fronto-occipital and uncinate fasciculi.

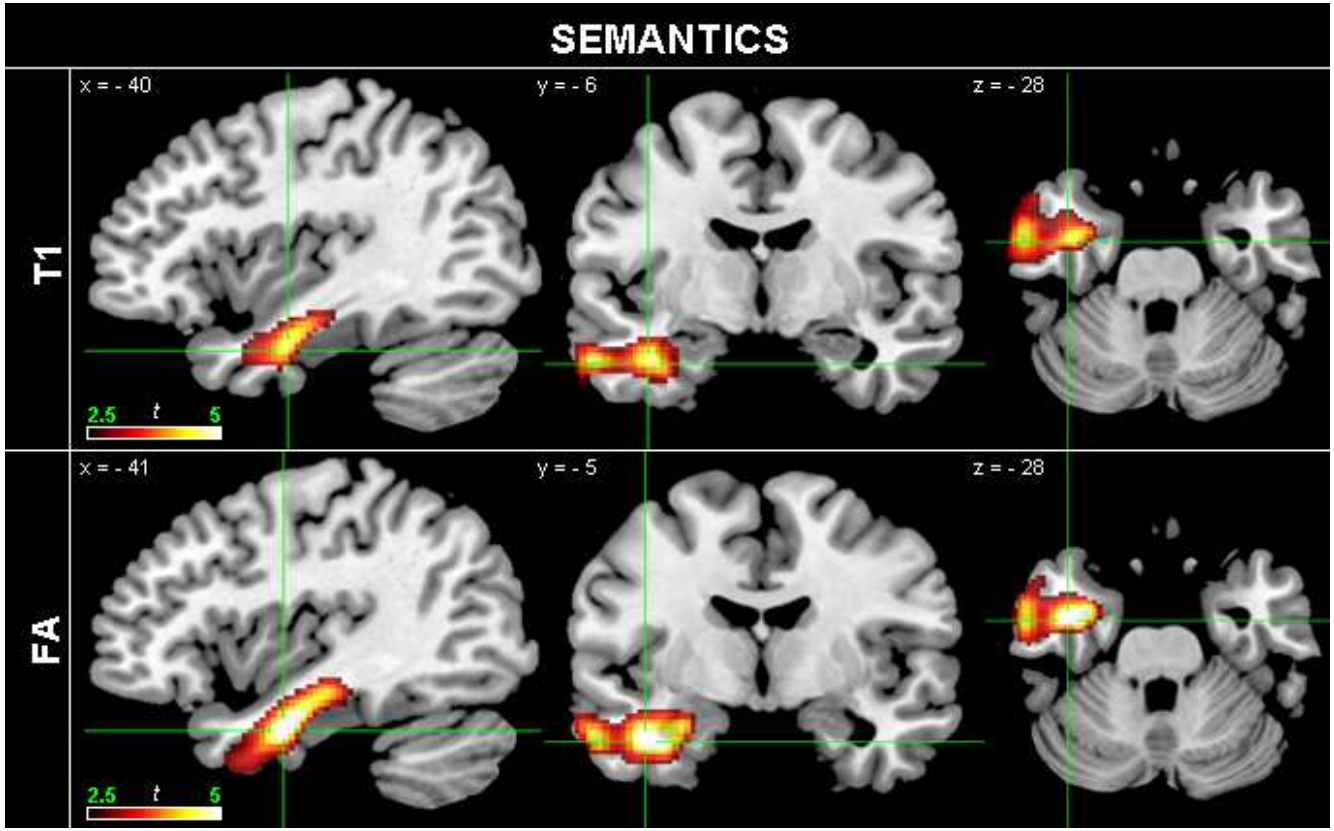

Figure 6.3. Semantic clusters from VBCM analysis. T1-weighted cluster (top) = 1261 voxels, $p < .005$ voxel-level, $p < .001$ FWE-corrected cluster-level. FA cluster (bottom) = 2134 voxels, $p < .005$ voxel-level, $p < .001$ FWE-corrected cluster-level.

Cognition

As reported in Chapter 5 scores on the cognitive factor did not significantly relate to any regions in the T1-weighted image analysis. This was replicated in the FA analysis, with no significant clusters surviving correction for multiple comparisons. However, a significant correlation was identified between cognitive performance and ACM values in a cluster in the right hemisphere. The cluster, shown in Figure 6.4, overlapped with the very anterior extent of the arcuate fasciculus in the frontal lobe and surrounding cortical areas including mid to posterior insula, premotor cortex (BA 6), rolandic operculum (BA 48), and anterior/mid portions of the STG (with minimal extent into MTG).

The result for cognition in ACM was located in the contralesional hemisphere, outside the area where our participants' lesions were located on the T1-weighted images. Therefore we conducted comparisons between our chronic stroke aphasic participants and a group of age- and education-matched healthy controls (n = 19) to ascertain whether this cluster represented an area where performance related to connectivity because of increased or decreased connectivity in some of our aphasic participants. Details of the control group are given in Supplementary Information.

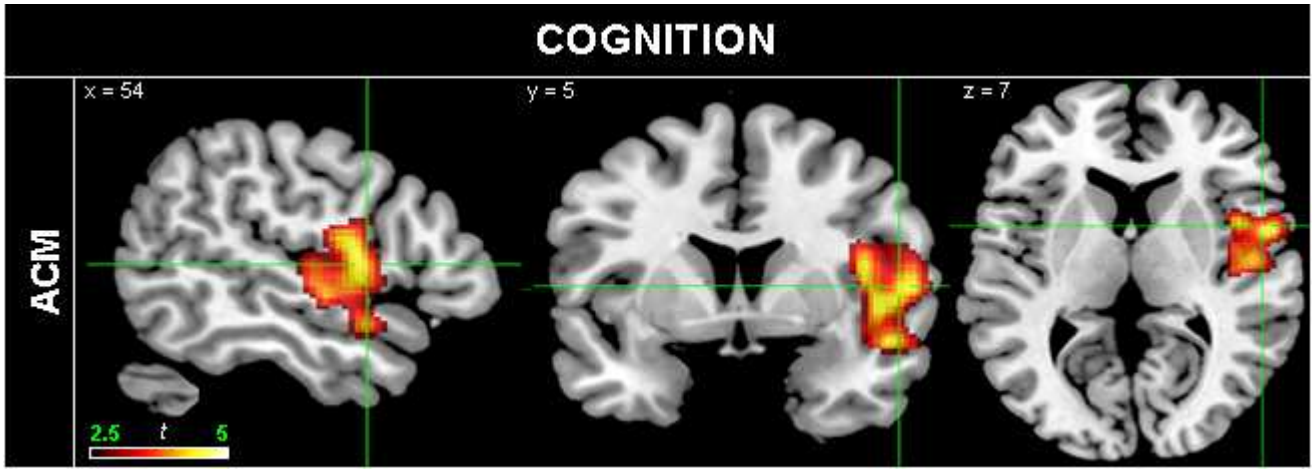

Figure 6.4. Cognitive cluster from VBCM analysis. ACM cluster = 1930 voxels, $p < .005$ voxel-level, $p < .001$ FWE-corrected cluster-level.

This comparison was conducted by splitting the aphasic participant group based on their scores on the cognitive factor, and labelling the top half of the group "High" (n = 16) and the bottom half of the group "Low" (n = 15). We then conducted a voxel-based morphometry (VBM) analysis (Ashburner & Friston, 2000) comparing voxel-level ACM values between the "High" group and the control group, within the right hemisphere cluster identified as relating to cognition in the VBCM. A separate VBM analysis then compared the "Low" group and control group. The VBM analysis showed that the "High" group on average had higher ACM within the right hemisphere cluster than healthy controls, as shown in Figure 6.5. The "Low" group did not show any significant differences from controls in ACM within the right hemisphere cluster. Therefore, the cognitive cluster in the ACM VBCM analysis appears to reflect the fact that aphasic participants who performed well on cognitive tasks showed increased connectivity in this region of the right hemisphere (relative to controls)[3].

[3] Similar follow-up analyses for all of the left hemisphere correlations were conducted and all revealed diminished connectivity relative to controls.

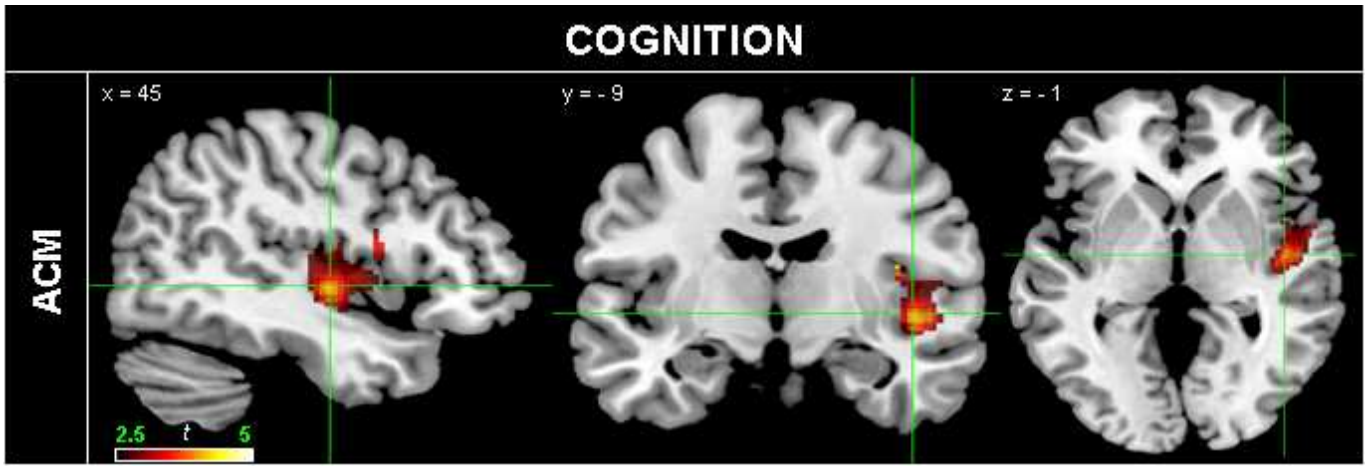

Figure 6.5. Clusters where "high" cognition aphasic participants had significantly higher ACM values than control participants in a follow-up VBM analysis. (Three clusters were identified: 649 voxels at $p < .005$ voxel-level, $p < .05$ FWE-corrected cluster-level; 87 voxels at $p < .005$ voxel-level, $p < .05$ FWE-corrected cluster-level; 40 voxels at $p < .005$ voxel-level, $p < .05$ FWE-corrected cluster-level). MNI co-ordinates shown: x = 45, y =-9, z = -1.

Comparison Across Imaging Methods and Language Functions

The results obtained for phonological performance were highly consistent over image types (T1-weighted, FA, and ACM). However, this was not the case for semantics. Whilst the semantic T1-weighted and FA clusters overlapped heavily, no semantic ACM clusters were identified in the VBCM analysis. While one interpretation of this result is that damage to the ventral pathway results in more localised disruption than damage to the dorsal pathway, explorations of the impact of constrained simulated lesions on ACM values along both pathways show a similar amount of long-range disruption (see Chapter 3).

Another interpretation of the divergence across measures for the semantic factor focuses on the differing neural distribution of white matter pathways along the dorsal and ventral routes. Areas found to correlate with phonological performance in both local grey and white matter measures (T1-weighted imaging and FA) overlapped with one major language pathway, the arcuate fasciculus (shown in Figure 6.6). In contrast, semantic performance related to local measures in a cluster which overlapped with a number of different ventral white matter pathways, likely to include at least the inferior longitudinal, inferior-fronto-occipital, and uncinate fasciculi, pathways which have disparate origins and terminations (see Figure 6.6). As a result, the probability of the regression analysis employed in the VBCM finding a reliable cluster of voxels in the ACM values in this region was likely to be lower because of wider voxel-level variability in ACM values within and between participants. Indeed, the standard deviations across participants of ACM values in semantic cluster voxels were significantly higher than ACM values in phonological cluster voxels ($p = 0.012$).

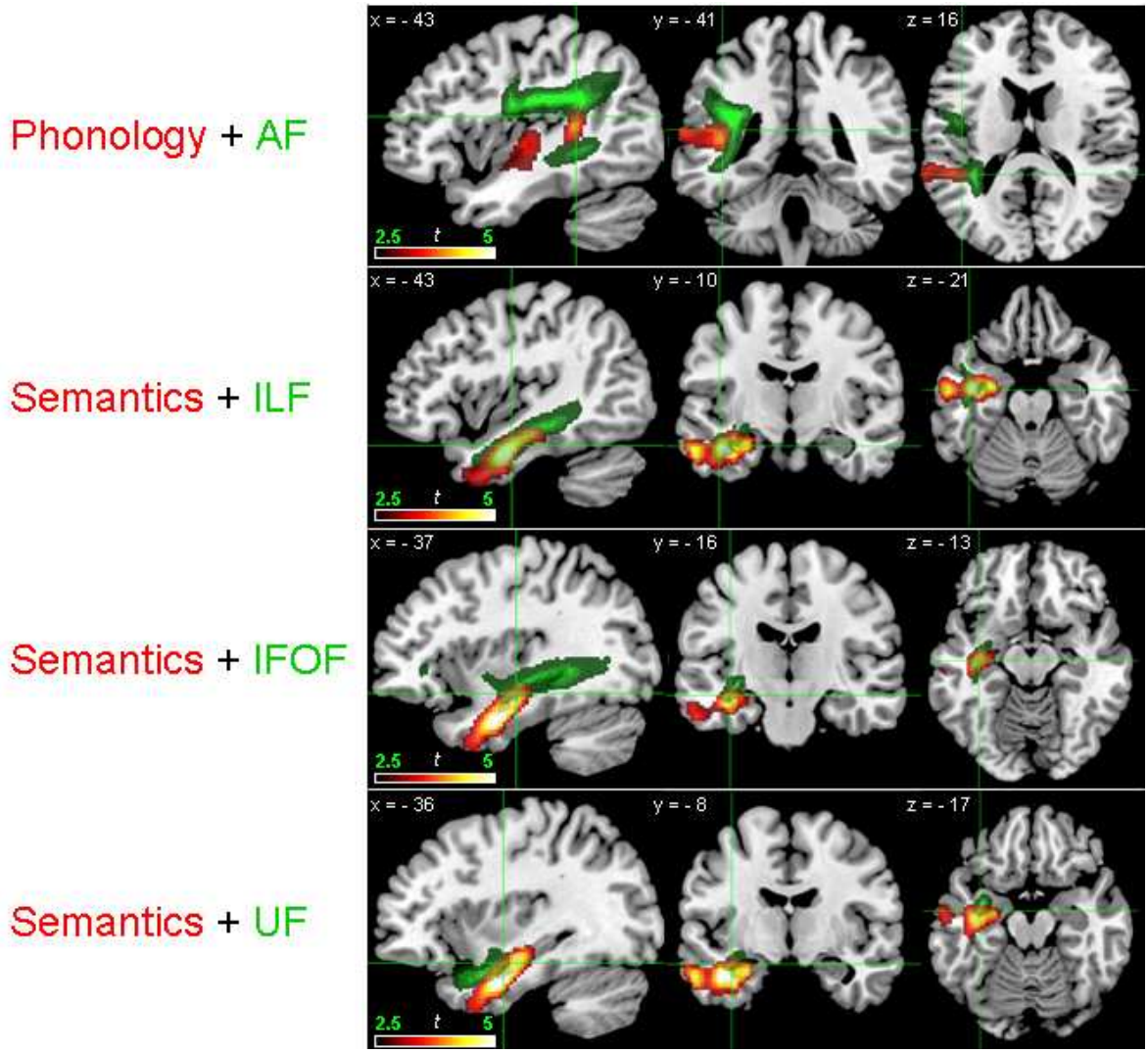

Figure 6.6. Phonological and semantic fractional anisotropy (FA) clusters (hot) overlaid on white matter language pathways they overlap with (green). The phonological cluster overlaps with the arcuate fasciculus (top row) and the semantic cluster overlaps with the inferior longitudinal fasciculus (second row), inferior fronto-occipital fasciculus (third row), and uncinate fasciculus (bottom row).

To test our hypothesis that the regression did not find significant clusters for semantics because of potentially large variance in voxel-wise ACM values in anterior temporal regions, we investigated whether semantic performance would correlate with *average* ACM across the area shown to correlate with semantics in the FA analysis. This would suggest that semantic performance did indeed correlate with anatomical connectivity in these regions, but that a consistent cluster of voxels was not identified

across individuals owing to voxel-level variability in ACM in this area. We conducted 'averaged analyses' for phonology and semantics. This involved taking the significant FA cluster locations for each factor, and then calculating each participant's average ACM value across all of the voxels within that cluster. We then regressed participants' average ACM values within the cluster against their score for that factor. For example, for the semantic analysis each participant's average ACM value across the semantic FA cluster was regressed against their score on the semantic factor.

As we would expect, phonological performance significantly predicted average ACM value in the phonological FA cluster ($\beta = .690$, $p < .001$), consistent with the results of the voxel-wise analysis. Participants' semantic performance was also found to significantly predict their average ACM value in the semantic FA cluster area ($\beta = .424$, $p = .017$), an effect which did not emerge in the original voxel-wise semantic analysis. This significant relationship with average ACM also contrasts with a voxel-level analysis conducted within the same region of interest (the semantic FA cluster), which revealed absolutely no significant results (at voxel-level $p < .005$). This suggests that the failure to identify a significant relationship between the semantic factor and voxel-level ACM is the consequence of the greater diversity of long-range white matter tracts found in this region, meaning that damage to any given tract is more variable for the ventral than dorsal pathways.

Discussion

In this study we investigated changes in cortical areas and white matter connectivity that underlie patterns of behavioural performance in participants with chronic stroke aphasia. In our voxel-level analyses, phonological processing was associated with overlapping brain regions in all three brain measures, with significant clusters emerging in regions including the primary auditory cortex and underlying dorsal route white matter in the T1-weighted, FA, and ACM analyses. Participants' semantic performance was shown to relate to a different pattern of changes in the imaging measures, with significant clusters emerging in the ventral language route and adjacent cortex in analyses of the local measures, T1-weighted imaging and FA, but not in the voxel-wise ACM analysis. Finally, cognitive performance did not correlate with any specific regions in the analyses of the local brain measures, T1-weighted imaging and FA. However, significant results did emerge in the analysis of the more global connectivity measure, ACM, with a region in the right frontal lobe being found to correlate with cognitive performance. Further investigation revealed that this was likely to reflect compensatory changes, with participants who scored highly on the cognitive tasks showing increased connectivity relative to controls in that region.

The different patterns of results across imaging types for different language tasks suggests that these different processes are likely to rely on brain networks that differ in the nature of their neuroanatomical distribution. In the case of phonology, the systematicity of inputs and outputs permits a direct pathway linking frontal to temporo-parietal language cortices (Plaut & Kello, 1999; Ueno et al., 2011). Semantic language processes, such as comprehension of spoken or written stimuli, require input from a variety of brain regions to be transmitted to and from the semantic hub in the anterior temporal lobe (Patterson, Nestor, & Rogers, 2007). Such a view is consistent with research demonstrating disruption to ventral white matter pathways as a result of anterior

temporal damage in semantic dementia (Acosta-Cabronero et al., 2011). Cognitive control is likely to require even more diverse cortical and connectivity network mappings than semantics. Domain-general cognitive control systems have been characterised as more highly distributed than the "processors" that they have control over, and have been associated with widely distributed bilateral brain regions (Power & Petersen, 2013). Hence, the different functions we have investigated appear to make use of different types of white matter networks. These networks appear to be graded in their distributed-ness, from the relatively direct bi-directional mapping of phonology, through the convergence of multiple information sources in and out of a central hub in semantics, to the highly distributed workings of the cognitive network. These networks are depicted schematically in Figure 6.7.

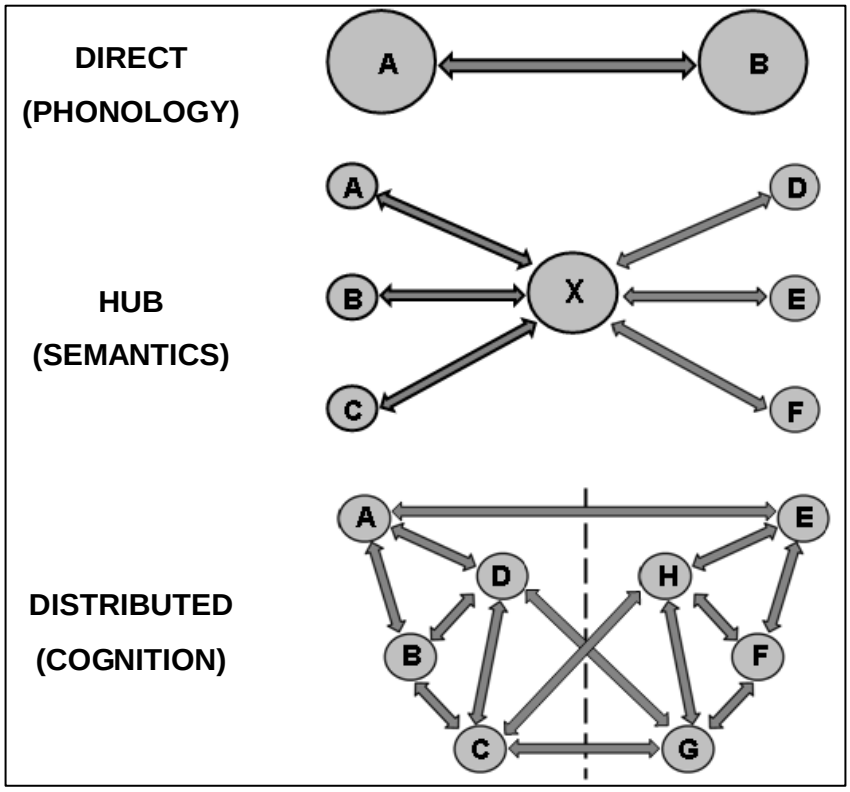

Figure 6.7. Schematic depicting different grades of distribution in the brain networks utilised by different behavioural functions. Phonological processing is subserved by a single bi-directional pathway (top), semantics depends upon a number of distributed inputs and outputs to and from a central hub (middle), and cognition is a function of a highly distributed bilateral network (bottom).

Considering the neural correlates of phonological processing, the cortical areas we identified accord with those found to be involved in phonological processing in functional neuroimaging. Left STG has previously been found to be more activated in repetition of pseudowords than real words in healthy individuals (Saur et al., 2008). Large-scale meta-analyses of functional neuroimaging studies of language have identified the left STG and STS as playing a role in phonological processing, particularly auditory processing of speech sounds (Price, 2010, 2012; Vigneau et al., 2006). The same region has also been implicated in speech production, potentially playing a role in feedback processes which occur during speech (Price, 2010, 2012; Pulvermüller & Fadiga, 2010). Price, Crinion, and Macsweeney (2011) proposed a generative model of speech production in which it is suggested that the posterior STS is involved in prediction of speech output post-articulation. This concurs with evidence suggesting that both speech production and speech perception require continuous feedback from auditory and or motor and somatosensory systems (Pulvermüller & Fadiga, 2010).

Bi-directional communication between auditory cortex and frontal language regions is likely to be subserved by the dorsal language pathway (Pulvermüller & Fadiga, 2010). Given its potential role in both phonological input and output processing it is unsurprising that the arcuate fasciculus (a constituent of the dorsal pathway) was included in our phonological cluster. Deficits in repetition, a task involving phonological input and output, have previously been found to relate to arcuate fasciculus damage in acute and chronic stroke aphasic individuals (Breier et al., 2008; Kümmerer et al., 2013), but our study is the first to confirm this using a direct measure of white matter connectivity. Work using tractography and functional neuroimaging in healthy individuals, found that cortical regions shown to be active during repetition, particularly of pseudowords, were connected via the arcuate fasciculus (Saur et al., 2008). Electro-

stimulation of the arcuate fasciculus has also been found to result in production of phonological paraphasias in picture naming (Duffau et al., 2002, 2008). Such evidence points towards phonological processing being supported by a bi-directional network linking temporo-parietal to inferior-frontal cortices via the arcuate fasciculus. Phonological deficits in our group of participants with chronic stroke aphasia localised to the posterior part of this network.

Although there is much evidence to suggest that the IFG contributes to phonological processes (e.g., Gough, Nobre, & Devlin, 2005; Price, 2010; Vigneau et al., 2006), it did not appear in our phonological cluster. This is likely to be due to the involvement of IFG in other elements of the language battery and the focus of our analysis on brain areas that *uniquely* correlate with a particular function. IFG is likely to play a role in semantic and cognitive processing (e.g., Binder, Desai, Graves, & Conant, 2009; Binney, Embleton, Jefferies, Parker, & Ralph, 2010; De Baene, Albers, & Brass, 2012; Gough et al., 2005; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997; Price, 2010, 2012), and as such it would not be apportioned any unique variance in our regression model. This of course does not mean that the IFG does not support phonological processing, merely that this is not its exclusive role. Although different functions can be localised to different regions within the IFG (e.g., Gough et al., 2005), it is unlikely that the stroke lesions of the current sample would impinge upon one small functional subregion of the IFG selectively.

Our participants' semantic performance correlated with a large cluster in the anterior temporal lobe, much of which overlaps with ventral white matter, in both the T1-weighted and FA analyses. This is in line with findings from structural and functional imaging studies in healthy individuals and patient groups. Cortical areas included in our semantic cluster, such as anterior middle temporal, inferior temporal and fusiform gyri, have been shown to be activated during tasks which require semantic processing in

healthy individuals (Binder, Desai, Graves, & Conant, 2009; Gesierich et al., 2012; Price, 2012; Vigneau et al., 2006; Visser, Jefferies, & Lambon Ralph, 2010; Visser, Jefferies, Embleton, & Lambon Ralph, 2012). Rates of semantic errors produced by individuals with stroke aphasia in picture naming tasks have been found to relate to integrity of the anterior temporal lobe, particularly the anterior to mid MTG (Schwartz et al., 2009). Reductions in the rate of such errors have been found to relate to changes in temporal lobe activations following therapeutic interventions (Fridriksson, Richardson, et al., 2012).

The fact that our semantic cluster overlaps with pathways of the ventral language route is in keeping with previous findings implicating the ventral route in tasks involving semantics such as spoken word comprehension. For example, a recent study of acute stroke aphasics found that the lesions of individuals with comprehension deficits overlapped with the location of the ventral language pathway in healthy individuals (Kümmerer et al., 2013). Comprehension performance by chronic stroke aphasics has also been found to relate to ventral route integrity, with decreased FA in ventral white matter relating to poorer comprehension performance (Rolheiser et al., 2011). Semantic paraphasias have been induced by intra-operative stimulation of the inferior fronto-occipital fasciculus, which has been claimed to constitute at least part of the ventral language route (Duffau et al., 2009; Duffau, 2008; Mandonnet et al., 2007). Other potential constituents of the ventral pathway that have been implicated in language comprehension include the inferior longitudinal and uncinate fasciculi (Turken & Dronkers, 2011).

The ventral route's role in processing meaning necessitates bi-directional connections between multiple, widely distributed cortical areas and the semantic hub in the anterior temporal lobe (Patterson et al., 2007). Tractography in healthy individuals has shown that there is convergence of white matter pathways in a caudo-rostral direction

along the anterior temporal lobe (Binney, Parker, & Lambon Ralph, 2012). In order to carry out its role as an amodal semantic hub, the anterior temporal lobe requires bi-directional connections to areas such as the primary auditory cortex, visual areas, and frontal areas, such that it can process (and combine) different kinds of input information and also produce output in a range of modalities. Ventral route pathways such as the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus, all constitute ideal anatomical conduits for such interactions.

Frank semantic representational impairments are relatively rare in stroke aphasia, partly due to the vasculature of the ATL, which has a dual blood supply in most individuals (Borden, 2006; Conn, 2003), but also because semantic knowledge tends to be bilaterally distributed (Coccia, Bartolini, Luzzi, Provinciali, & Lambon Ralph, 2004; Jefferies & Lambon Ralph, 2006; Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). Semantic representational deficits are, however, a key feature of semantic dementia. The bilateral temporal lobe atrophy seen in semantic dementia is likely to, at least in more advanced stages, impact upon all white matter pathways of the ventral route as they pass through the inferior anterior temporal lobe (Acosta-Cabronero et al., 2011; Agosta et al., 2010; Galantucci et al., 2011; Schwindt et al., 2011). In contrast, in stroke aphasia lesions are more likely to impact upon specific components of the ventral route. Of course more than one pathway may be damaged in stroke aphasia, but usually this will result in deficits in accessing semantics from one or more modalities, rather than a core representational semantic deficit. So whilst damage to ventral route paths connecting to primary auditory cortex may result in impairments in spoken language comprehension (Robson, Sage, & Lambon Ralph, 2012), if, for example, connections with occipital areas are affected, alexia is a likely outcome (Epelbaum et al., 2008).

The convergence of distributed pathways in the ATL potentially explains why we found significant relationships between semantic performance in the ACM analysis when

it was averaged over a wider cluster but not in our original voxel-level analysis. Given that a number of different ventral white matter pathways are involved in semantic processing, and that stroke lesions are likely to impinge on different pathways across individuals, the variability of the ACM values within each voxel in the ventral route is likely to be high. As a result, the fact that the regression did not identify a significant semantic ACM cluster is perhaps not surprising. Unlike FA, ACM values within a voxel reflect connectivity to that voxel from the rest of the brain, rather than integrity of that voxel. As such, the results in ACM reveal areas where connectivity levels have changed as a result of both local and more distant brain changes, including lesions. By combining these two complementary white matter metrics, we can better understand the patterns of performance shown by individuals with stroke aphasia, as we can take account of direct and more indirect changes that can occur in language processing networks.

The fact that ACM reflects different types of changes in brain networks to those seen on more local brain measures, is evidenced by the results seen for our cognitive factor. The lack of a relationship between either the T1-weighted images or FA maps and cognitive performance is likely to reflect the fact that this domain-general function is highly distributed in terms of cortical areas and white matter connectivity (Dosenbach et al., 2007; Ham & Sharp, 2012; Power & Petersen, 2013; Siegel et al., 2011). However, because ACM is a more global measure it can detect long-range changes in connectivity that arise as a result of focal damage. In this case the ACM changes were located as far away as the contralesional hemisphere, and it is worth noting that such changes would be missed if whole-brain tractography was not employed. Our ACM analysis revealed an area of right hemisphere where better performance on cognition related to increased ACM. These changes appeared to be compensatory in nature as individuals with higher scores on the cognitive factor showed higher ACM values in this region than control participants. Cognitive status has previously been shown to be a key predictor of anomia

therapy outcome (Lambon Ralph et al., 2010), therefore any compensatory changes underpinning improved cognitive performance could play a significant role in recovery processes.

The lack of relationship between left hemisphere neural measures and cognitive performance in this group of participants is likely to reflect the fact that cognition relies on a widely distributed network, which involves multiple left (and right) hemisphere structures. Damage to any part of the network may result in disruption to performance on general cognitive measures. The location of damage to the network and extent of cognitive impairment is variable within our participant group, who were selected on the basis of problems with language rather than general cognition. Given this level of variability, it is therefore unsurprising that local brain measures did not reliably correlate with cognitive performance in this group. However, it would appear that no matter which left hemisphere component of the cognitive network is damaged, there is related upregulation in a consistent component of the right hemisphere cognitive network, which was identifiable using ACM.

The right hemisphere cognitive cluster overlapped with the anterior termination of the arcuate fasciculus in the frontal lobe, and surrounding cortex included mainly premotor cortex, mid to posterior insula, and the rolandic operculum (BA 48). Catani et al. (2012) state that the anterior segment of the arcuate fasciculus corresponds to the third branch of the superior longitudinal fasciculus, and that dysfunction of this white matter path in the frontal lobe is related to cognitive impairments such as deficits in memory, inhibition and abstract thinking. Cortical areas included in the cluster have previously been implicated in relational integration, a key component of Raven's Coloured Progressive Matrices (Prabhakaran et al., 1997; Raposo, Vicens, Clithero, Dobbins, & Huettel, 2011; Raven, 1962), a task which loaded heavily on the cognitive factor. Mental arithmetic, particularly difficult arithmetic, and performance on executive function tasks

such as the Stroop task have also been associated with such areas (Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Keller & Menon, 2009; Wu et al., 2009). Our results suggest that connectivity to areas subserving such functions may be enhanced in those chronic stroke aphasic participants with better cognitive processing. Functional imaging data would be needed to verify whether participants with higher structural connectivity values in this region are actually utilising this region more than controls in order to perform cognitive tasks.

Crofts et al. (2011) have previously demonstrated contralesional hemisphere increases in a structural measure called 'communicability' in individuals with chronic focal subcortical stroke lesions. Although Crofts et al. (2011) did not relate their brain network changes to behavioural performance of participants, they suggested that potentially adaptive brain changes may arise as a result of dendritic branching, synaptogenesis, or development of new white matter connections (Crofts et al., 2011). Similar processes could potentially be involved in the ACM increases seen to relate to improved cognitive performance in this study, although further work involving longitudinal imaging is clearly needed to explore these possibilities.

Conclusions

In this study, we have related PCA-derived scores of core language abilities to direct measures of white matter connectivity amongst chronic stroke aphasic participants for the first time. Acquiring and comparing results across the complementary imaging measures of T1-weighted imaging, FA, and ACM, allowed us to consider the structural impact of left hemisphere stroke on the language network as a whole (Crinion et al., 2013). This included negative changes, indicating damage to different components of the dual route language system that corresponded to impaired performance on tasks tapping phonological and semantic processing. We also identified positive changes in

connectivity associated with higher performance on general cognitive measures, potentially reflecting post-stroke reorganisation. This has implications for conceptions of recovery and rehabilitation, as future work may allow exploitation of the plasticity which we have found evidence of in the adult brain to enable more effective recovery from aphasia.

Supplementary Information

Behavioural Assessments

The language assessments that all stroke aphasic participants completed were: nonword minimal pairs (Psycholinguistic Assessment of Language Processing [PALPA] 1; Kay, Lesser, & Coltheart, 1992), word minimal pairs (PALPA 2; Kay et al., 1992), nonword immediate repetition (PALPA 8; Kay et al., 1992), word immediate repetition (PALPA 9; Kay et al., 1992), nonword delayed repetition (PALPA 8; Kay et al., 1992), word delayed repetition (PALPA 9; Kay et al., 1992), spoken word-to-picture matching (Category Comprehension Test in Cambridge Semantic Battery), written word-to-picture matching (Category Comprehension Test in Cambridge Semantic Battery), the 64-item picture naming test (Cambridge Semantic Battery), the Boston Naming Test (Goodglass, Kaplan, & Barresi, 2000), the Camel and Cactus semantic association test – picture version (Cambridge Semantic Battery), 96-item synonym judgement (Jefferies, Patterson, Jones, & Lambon Ralph, 2009), and spoken sentence comprehension (Comprehensive Aphasia Test; Swinburn, Porter, & Howard, 2005).

The additional cognitive tasks were: the Brixton Spatial Rule Anticipation Task (Hayling & Brixton Tests; Burgess & Shallice, 1997), Raven's Coloured Progressive Matrices – Sets A, AB, and B (Raven, 1962), Forward Digit Span (Wechsler Memory Scale-Revised; Wechsler, 1987), and Backward Digit Span (Wechsler Memory Scale-Revised; Wechsler, 1987).

On all of the language assessments, apart from the CAT sentence comprehension test (Swinburn et al., 2005), participants were scored on their first response. For sentence comprehension two points were given for each prompt correct response and one point was given for delayed correct responses or self-corrections, as per the scoring system for the CAT. On naming assessments responses were deemed correct if they were produced

within five seconds of presentation. Minor dysfluencies in responses were marked correct. Repetition of spoken stimuli was provided if requested by participants.

Lesion Overlap Map

The lesion overlap map, shown in Figure 6.1, was generated using Seghier et al.'s (2008) automated lesion identification procedure, implemented with default settings apart from the *U* threshold, which was set at 0.5. Data from 19 healthy control participants (see below) were included in the procedure to identify abnormal tissue.

Healthy Control Participants

A group of healthy control participants was used in the unified segmentation-normalisation and lesion identification procedure (Seghier et al., 2008). The same group was also used in the VBM analysis comparing participants who scored 'High' and those who scored 'Low' on Factor 3 to healthy controls. The control group included 8 females and 11 males. All were right-handed and had no history of neurological illness. The control group's mean age was 68.21 years (SD = 5.99) and mean number of years in education was 13.06 years (SD = 2.77).

Table 6.3

Participants' Scores on the Behavioural Assessment Battery

	Nonword Repetition: Immediate	Nonword Repetition: Delayed	Word Repetition: Immediate	Word Repetition: Delayed	64-Item Naming	Boston Naming Test	Nonword Minimal Pairs	Word Minimal Pairs	Spoken Word to Picture Matching	Written Word to Picture Matching	CAT Spoken Sentence Comprehension	96 Synonym Judgement	Camel and Cactus Test: Pictures	Brixton Spatial Anticipation Test[a]	Raven's Coloured Progressive Matrices[b]	Forward Digit Span[a]	Backward Digit Span[a]
DBb	**0.00**	**0.00**	**37.50**	**0.00**	**0.00**	**0.00**	**22.22**	**52.78**	**57.81**	**31.25**	**12.50**	**48.96**	**53.13**	**38.18**	**30.56**	**25.00**	**0.00**
ES	**0.00**	**0.00**	**0.00**	**0.00**	**4.69**	**0.00**	**48.61**	**54.17**	**78.13**	**90.63**	**25.00**	**72.92**	**73.44**	**40.00**	66.67	**0.00**	**0.00**
ESb	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**54.17**	**50.00**	**87.50**	**60.94**	**34.38**	**52.08**	**43.75**	**23.64**	38.89	**0.00**	**0.00**
KW	**0.00**	**0.00**	**3.75**	**0.00**	**1.56**	**0.00**	**75.00**	**65.28**	**95.31**	**92.19**	**84.38**	**82.29**	89.06	50.91	80.56	**50.00**	42.86
BS	**3.33**	**0.00**	**5.00**	**1.25**	**3.13**	**1.67**	**65.28**	**75.00**	**92.19**	100.00	**31.25**	**78.13**	**84.38**	**38.18**	91.67	**0.00**	**0.00**
KL	**0.00**	**0.00**	**6.25**	**0.00**	**4.69**	**1.67**	**75.00**	**77.78**	**92.19**	98.44	**28.13**	**68.75**	**78.13**	61.82	88.89	**0.00**	**0.00**
LM	**13.33**	**3.33**	**27.50**	**0.00**	**1.56**	**1.67**	**43.06**	**54.17**	**67.19**	**53.13**	**28.13**	**57.29**	**68.75**	**32.73**	61.11	**0.00**	**0.00**
DB	70.00	**30.00**	**85.00**	**83.75**	**7.81**	**8.33**	87.50	**58.33**	**64.06**	**76.56**	**31.25**	**59.38**	**82.81**	**40.00**	86.11	**37.50**	**14.29**
PE	**13.33**	**3.33**	**45.00**	**41.25**	**20.31**	**11.67**	**77.78**	86.11	96.88	100.00	**50.00**	**79.17**	**84.38**	**41.82**	80.56	**25.00**	28.57
KS	73.33	80.00	93.75	95.00	**31.25**	**13.33**	94.44	95.83	**71.88**	**67.19**	**84.38**	**84.38**	**68.75**	52.73	86.11	100.00	57.14
KK	**33.33**	**3.33**	**56.25**	**26.25**	**42.19**	**15.00**	**72.22**	95.83	**93.75**	**95.31**	**46.88**	**81.25**	**84.38**	76.36	100.00	**0.00**	**0.00**
WM	**36.67**	**30.00**	**55.00**	**41.25**	**39.06**	**25.00**	**47.22**	**63.89**	**92.19**	**75.00**	**50.00**	**61.46**	**51.56**	**43.64**	61.11	**37.50**	28.57
GL	93.33	63.33	100.00	**81.25**	**68.75**	**31.67**	98.61	97.22	96.88	**95.31**	**65.63**	**75.00**	**73.44**	58.18	91.67	**37.50**	28.57
DCS	**40.00**	56.67	**72.50**	**68.75**	**67.19**	**43.33**	97.22	97.22	100.00	98.44	**93.75**	91.67	95.31	81.82	100.00	62.50	57.14
JSa	**30.00**	**3.33**	**75.00**	**65.00**	**62.50**	**46.67**	**75.00**	**77.78**	**92.19**	98.44	**59.38**	**81.25**	**76.56**	67.27	83.33	**50.00**	28.57

	Nonword Repetition: Immediate	Nonword Repetition: Delayed	Word Repetition: Immediate	Word Repetition: Delayed	64-Item Naming	Boston Naming Test	Nonword Minimal Pairs	Word Minimal Pairs	Spoken Word to Picture Matching	Written Word to Picture Matching	CAT Spoken Sentence Comprehension	96 Synonym Judgement	Camel and Cactus Test: Pictures	Brixton Spatial Anticipation Test[a]	Raven's Coloured Progressive Matrices[b]	Forward Digit Span[a]	Backward Digit Span[a]
JSc	**36.67**	63.33	**90.00**	91.25	**71.88**	**53.33**	**75.00**	86.11	98.44	98.44	**75.00**	**76.04**	**82.81**	**43.64**	77.78	62.50	42.86
JA	**36.67**	**40.00**	**85.00**	**78.75**	**79.69**	**63.33**	90.28	95.83	100.00	98.44	**78.13**	**63.54**	87.50	61.82	80.56	**37.50**	**0.00**
JJ	**36.67**	**23.33**	**82.50**	**73.75**	**85.94**	**63.33**	**51.39**	**80.56**	98.44	98.44	**56.25**	93.75	**53.13**	**43.64**	41.67	62.50	42.86
JM	83.33	83.33	100.00	98.75	**81.25**	**63.33**	93.06	95.83	100.00	100.00	100.00	**82.29**	**81.25**	76.36	94.44	**50.00**	57.14
JSb	63.33	**36.67**	**86.25**	**81.25**	**75.00**	**63.33**	**76.39**	88.89	**93.75**	**90.63**	**84.38**	**75.00**	**78.13**	60.00	86.11	62.50	28.57
ER	**53.33**	**36.67**	**70.00**	**81.25**	**71.88**	**65.00**	81.94	88.89	**95.31**	**93.75**	**56.25**	**84.38**	90.63	**41.82**	38.89	**25.00**	**0.00**
HN	**36.67**	**23.33**	**83.75**	**80.00**	**65.63**	**65.00**	**77.78**	**76.39**	**93.75**	**93.75**	**37.50**	**85.42**	**85.94**	**25.45**	75.00	**50.00**	42.86
BH	86.67	80.00	100.00	96.25	95.31	**66.67**	93.06	94.44	98.44	**93.75**	**78.13**	**83.33**	**73.44**	67.27	66.67	62.50	57.14
EB	83.33	**53.33**	100.00	100.00	**81.25**	**66.67**	94.44	98.61	98.44	100.00	**71.88**	94.79	90.63	80.00	100.00	75.00	57.14
DM	**60.00**	**10.00**	**73.75**	**68.75**	**75.00**	**71.67**	80.56	93.06	98.44	98.44	**56.25**	95.83	98.44	50.91	91.67	**37.50**	**0.00**
DS	**56.67**	**33.33**	**88.75**	91.25	**84.38**	**73.33**	**79.17**	**77.78**	100.00	100.00	87.50	93.75	89.06	72.73	72.22	**50.00**	28.57
AG	73.33	83.33	**77.50**	**87.50**	**87.50**	78.33	100.00	98.61	100.00	100.00	87.50	**89.58**	**75.00**	56.36	75.00	100.00	100.00
LH	**56.67**	**50.00**	**82.50**	88.75	**81.25**	78.33	95.83	97.22	96.88	100.00	90.63	92.71	87.50	76.36	88.89	87.50	57.14
JMf	93.33	66.67	96.25	98.75	96.88	80.00	90.28	95.83	100.00	100.00	**71.88**	91.67	93.75	50.91	83.33	62.50	57.14
AL	90.00	90.00	100.00	98.75	**93.75**	88.33	91.67	100.00	100.00	100.00	**84.38**	93.75	**79.69**	60.00	91.67	87.50	85.71
TJ	93.33	83.33	98.75	92.50	95.31	95.00	87.50	98.61	98.44	100.00	**68.75**	**88.54**	**70.31**	52.73	50.00	75.00	28.57

Scores are given as percentages. Scores in bold are those which fall below the cut-off for normal performance. The cut-off was calculated as 2 standard deviations below the mean performance of the healthy control group. a. Cut-off based on published norms. b. No cut-off available.

CHAPTER 7

GENERAL DISCUSSION

The overarching goal of this thesis was to explore the extent to which variation in white matter connectivity could allow us to understand behaviour in chronic stroke aphasia. This issue was explored across four studies, involving a case-series of chronic stroke aphasic participants, a detailed neuropsychological testing battery and advanced structural neuroimaging. The findings of these papers related to issues around classifying performance of individuals with chronic stroke aphasia, relating that performance to structural neuroimaging data, and the ability of different white matter measures, including both local and more global measures, to help explain patterns of impairment and sparing of abilities in chronic stroke aphasia. In what follows, the results of Chapters 3 to 6 will be summarised briefly before considering the broader theoretical implications of these results. The potential clinical applications of these results will then be explored. Finally, the potential directions for future work suggested by this work as a whole will be considered.

Summary of Thesis Findings

Chapter 3 explored whether information regarding white matter connectivity, particularly in the dorsal and ventral language routes, could aid understanding of the behavioural performance of individuals with chronic stroke aphasia. The impact on ACMs of constrained 'lesion' masks placed within key components of the dual route system was first assessed, before ACMs were employed in case examples of participants with real stroke lesions and aphasia. Structural T1-weighted scans, FA maps, and ACMs were presented from two individuals with posterior stroke lesions and differing language profiles and two individuals with anterior stroke lesions and differing language profiles. By taking into account the connectivity information in the ACMs, the language differences between the two participants with posterior lesions and those with anterior lesions could be better explained.

Turning first to the posterior pair, the fact that participant PE presented with more extensive dorsal route connectivity reductions than participant EB, despite their largely overlapping lesions, helped to explain the fact that PE demonstrated impaired performance on all tasks requiring spoken output, whilst EB showed impairments only for more demanding phonological tasks. Dorsal route connectivity also appeared to be a key distinguishing factor in the anterior pair. Participant KW showed evidence of greater abnormalities in dorsal route connectivity than did participant DS, which may partly explain why KW's performance on all tasks involving spoken responses was severely impaired, whilst DS was only mildly impaired on naming and some phonological tasks. These contrasting participant pairs demonstrated the fact that extent of dorsal route connectivity abnormality appeared to be an important determinant of severity of phonological language deficit.

A fifth participant whose stroke lesion fell outside the perisylvian language area but who demonstrated impaired language performance was also presented. Participant KS' performance on tasks of input and output phonology was within normal limits, but was impaired on comprehension of single spoken and written words and other semantic tasks. Examination of KS' ACM revealed reduced connectivity within the ventral language route. This result supported the notion that the ventral path plays a role in semantic processes, including those involved in language comprehension.

Together the case examples presented in **Chapter 3** demonstrate that taking white matter connectivity into account can aid in lesion-symptom mapping, with the character and severity of language deficits reflecting the location and extent of connectivity abnormalities. The results also support the notion of a dual route framework, with phonological processing occurring primarily via the dorsal route and semantic processing via the ventral route. Finally, **Chapter 3** also demonstrated, for the first time, the utility

of ACM in chronic stroke aphasia, and the fact that it can provide whole-brain connectivity information that is complementary to that in FA maps.

In **Chapter 4** the use of ACM in chronic stroke aphasia was explored further, this time at a group level. Rather than the qualitative comparisons between case examples employed in Chapter 3, quantitative differences in connectivity between a group of individuals with chronic stroke aphasia and controls were evaluated. This was followed by identification of connectivity differences between groups of individuals with different aphasic subtypes and controls. VBM analyses aimed at identifying abnormalities in the aphasic group compared to the control group returned similar results in T1-weighted imaging and FA. Both showed extensively overlapping, widespread, left hemisphere reductions. In the ACM results there was more specific delineation of affected connecting structures, with evidence of reductions in connectivity in both the dorsal and ventral language routes relative to controls. In the analyses of aphasic subtypes the T1-weighted results showed extensive overlap between subtypes in the brain areas where tissue concentration was reduced relative to controls. This was particularly the case for the Broca's and mixed nonfluent groups. Differences between subtypes were most pronounced in the ACM analyses. The anomic subgroup in particular showed a much smaller area of reduced connectivity compared to controls, relative to the other subgroups.

Analyses were also carried out to identify whether there were any regions where aphasic participants showed higher brain measures than controls. In the T1-weighted and FA VBM analyses no such areas were identified. However, in the ACM VBM analysis a cluster of higher connectivity in aphasic participants relative to controls was identified in the right hemisphere arcuate fasciculus. The results of the subtype analyses suggested that this effect was driven by the anomic participants. The fact that the area of higher connectivity was found in the homologue of a key language pathway, in the least severe

subgroup of a heterogeneous chronic stroke aphasic group, was interpreted as suggesting that these increases may potentially represent positive adaptive changes. **Chapter 4** therefore further established the utility of ACM in understanding language performance in chronic stroke aphasia, allowing identification of group-level reductions and increases in connectivity.

In **Chapter 5** a data reduction method designed to capture variation in aphasic behaviour in a way that is optimal to relate to underlying brain structure was described. This method involved using rotated PCA to distil behavioural factors that reflected participants' performance across a battery of language assessments. These orthogonal factors were then used as continuous regressors in voxel-level analyses of T1-weighted imaging data. The PCA generated three factors that accounted for participants' performance: phonology, semantics, and cognition. The phonological factor, which correlated strongly with an unrotated general 'severity' factor, explained the most variance in participant performance, followed by the semantic factor, with the cognitive factor explaining least variance. This suggests that in this heterogeneous chronic stroke aphasic cohort phonological ability is the main determinant of language impairments. When participants' PCA factor scores were plotted against their BDAE classifications, although there was some consistency between the measures, it was evident that there was considerable variation within aphasic subtypes and blurring of boundaries between subtypes, in terms of language performance. It was argued that the more refined and graded information regarding participants' language abilities offered by their PCA factor scores is likely to be more pertinent than aphasia subtype if one is interested in identifying neural bases of different language abilities.

The fact that the rotated factors were orthogonal meant that they could be entered simultaneously into a voxel-wise lesion analysis, allowing identification of brain regions uniquely associated with each factor. Areas found to correlate with the PCA-derived

behavioural factors in structural T1-weighted data converged with evidence from functional neuroimaging. Phonological performance was found to correlate with left hemisphere mid to posterior MTG, STG, and STS, Heschl's gyrus, and white matter underlying the primary auditory cortex, likely to correspond to part of the dorsal language route. Semantic performance correlated with tissue concentration in left anterior temporal lobe regions including anterior MTG, STG, ITG, and fusiform gyrus, and underlying white matter likely to correspond to part of the ventral language route. Cognitive performance did not correlate with any brain regions in the T1-weighted analysis, which was interpreted as potentially reflecting the highly distributed nature of modality-independent cognitive processes. The findings of **Chapter 5** therefore support the characterisation of the dorsal route and perisylvian regions as subserving phonological processing, and of the ventral route and extrasylvian regions as subserving semantic processing.

Chapter 6 unified work from the previous chapters by correlating the PCA-derived behavioural predictors described in Chapter 5 with participants' T1-weighted scans, FA maps, and ACMs. This approach enabled investigation of abnormalities in global and local white matter measures, as well as cortical abnormalities, underlying patterns of impaired and intact performance in chronic stroke aphasia. Participants' phonological performance was found to correlate with overlapping clusters in the T1-weighted, FA, and ACM analyses, focused mainly on the primary auditory cortex and underlying dorsal route white matter. Semantic performance correlated with clusters in the anterior temporal lobe, including the ventral language route, in the T1-weighted and FA analyses. No significant clusters emerged in the voxel-wise ACM analysis of semantics, although semantics did correlate significantly with anterior temporal regions in a subsequent analysis of "average ACM" values. Cognitive performance did not significantly relate to any regions in the T1-weighted or FA analyses, but strikingly it did

significantly relate to a cluster on the more global connectivity measure, ACM. Higher ACM values in a right hemisphere frontal lobe cluster were found to correlate with better cognitive performance. Follow-up analyses comparing stroke aphasic participants to controls revealed that this cluster represented an area where those aphasic participants who performed well on cognitive tasks showed increased connectivity relative to controls. This result was therefore interpreted as potentially reflecting compensatory changes in connectivity in the contralesional hemisphere, in participants who demonstrated better cognitive performance.

The different patterns of results obtained for each of the behavioural factors across the three imaging measures was interpreted as suggesting that different behavioural abilities make use of different kinds of white matter networks. These networks appear to be graded in degree of neuroanatomical distribution, from the direct bi-directional dorsal route mappings computed in phonology, to the convergence of multiple distinct ventral route pathways in and out of an anterior temporal lobe hub in semantic processing, through to the highly distributed, bilateral network supporting cognitive processing. Hence, not only did the use of ACM allow identification of negative and positive changes in connectivity which related meaningfully to behavioural performance in individuals with stroke aphasia, but also, through comparison with measures of local integrity, it offered new insights and hypotheses concerning the underlying structure of neural networks supporting different functions. Employing complementary imaging measures revealed differences in the organisation of the structural connectivity networks underlying different language processes, and the abnormalities in such networks that underpin variations in aphasic behaviour.

Theoretical Implications

Stroke Aphasia: Classification of Behavioural Performance

As noted previously, although classification systems such as the BDAE (Goodglass et al., 2000; Goodglass & Kaplan, 1983) and WAB (Kertesz, 1982) may provide broad descriptive information regarding an aphasic individual's language profile, they suffer from a number of limitations. Such limitations include the fact that individuals do not always fit neatly into a particular subtype (Brust et al., 1976), as there can be variation in performance within aphasic subtypes and overlap in performance between aphasic subtypes (Brust et al., 1976; Caramazza & McCloskey, 1988; Marshall, 2010). This point was demonstrated by participant PE in the current thesis, whose language performance overlapped with *both* conduction and Wernicke's aphasia profiles. This issue was highlighted in Chapter 5 when participants' BDAE profiles were plotted according to their performance on different behavioural abilities. An alternative method for capturing aphasic behaviour is described in Chapter 5, using PCA to capture individuals' abilities. The PCA output showed that participants' performance on a large battery of neuropsychological assessments was primarily determined by their phonological ability, followed by their semantic ability, with a smaller contribution to performance being made by more general cognitive ability.

The output of a PCA is influenced by both the assessments and participants included in the analysis. The results reported in Chapter 5 represent findings from an unselected, representative sample of chronic stroke aphasic individuals. The separation between phonological and semantic performance appears to be relatively stable even across different aphasic groups. A case-series study using PCA in a group of sub-acute and chronic aphasic individuals found that naming performance was explained by phonological and semantic factors (Lambon Ralph et al., 2002). A recent study of

individuals with acute stroke aphasia by Kümmerer et al. (2013) found that repetition and comprehension performance separated onto two different factors when PCA was employed. This may reflect the fact that repetition depends heavily on phonology, whilst comprehension also requires semantic processing. A study involving 15 participants with primary progressive aphasia found that performance across a battery of language assessments was explained by two behavioural factors, phonology and semantics (Henry, Beeson, Alexander, & Rapcsak, 2012). Thus, whilst the results presented in Chapters 5 and 6 are dependent upon the individuals' whose data constitute the input for the PCA, this seems to be a reliable approach to capturing the key salient underlying dimensions that determine performance in acquired language disorders.

Stroke Aphasia: Identifying Underlying Brain Bases

In Chapter 1 it was noted that the lesion-symptom approach has provided valuable insights into the neuroanatomical substrates of different language processes and how damage to such substrates underpins different language deficits. However, it was also noted that exceptions to expected mappings between sites of damage and aphasia types have been found (e.g., Basso, Lecours, Moraschini, & Vanier, 1985; Vignolo, Boccardi, & Caverni, 1986; Willmes & Poeck, 1993). Such exceptions could occur due to shortcomings in lesion-symptom mappings at both the brain (lesion) and behaviour (symptom) level. The contribution of the current work to improving mappings at a brain level will be discussed in subsequent sections. At the behaviour level, the fact that the previously described PCA-derived factors capture aphasic performance in a more precise way than labels such as aphasia classifications, means that they also constitute more effective correlates for voxel-wise lesion-symptom analyses. In Chapter 5 a VBM analysis comparing the lesion profiles of different aphasic subtypes on T1-weighted images was shown to provide little information regarding the neuroanatomical bases of

specific language abilities, with a high degree of overlap between subtypes. PCA-derived factor scores were shown to be more appropriate lesion correlates for a number of reasons. Firstly, as has been noted elsewhere, continuous behavioural correlates offer more graded, more sensitive, regressors for lesion analysis than categorical lesion correlates such as BDAE subtypes or impaired or intact performance on a given language task (Bates et al., 2003; Borovsky et al., 2007; Tyler et al., 2005a).

The brain areas found to correlate with participants' phonological and semantic performance in Chapter 5 largely correspond with findings using other methodologies such as functional neuroimaging and rTMS. Congruence between results obtained using these different methodologies is reassuring, as each approach inevitably has its own limitations. Cross-method validation strengthens the confidence with which conclusions can be drawn regarding the involvement of particular brain regions in particular cognitive processes. However some cross-method differences are to be expected, for example results found using functional imaging are likely to differ in some respects to those found using lesion analysis. One reason to anticipate such differences is that functional imaging will reveal all areas *involved* in carrying out a task, whilst lesion analysis will reveal the areas that are *necessary* to carry out that task, and the two may not necessarily be equivalent (D'Esposito & Wills, 2000; Price & Friston, 2005; Rorden & Karnath, 2004; Sarter, Berntson, & Cacioppo, 1996).

Even results of rTMS studies, which can be seen as partially bridging the gap between functional neuroimaging and lesion studies, cannot be expected to be identical to those from lesion studies. An rTMS study may, for example, report slowed reaction times following stimulation to a brain region. However, the same brain region would not necessarily be expected to emerge in an analysis correlating performance on the same task with lesion location. Whilst that brain region may contribute to faster, more efficient responses in a healthy brain, hence the slowing effect of rTMS, it may not be critical to

accurate performance of the task and as such would not emerge in a lesion analysis if accuracy was used as a behavioural predictor.

As noted in Chapter 5, some brain regions found to be activated during phonological or semantic tasks in studies employing other methodologies did not emerge in our lesion analyses. Areas that did emerge in the current work can be presumed to be critical to the behavioural process in question. However, brain areas that did not emerge cannot be presumed to be non-essential for the same behavioural process. Just as the results of the PCA depend upon the behavioural performance of the participants' whose data is entered into the analysis, the results of the VBCM analysis also depend upon the lesion distribution of the individuals' whose scans are entered into the analysis. Therefore, some regions found using other methodologies may not have emerged in the current work owing to low frequency of lesion in the participant group in certain brain regions. For this reason the results of the lesion analysis must be interpreted in the context of the lesion overlap map for the cohort.

In the current work there was good lesion coverage of the left perisylvian cortex, however there are voxels where no participants had lesions in extrasylvian cortex and of course the contralesional hemisphere. A further reason for potential absence of certain brain region in results is that the approach employed, i.e., entering all PCA factors into the lesion analysis concurrently, reveals areas that covary uniquely with each behavioural factor. Therefore areas that contribute to more than one behavioural factor would not have emerged as significantly related to any of the behavioural factors. This could be the reason that, for example the IFG did not emerge as relating to phonological or semantic processing. Additionally, it is also possible that different functional subregions of the IFG (Gough et al., 2005) were not selectively damaged in our sample. So, whilst methods such as functional neuroimaging are better suited to capturing all cortical regions

recruited by a given task, the current approach can be employed to identify which grey and white matter regions are necessary for specific behavioural abilities.

The results reported in the current thesis illustrate the fact that PCA factor scores represent effective behavioural regressors when attempting to locate the brain bases of variations in language performance using voxel-level statistical analyses. Work presented in this thesis also aimed to improve lesion-symptom mapping by providing insights on the brain side of the brain-behaviour relationship. Lesion-symptom analyses have previously tended to focus on integrity of grey matter areas underpinning language performance. In the current thesis attempts have been made to go beyond that grey matter bias and to take white matter information into account when assessing neural substrates of language performance.

White Matter Pathways and Language

In Chapter 3 the fact that taking white matter information into account can help explain patterns of performance in stroke aphasia was illustrated in a small group of case examples. Both the local information regarding white matter microstructure in the FA maps, and the more global information regarding structural connectivity in the ACMs, proved useful in understanding participants' language performance. In Chapter 3 and subsequent chapters, whilst FA provided complementary information to that available in the other image types, it was ACM that yielded particularly novel information. This is unsurprising as FA, like T1-weighted imaging, reflects local tissue microstructure. As a more global measure, ACM was able to provide insights into wider abnormalities in the networks underlying language performance seen in stroke aphasia. These abnormalities even included potential increases in connectivity underlying better performance amongst our aphasic participants. Chapter 3 demonstrated that evaluating long-range connectivity information as well as FA can provide useful insights at the individual level. For

example, when reviewing the T1-weighted scan, FA map, and ACM of participant PE, one can see that whilst damage is only evident to the posterior end of the dorsal language route on the T1-weighted image and the FA map, the ACM reveals abnormal connectivity further along the dorsal route. This more extensive disruption of the dorsal language route sheds light on the fact that PE's performance was impaired on any assessment regarding a spoken response, particularly repetition, in line with the phonological role of the dorsal route. Results such as this demonstrate the fact that stroke lesions can cause disruptions in language networks that extend beyond the lesion boundaries and that consideration of this wider disruption is likely to aid understanding of language deficits and prognosis.

In Chapter 4 white matter measures were able to better differentiate aphasic subtypes at the group-level than T1-weighted imaging alone, demonstrating that white matter connectivity (both local and global) is a critical determinant of aphasia profile. This would align with Doricchi et al.'s (2008) claim that long-range white matter pathway disruption may have substantially greater behavioural implications than cortical damage, due to its potentially more widespread effects. In Chapter 6 variation in performance on different core behavioural abilities, as indexed by PCA factor scores, was found to relate to white matter measures in group analyses. For phonology, semantics, and cognition, either one or both white matter measures were found to significantly relate to performance levels. The cluster found to relate to semantics in particular appeared to be largely located in a region of ventral white matter, whilst the result for cognition only emerged in the ACM analyses. The results presented in Chapters 3, 4, and 6 collectively demonstrate that long-range white matter connectivity information, as well as local information regarding local white matter microstructure, can help to further understanding of the neural underpinnings of aphasic performance and the operation of the normal language processing system.

Dorsal and Ventral Language Routes

Recent cognitive and neuroanatomical models of language suppose the existence of a dual route framework in which the dorsal pathway is involved in phonological processing, such as the mapping of sound to articulation involved in spoken word production, and the ventral route is the path by which sound is mapped onto meaning in processes such as comprehension (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hickok & Poeppel, 2004, 2007; Saur et al., 2008; Ueno et al., 2011). All of the results reported across Chapters 3 to 6 are in keeping with such a dual route framework. The validity of the phonology-semantics distinction, which was established at a behavioural level using PCA, is evident at the brain level in the current neuroimaging results. At both the individual case and larger case-series levels the current results suggest that the character and severity of aphasic deficits depends upon the location and extent of disruption within the dual route system. Extent of abnormality in the dorsal language route and surrounding cortex consistently relates to phonological performance, whilst abnormalities affecting the ventral language route and adjacent cortex, are repeatedly shown to relate to semantic processing ability. It is noteworthy that the current results provide evidence that this relationship between the dorsal route and phonology and the ventral route and semantics, which has been reported in the acute stage following stroke (Kümmerer et al., 2013), persists even into the chronic stage, where opportunities for reorganisation may have occurred (in accordance with Rolheiser et al., 2011).

Previous research involving stroke aphasic participants has tended to focus on effects of disruption to either the dorsal route (e.g., Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Schwartz, Faseyitan, Kim, & Coslett, 2012) or the ventral route (e.g., Turken & Dronkers, 2011). Very few studies have looked at how language performance relates to both dorsal and ventral route abnormalities in heterogeneous

stroke aphasic samples, two recent exceptions to this are studies by Kümmerer et al. (2013) and Rolheiser et al. (2011). Kümmerer et al. (2013) showed that in a group of 100 acute aphasic participants repetition performance related to dorsal route integrity, whilst comprehension performance related to ventral route integrity. However, the method employed in this study, and several others (e.g., Schwartz et al., 2012; Turken & Dronkers, 2011) does not involve directly relating aphasic participants' performance to measures of white matter integrity or connectivity. Instead the methodology employed in this case involved correlating participants' performance with high resolution T1-weighted scans to obtain lesion maps associated with each language task. The likely impact on dorsal and ventral paths is then inferred by the amount of overlap between these lesion overlap maps and the location that the pathways are assumed to be in based on previous imaging in healthy individuals. Whilst such an approach offers benefits such as obviating the need to acquire and process diffusion data for aphasic participants, it cannot be used to identify any effects beyond the T1-weighted image lesion boundaries.

Rolheiser et al., (2011) considered dorsal and ventral changes and their relationship to language performance in 24 cases of chronic aphasia, and directly related performance to participants' own white matter measures as measured by FA. Their results showed that phonological production and comprehension tasks related to dorsal route FA, while semantic comprehension and production tasks related to FA in the ventral route. Syntax, meanwhile, was found to relate to FA in both the dorsal and ventral route.

The current work expands upon Rolheiser et al.'s (2011) findings in chronic stroke aphasia in a number of ways. Firstly, rather than using individual language assessments to relate to imaging data, PCA factor scores have been employed. This means that the underlying abilities that language assessments tap are correlated with brain measures, rather than the analyses depending on the particular demands of an

individual test. Another way in which the current work extends that of Rolheiser et al. (2011) is the use of the complementary measure of ACM in addition to FA. Overall the results of the current work concur with those from Rolheiser et al. (2011), with phonology relating to dorsal route measures and semantics relating to ventral route measures. Only one sentence-level task was employed in the current work, spoken sentence comprehension. Therefore it unsurprising that no 'syntax' factor emerged in the PCA for correlation with imaging data. Whilst the current results do not provide any information to support Rolheiser et al.'s (2011) argument that syntax is processed across both pathways, they are certainly not at odds with the notion of a synergistic system. However, functional neuroimaging data are needed to further investigate the extent of interaction between the dorsal and ventral route in language tasks (Cloutman, 2012), and to potentially resolve some of the debate surrounding how syntax is processed in the dual route system (Bornkessel-Schlesewsky & Schlesewsky, 2013; Friederici, 2009, 2012; Griffiths et al., 2012; Papoutsi et al., 2011; Rolheiser et al., 2011).

As well as being consistent with a framework wherein phonology is processed primarily via a dorsal route and semantics via a ventral route, the current results accord with the notion that phonology is primarily a result of perisylvian activity and semantics extrasylvian activity (Price et al., 1997). These two frameworks could represent complementary mechanisms underpinning language processing, with phonological processing occurring primarily in perisylvian cortical regions connected via the dorsal route, and semantic processing involving more extrasylvian cortical regions, such as the anterior temporal lobe, which are connected to other extrasylvian regions and perisylvian language regions via the ventral route. That is, the peri-extrasylvian distinction may be key when considering cortical components of the language network, with dorsal-ventral distinctions being key in the white matter pathways connecting the cortical components.

Evidence of Potential Post-Stroke Adaptation

In addition to relationships between impaired performance and diminished T1-weighted concentration, FA, and ACM, the current thesis found exciting evidence of increased ACM, potentially reflecting positive changes. Turning first to the results reported in Chapter 4, which showed that aphasic participants had higher ACM relative to controls in a cluster in the right hemisphere arcuate fasciculus. Follow-up analyses revealed that this increased connectivity was particularly evident in the anomic subgroup, the least severe subgroup of the heterogeneous aphasic cohort. Of course longitudinal neuroimaging and behavioural data would be required to make definite claims regarding whether this higher connectivity played a role in language recovery post-stroke. However, the fact that the region of higher connectivity was located on the right hemisphere homologue of the dorsal language route, and that it was found amongst participants with the least severe language impairment, points to the possibility that these connectivity changes could have potentially played a role in supporting language recovery.

Potentially positive changes in the right hemisphere arcuate fasciculus have previously been reported in chronic stroke aphasia. Schlaug et al. (2009) found positive changes in the right hemisphere arcuate fasciculus following a therapeutic intervention, in a small group of chronic stroke aphasic participants. Following an intensive programme of melodic intonation therapy, Schlaug et al.,'s (2009) participants showed increased number and volume of fibres in the right arcuate fasciculus and improved language performance, relative to pre-therapy. It is interesting to note that the current work also reports potentially positive changes in the right hemisphere dorsal route homologue in a chronic aphasic sample. The mechanisms underlying the right hemisphere changes observed in the current work are unclear at present, but future work could explore the potential role of processes such as dendritic branching, synaptogenesis,

and development of new white matter pathways (Crofts et al., 2011; see also Zatorre, Fields, & Johansen-Berg, 2012).

In Chapter 6, rather than comparing aphasic participants and controls on a voxel-by-voxel basis, participants' continuous scores on different abilities where regressed against their imaging data. In addition to revealing several regions in the ipsilesional hemisphere where brain measures covaried with performance, these analyses also revealed a single cluster in the contralesional hemisphere. This right hemisphere cluster, which emerged in the ACM analyses, significantly related to performance on the cognitive factor. Follow-up analyses revealed that participants who scored 'high' on the cognitive factor had increased ACM relative to controls within this right hemisphere cluster, in contrast to follow-up analyses conducted for all other results. These increased ACM values relative to controls were seen as potentially reflecting positive adaptive changes in connectivity in those chronic stroke aphasic participants with higher cognitive functioning.

The cluster where ACM related significantly to cognitive ability overlapped with the anterior end of the arcuate fasciculus and surrounding frontal lobe cortex including premotor cortex, the mid to posterior insula, and the rolandic operculum. Damage to this portion of arcuate fasciculus has previously been associated with impairments in cognitive processes such as memory, inhibition, and abstract thought (Catani et al., 2012). The cortical regions encompassed by the cluster have also been previously found to be involved in cognitive processes, such as relational integration, mental arithmetic, and executive functioning (Alexander et al., 2007; Keller & Menon, 2009; Prabhakaran et al., 1997; Raposo et al., 2011; Wu et al., 2009). Those participants who had higher cognitive factor scores appear to have higher connectivity to these regions important for cognitive processes. Whilst the possibility that these participants could have had higher connectivity than average pre-morbidly cannot be ruled out, it seems more likely that

some kind of reorganisation processes post-stroke may explain this increased ACM relative to controls. Of course whether this increased structural connectivity relates to increases in function in this area, and if so how and when, would require further exploration with functional imaging.

If these right hemisphere connectivity increases do indeed reflect some kind of reorganisation, what functional purpose could they serve? Whilst the cohort in the current study were recruited on the basis of having chronic aphasia, rather than cognitive impairments, meaning that their lesions were more focused on brain regions key to language than being distributed throughout the cognitive network, in many cases participants' lesions would have been likely to have interfered with the functioning of at least the left hemisphere component of the cognition network. For example, regions including the anterior inferior parietal lobule and anterior insula have been identified as being involved in fronto-parietal control networks (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), and are likely to have been impacted upon in many cases. This could be the result of direct or indirect lesion effects on cortical components or connections between cortical components of the network. As a result, individuals may have come to rely more heavily upon components of the cognitive network in their unlesioned hemisphere. Post-stroke cognitive ability has been found to impact upon wider functioning, for example ability to complete activities of daily living (Mok, 2004; Zinn et al., 2004). Evidence also suggests that cognitive functioning may affect response to rehabilitative interventions, with cognitive performance previously being found to predict outcomes in anomia therapy (Lambon Ralph, Snell, et al., 2010). Improving general cognitive performance, for example by increasing use of the contralesional hemisphere, could therefore potentially benefit the recovering individual in a number of ways, beyond simply improving performance on cognitive assessments.

The fact that the potentially adaptive connectivity abnormalities found in Chapter 4 and Chapter 6 are in different locations is to be expected based upon the different behavioural correlates in each case. The Chapter 4 right hemisphere ACM cluster was located over the posterior part of the arcuate fasciculus, whilst the Chapter 6 cluster was located much more anteriorly, in the frontal lobe. This reflects the fact that the Chapter 4 cluster represented an area where higher connectivity related to a better language performance, whilst the Chapter 6 cluster represented an area where higher connectivity related to better general cognitive performance. This aligns with previous work in which the posterior extent of the dorsal route has been associated more with language, whilst the anterior tip in the frontal lobe has been related to cognitive processes (Catani et al., 2012). The anatomical separation of the two results is therefore entirely reasonable, particularly when one takes into account the fact that only four of the 16 individuals with 'high' cognitive scores were classified as anomic, and only four of the nine individuals with anomia had 'high' cognitive scores. Although we might have expected the posterior arcuate result seen in the VBM group comparison to also obtain in the VBCM case, it is possible that the relationship between the right posterior arcuate ACM and behavioural performance is non-linear and hence did not emerge using the linear approach adopted in VBCM.

Within the aphasia literature there has been much debate regarding the role of the contralesional hemisphere in language recovery. Whilst results of some studies have suggested that right hemisphere regions, particularly homologues of lesioned language cortices, may contribute to recovery of language function (e.g., Basso et al., 1985; Blank, Bird, Turkheimer, & Wise, 2003; Crinion & Price, 2005; Heiss, Thiel, Kessler, & Herholz, 2003; Leff et al., 2002; Weiller et al., 1995), others suggest that it is perilesional tissue that is key to recovery, including recovery induced by therapeutic interventions (e.g., Baker, Rorden, & Fridriksson, 2010; Fridriksson et al., 2012; Spironelli & Angrilli,

2009). The picture that has emerged from studies such as these, is that both hemispheres may potentially contribute to language recovery, with the extent to which each is involved depending on factors such as lesion size, aphasia severity, the particular language function, and time post-stroke (Crinion & Leff, 2007; Crosson et al., 2007; Heiss et al., 1997; Mimura et al., 1998; Price & Crinion, 2005; Saur et al., 2006, 2010). The majority of the aforementioned studies report functional changes supporting language recovery. However, the relationship between functional and structural plasticity is not clear at present (Draganski & May, 2008) and requires further investigation.

The potentially adaptive abnormalities found in Chapters 4 and 6 were only apparent using ACM. This clearly illustrates the value of this novel method in the study of stroke aphasia. The fact that ACM is a whole-brain method, which can reflect changes in connectivity to and from any brain voxel, means that it was ideally suited to identifying potential increases in connectivity, even those remote from the lesion itself.

Neuroanatomical Networks Underlying Different Behavioural Abilities

Employing complementary imaging measures in Chapter 6 allowed visualisation of structural abnormalities throughout the entire language network. This included both local changes in grey and white matter, reflected in T1-weighted and FA images, but also changes in connectivity arising due to more distant abnormalities, reflected in ACM values. The fact that these complementary measures reflect different properties of brain tissue meant that the pattern of results obtained across the different measures could be examined for each behavioural process of interest. The pattern of results obtained in Chapter 6 suggests that the three behavioural processes, phonology, semantics, and cognition, are all subserved by structural networks which differ in their level of distribution. Whilst all higher-level processes are likely to come about as a result of the workings of networks, rather than individual brain regions (Mesulam, 1990; Price &

Friston, 2005), the networks supporting some processes would appear to be more widely distributed than others, in terms of both cortical components and connectivity between those components.

Previous work has highlighted the involvement of the left hemisphere posterior superior temporal gyrus and sulcus in phonological processing. This includes both input and output phonology, with the region being implicated in both auditory processing of incoming speech sounds and in speech production, potentially as a result of involvement in feedback or prediction processes (e.g., Price, Crinion, & Macsweeney, 2011; Price, 2010, 2012; Pulvermüller & Fadiga, 2010; Vigneau et al., 2006). The inferior frontal gyrus, particularly posteriorly, is also often implicated in phonological processes, including those involved in receptive and expressive tasks (Gough et al., 2005; Price, 2010; Vigneau et al., 2006). Given that both of these areas have been implicated in phonological processing, and that they are broadly connected via the dorsal language route (Catani & ffytche, 2005; Catani et al., 2005; Catani & Mesulam, 2008a; Glasser & Rilling, 2008; Parker et al., 2005), it seems reasonable that interactions between temporo-parietal and inferior frontal regions via the dorsal route map between phonological inputs and outputs (Dick & Tremblay, 2012; Pulvermüller & Fadiga, 2010; Rauschecker & Scott, 2009). Indeed, interaction between temporo-parietal and frontal language regions via the dorsal route during repetition tasks has been demonstrated using functional and diffusion-weighted imaging (Saur et al., 2008), and damage or disruption to the dorsal route has been associated with production of phonological errors in naming tasks and impaired repetition performance (Berthier, Lambon Ralph, Pujol, & Green, 2012; Breier et al., 2008; Duffau et al., 2002, 2008; Kümmerer et al., 2013; Schwartz et al., 2012; Ueno et al., 2011). Results obtained in Chapter 6 across all three imaging measures, T1-weighted, FA, and ACM, revealed associations with phonological performance in posterior left superior temporal gyrus and sulcus and the dorsal language route. The

findings of the current thesis, together with previous work, therefore suggest that phonological processing depends upon a relatively direct network with cortical nodes in temporo-parietal and inferior frontal cortices, which interact via a bi-directional dorsal route connection (see Figure 6.7).

The pattern of results found across the different imaging measures for semantics suggests that computing meaning involves a more widely distributed network than phonological processing. The current findings are in keeping with a 'hub-and-spoke' conceptualisation of semantics, in which semantic representations are generated in a central hub, through bi-directional interaction with multiple modality-specific, distributed brain regions (spokes) (Patterson et al., 2007; Pobric, Jefferies, & Lambon Ralph, 2010). Previous work using functional neuroimaging, computational modelling, rTMS and patient data has provided evidence for a semantic hub in the anterior temporal lobe (Binney, Embleton, Jefferies, Parker, & Ralph, 2010; Hoffman, Jones, & Lambon Ralph, 2012; Hoffman & Lambon Ralph, 2011; Lambon Ralph, Sage, Jones, & Mayberry, 2010; Pobric et al., 2010; Rogers et al., 2004; Visser, Jefferies, & Lambon Ralph, 2009), whilst probabilistic tractography results have demonstrated a convergence of white matter connectivity from distributed brain regions (spokes) towards the anterior temporal lobe hub (Binney et al., 2012).

Damage to different components of the 'hub-and-spoke' system has been noted to result in very different neuropsychological deficits. For example, individuals with damage to the anterior temporal lobe hub arising as a result of semantic dementia, have been shown to present with cross-modality, core semantic deficits (Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006; Mayberry, Sage, & Lambon Ralph, 2011). Individuals with damage further from the anterior temporal lobe hub, affecting the spokes of the semantic system, have been found to present with modality-specific impairments, such as pure word deafness (Poeppel, 2001), pure alexia (Epelbaum et al., 2008), and visual

agnosia (Karnath, Rüter, Mandler, & Himmelbach, 2009). In the current work analyses relating semantic performance to T1-weighted imaging revealed a significant cluster in the anterior temporal lobe, which encompassed part of this semantic network. The FA findings overlap with those found in T1-weighted imaging, with values in the anterior temporal lobe relating significantly to semantic performance. However the FA cluster spread more superiorly and posteriorly up the temporal lobe, along the MTG and underlying white matter. As shown in Figure 6.6, the FA cluster encroached on different ventral route pathways, including the ILF, IFOF, and the UF. In this group of individuals with chronic stroke aphasia, impaired semantic performance appears to relate to partial damage to the semantic hub and, in any given case, some subset of the pathways connecting the hub to its spokes. Unlike semantic dementia, in which pervasive damage covering the entire semantic hub bilaterally relates to severe, frank semantic deficits, in this group of individuals partial damage to the hub-and-spoke system relates to partial semantic deficits. Differences in the nature of the semantic deficits demonstrated by individuals with stroke aphasia and those demonstrated by individuals with semantic dementia have been described previously (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010; Tsapkini, Frangakis, & Hillis, 2011).

Other conceptualisations of semantics exist besides the hub-and-spoke model, although the results of the current work are not as readily compatible with such accounts. One alternative model suggests that information pertaining to different concepts is distributed throughout the relevant sensory processing areas in the brain and that rather than such information converging in a central hub, where semantic representations are computed, concepts emerge as a result of activation across the different sensory areas alone (Martin, 2007; Simmons & Martin, 2009). The current results do not appear to support such a framework, as within such an ‘all-spokes-no-hub’ model, it would be hard to explain the T1-weighted and FA clusters found in the anterior temporal lobe. Simmons

and Martin (2009) argue that the anterior temporal lobe may play a role in processing information regarding unique entities or social concepts, such as familiar or famous faces, rather than multi-modal semantic information. Given that the assessments that loaded on the semantic factor did not involve social concepts or familiar or famous faces, the current results do not appear to support Simmons and Martin's (2009) claim.

The fact that the angular gyrus has consistently been shown to be activated during different semantic tasks, its proximity to brain regions known to be involved in different kinds of sensory processing, and evidence implicating its involvement in various neuropsychological disorders (Binder et al., 2009; Cabeza, Ciaramelli, & Moscovitch, 2012; Price, 2010; Seghier, Fagan, & Price, 2010) have lead some authors to argue that the angular gyrus constitutes a semantic hub (Binder et al., 2009). Although the current results do not explicitly support such a model, with no evidence of a relationship between the angular gyrus and semantics emerging, they are not incompatible with the existence of such a hub. It is possible that a relationship between semantic ability and the angular gyrus may exist but was not found due to a lack of power in that brain region. However, this seems unlikely as lesion overlap in the angular gyrus ranged from four to 19 participants. Alternatively, the angular gyrus could have failed to emerge due to an absence of unique variance associated with semantics (Cabeza, Ciaramelli, & Moscovitch, 2012), as previously outlined in relation to the absence of the IFG.

It has been noted that ‘angular gyrus’ refers to a large region with heterogeneous anatomical and functional subdivisions (Seghier et al., 2010). This, rather than the fact that the area serves as a ‘semantic hub’, could explain the fact that it has been seen to be activated in many different types of tasks and that it has been implicated in a variety of neuropsychological deficits. Indeed, if this is the case, then the absence of the angular gyrus in our results is not surprising, given its focus on identifying areas uniquely associated with a given ability identified in the analysis. The current results clearly

highlight the anterior temporal lobe hub, as T1-weighted image concentration and FA in the anterior temporal lobe significantly related to semantic performance. On a methodological note, the fact that the current work was able to identify effects in the anterior temporal lobe, which has not always been the case in previous imaging work, is in part due to the use of distortion correction techniques (Embleton, Haroon, Morris, Lambon Ralph, & Parker, 2010; see also Binney et al., 2012; Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010).

The fact that a significant correlation between *average* ACM in the anterior temporal lobe and semantic performance was identified in Chapter 6, whilst no such relationship occurred in the original voxel-level analysis was interpreted as reflecting the nature of the semantic network. As noted previously, the FA cluster for semantics encompassed a number of ventral white matter pathways in the anterior temporal lobe. Whilst average anatomical connectivity in this region related to semantic performance, a relationship at the voxel level may not have been identified because across the sample in this study, there is likely to be variability in terms of which of the number of tracts making up the ventral pathways is damaged, which in turn means that there is no consistent long-range connection associated with semantic processing.

The cognitive factor, which was interpreted as representing domain-general cognitive control processes, showed a very different profile of results across imaging measures. As previously noted, whilst no results emerged in the analyses of T1-weighted or FA data, cognition related to a right frontal cluster in the ACM analysis. Cognition not relating to any regions in the more local measures, but to a region in the more global measure, was interpreted as reflecting the fact that cognition is even more highly distributed than semantic processing. This is in keeping with previous studies which have shown that cognitive control is subserved by highly distributed bilateral networks (e.g., Dosenbach et al., 2007; Ham & Sharp, 2012; Power & Petersen, 2013; Seeley et al.,

2007). Authors have previously distinguished between the working of 'processors' which operate on particular types on information and 'controllers' which influence how the processors operate and ensure that they meet task demands (Norman & Shallice, 1986; Power & Petersen, 2013). The demands of the tasks that load on the cognitive factor in the current study, which include executive functions such as set shifting, relational integration, non-verbal reasoning, decision-making, and working memory, suggest that the cognitive factor captures the working of such a 'controller'. It has been suggested that controllers are likely to be more widely distributed, in terms of underlying neuroanatomy, than the processors that they operate on, owing to the range of areas they are required to interact with (Power & Petersen, 2013). The fact that the current results implicate a widely distributed network underpinning the cognitive factor is therefore in accord with previous work. It should be borne in mind that the pattern of results obtained across the three imaging measures emerged in the context of stroke aphasia, in a cohort with individual, focal lesions. A different pattern of results might be expected to emerge in a group of individuals with more diffuse damage, with aetiologies such as traumatic brain injury (e.g., Kinnunen et al., 2011).

In summary, the current results suggest that phonological processing depends on a network in which frontal and temporo-parietal cortical areas interact via a bi-directional dorsal route connection. Semantic processing, meanwhile, would appear to be subserved by a hub-and-spoke arrangement, with information from distributed cortical areas being transferred to and from an anterior temporal lobe hub, via ventral route pathways. Finally, cognition is likely to be underpinned by a large-scale, widely distributed bilateral network. The cortical nodes and white matter pathways described as comprising these phonological, semantic, and cognitive networks are likely to be involved in more than just the processes described in the current work. As noted by previous authors, it is unlikely that there is a one-to-one mapping between structure and function in the brain,

and the function carried out by an area is likely to be determined by the areas with which it is interacting and the current task demands (Price & Friston, 2005).

Clinical Applications

What sort of impact can neuroimaging findings, such as those reported in the current thesis, have in terms of improving outcomes for individuals affected by stroke aphasia in future? In recent years neuroimaging has been increasingly widely employed for diagnosis of stroke and prognosis of its behavioural consequences such as aphasia. For example, CT scanning, and increasingly MRI scanning, is now routinely used to identify the aetiology and location of damage when a patient presents acutely. Imaging can also be used to help identify tissue that may be salvaged by clinical interventions such as reperfusion (Hillis, 2005; Merino & Warach, 2010; Olivot & Albers, 2011; Stinear & Ward, 2013). Until very recently neuroimaging information has only allowed clinicians to provide very broad predictions with regards to prognosis for recovery from aphasia (and other behavioural impairments). Typically, detailed predictions regarding how much recovery an individual is likely to make and the kind of language profile they may exhibit chronically are not provided to affected individuals and their families. However, more sophisticated ways of employing neuroimaging data and combining these data with other relevant information, such as demographic data, to provide more detailed predictions regarding recovery are emerging, as exemplified by the PLORAS system (Price, Seghier, & Leff, 2010). The PLORAS system enables a clinician to enter an individual's acute scan into a database and to predict, based on scans and outcomes from many previous individuals, their likely language outcome in terms of speech production and comprehension ability. Outcome is predicted based on both lesion-based factors and other important variables that may affect recovery such as the individual's age and handedness, and even speech therapy input (Price et al., 2010; see Stinear, Barber, Petoe,

Anwar, & Byblow [2012] for a similar system for predicting motor outcome following stroke). The work presented in this thesis suggests that addition of information such as local and global white matter measures (for example in the form of FA maps and ACM) may further increase the ability of such systems to accurately predict chronic language outcomes.

Neuroimaging, including diffusion-weighted imaging, also has great potential for determining the type of therapy strategy that a speech and language therapist may choose to employ with an individual (Stinear & Ward, 2013). This area has, however, been relatively underexplored as yet. The current work suggests that global connectivity information such as that available in ACM would be useful in this regard. Whilst both T1-weighted scans and FA maps could provide information regarding the integrity of components of a particular white matter pathway, they cannot show whether connectivity related to that pathway is intact. Thus, by using ACM in concert with such local measures, a fuller picture would be gained regarding the neuroanatomical resources an individual had available to utilise during therapeutic interventions. Based on such information, speech and language therapists may choose to employ interventions that optimise use of pathways with more intact connectivity. For example, a therapist may employ more semantic interventions to maximise use of the ventral route in cases of dorsal route damage or reductions in connectivity. Employing more bespoke interventions, taking into account factors including the neuroanatomical resources of individuals, may potentially improve outcomes for individuals with stroke aphasia.

Neuroimaging has also been used in more recent studies in an attempt to elucidate the mechanisms by which therapeutic gains are achieved. Whilst much of this work has been done using functional neuroimaging (e.g., Crinion & Leff, 2007; Crosson et al., 2007, 2010; Fridriksson et al., 2012; Meinzer & Breitenstein, 2008; Meinzer et al., 2008, 2013; Rapp, Caplan, Edwards, Visch-Brink, & Thompson, 2013), recent studies have

shown that structural connectivity information may potentially help to identify mechanisms underlying successful therapeutic interventions (e.g., Schlaug et al., 2009). Information regarding the functional and structural mechanisms underlying successful therapy, such as functional recruitment of perilesional tissue, or increases in structural connectivity in the contralesional hemisphere, could guide therapeutic interventions. Whilst the current results illustrate the fact that both local and global white matter information could potentially aid in prognosis and development of therapeutic strategies in stroke aphasia, further work is clearly required for such information to be employed routinely in the clinical context.

Conclusions and Directions

The work reported in this thesis demonstrates that PCA can be employed to capture core abilities of individuals with chronic stroke aphasia and that such PCA-derived measures constitute effective regressors for analyses of lesion data. A similar approach has recently been employed in acute stroke aphasia (Kümmerer et al., 2013) and in primary progressive aphasia (Henry et al., 2012). The current results show, for the first time, that such PCA-derived scores relate meaningfully to white matter measures in the brains of individuals with chronic stroke aphasia. Future investigations of other multifaceted disorders, such as Alzheimer's disease, could potentially relate PCA-derived measures of behaviour to neuroimaging data, to help elucidate relationships between behaviour and underlying brain pathology. This may be particularly informative if white matter measures were employed, in addition to more traditional neuroimaging data.

The current work illustrates that both local and global white matter information can be used, together with more traditional neuroimaging techniques, to provide information that can aid understanding of the behavioural performance of individuals with chronic stroke aphasia. Moreover, different patterns of results obtained by

combining complementary imaging measures can provide insights into the neuroanatomical bases of different behavioural abilities. Whilst such an approach could also be utilised in acute stroke aphasia, it has the potential to be particularly illuminating in longitudinal designs, charting participants from the acute to chronic phase. A longitudinal study, which combined PCA-derived behavioural measures with complementary imaging data that included local and global white matter measures, could potentially relate changes occurring post-stroke at both the behavioural and neuroanatomical level.

The kinds of neuroanatomical changes that such an approach could reveal include potentially compensatory changes such as those reported in Chapters 4 and 6. Longitudinal evidence of such changes could potentially strengthen claims regarding the role of structural connectivity changes in behavioural recovery. To more fully understand such changes and their relationship with behavioural outcomes, a longitudinal design could also incorporate functional neuroimaging. In this way, the relationship between changes at the structural, functional, and behavioural levels could be better understood.

Functional imaging work could include investigations of changes in activation in cortical regions during language tasks (as shown longitudinally by Saur et al. 2006) or changes in functional connectivity between cortical regions either during tasks or at-rest. Functional connectivity between left and right anterior superior temporal regions has been shown to be reduced in chronic stroke aphasic individuals relative to controls when engaging in speech comprehension tasks (Warren, Crinion, Lambon Ralph, & Wise, 2009). Stronger functional connectivity (measured using psycho-physiological interactions) between frontal and temporal regions, and higher integrity of both the dorsal and ventral route (measured using FA and MD), have been shown to relate to better syntactic performance in chronic stroke aphasia (Papoutsi et al., 2011). Employing a

longitudinal design, measuring and relating changes in structure, function, and behaviour, has the potential to reveal factors determining outcomes in stroke aphasia.

As noted previously, the results of the current work are consistent with a dual route model of language processing, in which the dorsal route is critically involved in phonological processing and the ventral route is associated with semantic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hickok & Poeppel, 2004, 2007; Saur et al., 2008; Ueno et al., 2011). Of course, interaction between the two routes is likely to occur during healthy language processing (Cloutman, 2012; Ueno et al., 2011; Wise, 2003) and recent studies have shown that complex language processes such as syntactic processing rely upon both routes (Bornkessel-Schlesewsky & Schlesewsky, 2013; Griffiths et al., 2012; Papoutsi et al., 2011; Rolheiser et al., 2011). Yet the form of this interaction is still poorly understood, and several neuroanatomical and temporal opportunities for interaction between dorsal and ventral routes have been identified, with top-down feedback potentially involved in synthesising the processing that occurs in the two routes (Cloutman, 2012). Clearly, more work is needed to understand the manner in which interaction between the two routes occurs. As well as explicating how such interactions occur in the healthy brain, future work could investigate how it is disrupted after damage, and how these changes relate to stroke aphasic deficits.

Finally, local and global white matter information that has been shown to be predictive of behavioural performance in this group of chronic stroke aphasic individuals could be incorporated into future therapy studies. Such studies could tailor interventions to individuals based on their structural connectivity profile, particularly the status of their dorsal and ventral language routes. Post-therapy outcomes for individuals who received tailored interventions could then be compared to those who received standard interventions, to assess whether tailoring therapy in such a manner proved beneficial. Clearly other neuroimaging data, such as functional data or perfusion data, could also be

used to help guide interventions. The major contribution of the current work is, however, the demonstration that local and global connectivity measures relate to language ability in chronic stroke aphasia, and as such it highlights that taking such information into account when delivering interventions could potentially lead to improved language outcomes for individuals affected by stroke.

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